**Inhalation Developmental
Toxicology Studies: Teratology Study
of Methyl Ethyl Ketone in Mice
Final Report**

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INHALATION DEVELOPMENTAL TOXICOLOGY STUDIES:
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No. NIH-Y01-ES-70153

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SUMMARY

Methyl ethyl ketone (MEK) is a widely used industrial solvent which results in considerable human exposure. In order to assess the potential for MEK to cause developmental toxicity in rodents, four groups of Swiss (CD-1) mice were exposed to 0, 400, 1000 or 3000 ppm MEK vapors, 7 h/day, 7 dy/wk. Ten virgin females and ~30 plug-positive females per group were exposed concurrently for 10 consecutive days (6-15 dg for mated mice). Body weights were obtained throughout the study period, and uterine and fetal body weights were obtained at sacrifice on 18 dg. Uterine implants were enumerated and their status recorded. Live fetuses were sexed and examined for gross, visceral, skeletal, and soft-tissue craniofacial defects.

Exposure of pregnant mice to these concentrations of MEK did not result in apparent maternal toxicity although there was a slight, treatment-correlated increase in liver to body weight ratios which was significant for the 3000-ppm group. Mild developmental toxicity was evident at 3000-ppm as a reduction in mean fetal body weight. This reduction was statistically significant for the males only, although the relative decrease in mean fetal body weight was the same for both sexes.

There was no increase in the incidence of intrauterine death in the fetuses of mice exposed to MEK, but there was an increased incidence of misaligned sternbrae (a variation) which was correlated to increasing exposure concentration. The increase was statistically significant for the 3000-ppm group. Although there were no significant increases in the incidence of malformations, several malformations were present at a low incidence which were not observed in the 0-ppm group or in the contemporary control data; cleft palate (1 fetus), fused ribs (2), missing vertebrae (1), and syndactyly (5 [all in the same litter]).

In summary, pregnant Swiss (CD-1) mice appear to be relatively insensitive to the toxic effects of MEK at the exposure levels employed in this study. However, the offspring of the mice exhibited significant signs of

toxicity at the 3000-ppm exposure level. Neither maternal nor developmental toxicity were observed at 1000 ppm MEK or below.

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INTRODUCTION

Methyl ethyl ketone (MEK) is a widely used industrial solvent with a 1984 production figure of 556 million pounds (Yang 1986 and references therein). Inhalation of MEK vapors and skin contact with liquid MEK are the major routes of human industrial exposure. Literature pertaining to the toxicology of (MEK) has been thoroughly reviewed through mid-1985 by R.S.H. Yang (Yang 1986); consequently, this introduction will deal specifically with aspects pertinent to reproductive and developmental toxicity studies.

The metabolism and pharmacokinetics of MEK have been studied in several laboratory species as well as in the man. DiVincenzo, Kaplan, and Dedinas (1976) reported the serum $t_{1/2}$ in male guinea pigs following a single intraperitoneal injection of MEK to be 270 min (4.5 h) and the clearance time to be 12 h. These were the longest values of any of several ketones, alcohols, or diones examined. Metabolites found in the serum and urine of animals exposed to MEK have been well-characterized, are formed by both oxidative and reductive pathways, and are similar for all species examined (Figure 1); guinea pigs (DiVincenzo, Kaplan, and Dedinas, 1976), rats (Dietz and Traiger 1979), rabbits (Sanoyeshi 1911), and humans (Perbellini, Brugnone and Mozzo 1984). The alcohols formed may subsequently enter into intermediary metabolism or be conjugated with sulfuric or glucuronic acid and excreted in the urine. However, at least in the human, urinary excretion is not a major elimination route as reported by Perbellini, Brugnone and Mozzo (1984) who found that only 0.1% of the original MEK dose could be accounted for by urinary excretion products in the human, e.g. MEK and 3-hydroxy-2-butanone. The major elimination routes for MEK and its metabolites remain undefined, although since MEK (as the parent compound) rapidly appears in expired air following dermal application of liquid MEK to the human skin, expiration may be a significant route of elimination (Wurster and Munies 1965).

Due to the high volatility of MEK, occupational exposures are likely to occur via inhalation whenever MEK is employed in poorly ventilated or confined environment. Since MEK is rapidly absorbed through the skin (described below)

unprotected dermal contact may also represent a significant exposure route. Munies and Wurster (1965) reported that MEK undergoes dermal absorption through human skin with subsequent release in expired air. The rate of dermal absorption is apparently quite rapid as evidenced by the release of MEK into expired air within 2-3 min following application of the solvent to the skin. The rates of elimination via expired air following oral or dermal exposures are similar indicating that the route of administration has little effect on the route of elimination.

Distribution of MEK throughout the human body is rapid due to its high solubility in blood ($[\text{blood}]/[\text{alveolar air}] \cong 104$). Nearly equal amounts were present in all tissues, e.g. brain, kidney, lung, fat, heart, muscle, and liver. Furthermore, a statistically significant correlation was found between environmental concentrations of MEK in an Italian shoe factory, and tissue and urine levels of MEK in exposed workers (Perbellini, Brugnone and Mozzo 1984).

Indirect evidence for hepatic cytochrome-P₄₅₀ monooxygenase induction by MEK was demonstrated by quantitating parent compound or major metabolites in male Wistar rats which had been exposed to a mixture of MEK and methyl butyl ketone (MBK) at a ratio of 750:225 ppm; 975 ppm total, or to 400 ppm MBK alone (Abdel-Rahman, Hetland and Couri 1976). MEK plasma values were lower immediately post-exposure to the MEK/MBK mixture after continuous exposure for 23 days than they were following a single 8-hr exposure, thus indicating that MEK and/or its metabolites apparently induced the cytochrome-P₄₅₀ system. The opposite was shown to be the case for MBK in the presence of MEK when neither MBK nor its metabolites were detectable in blood after a single 8-hr exposure, but increased to 24 mg% after the 23rd day of exposure. Plasma MBK levels for animals exposed to MBK alone were below detection limits following either a single 8-hr exposure or a 23-day continuous exposure to 400 ppm MBK, indicating that the presence of MEK affected the metabolism of the MBK. [The difference in total solvent concentration between the two exposure regimens should be kept in mind when considering these results. It is possible that the change observed in MBK metabolism following a 23-day exposure period was

not a specific alteration in the pharmacodynamics of MBK by MEK, but instead was due to general toxicity.]

Further evidence for hepatic changes following exposure of Sprague-Dawley rats to 800 ppm of MEK, 6 h/day, 5 days/wk for a duration of 4 weeks, was reported by Toftgard, Nilsen and Gustafsson (1981) who found increased liver weights and liver to body weight ratios in exposed animals. Microsomes prepared from the livers of exposed animals had a greater level of cytochrome P₄₅₀ per milligram of protein than did control liver microsomes, and demonstrated an increased ability to oxidize benzo[a]pyrene to the corresponding phenols and quinones. However, SDS-polyacrylamide gel electrophoresis of treated microsomes revealed no significant changes in the composition of the various cytochrome P₄₅₀s.

TOXICOLOGY

The acute toxicity of MEK is relatively low in rodent species (Yang 1986 and references therein). A 90-day inhalation study of MEK on male and female Fisher 344 rats exposed to 0, 1250, 2500, or 5000 ppm MEK, 6 h/day, 5 day/wk, produced no adverse effects on the clinical health or growth of either sex (Cavender, Casey and Salem 1983). No significant neurological lesions were observed following examination of the medulla oblongata and the right and left sciatic and tibial nerves. Evidence of hepatic MFO induction was indicated by significantly increased liver to body weight ratios in both sexes. No reports on similar studies in mice were found.

MEK is known to potentiate n-hexane neurotoxicity as well as that caused by other hydrocarbons and also potentiates the hepatotoxicity of chloroform. MEK has not been found to be mutagenic in either mammalian or bacterial cell test systems, but has been shown to induce aneuploidy in a yeast strain (Yang 1986 and references therein).

Reproductive and Developmental

Schwetz, Leong, and Gehring (1974) reported MEK to be embryotoxic, fetotoxic, and potentially teratogenic on the basis of results obtained from

an inhalation teratology study on Sprague-Dawley rats. Timed-pregnant rats were exposed to 0, 1000, or 3000 ppm MEK on 6-15 days of gestation (dg). MEK exposure had no effect on the number of resorptions, the fetal crown-rump length, the sex ratio, nor on maternal body weight or weight gain during gestation. Fetal body weight was slightly decreased for both exposure groups, however the decrease was significant for only the 1000-ppm group. Major fetal malformations were observed only in the 3000-ppm exposure group; one fetus in each of four litters. Two of these fetuses were acaudate and two were brachygnathic. There was a significant increase in the percent of litters containing fetuses with skeletal anomalies (reduced ossifications and extra ribs) for both exposure groups when compared to controls. Ninety-five percent of the litters in the 1000-ppm group were affected in this manner and 81% in the 3000-ppm group. The incidence of soft-tissue anomalies (subcutaneous edema and dilated ureters) was also greater in the MEK exposed groups than in the controls, and this increase was statistically significant for the 3000-ppm group.

As a result of the conclusions from the study of Schwetz, Leong, and Gehring (1974), Deacon et al. (1981) further investigated the embryo- and fetotoxicity of inhaled MEK in Sprague-Dawley rats. In this study sperm-positive rats were exposed to 400, 1000, or 3000 ppm MEK, 7 hr/day, 6-15 dg. Dams did not exhibit any clinical signs of toxicity; however, an unspecified reduction in weight gain in the 3000-ppm group was reported. This effect had not been observed in the earlier study [actual maternal weight data was not included in the report of Deacon et al. (1981)]. As in the earlier study, there was no effect of exposure on the mean number of live fetuses or resorptions per dam. However, in agreement with the previous study, the percent of litters with fetuses exhibiting delayed ossification of vertebral centra was increased in the highest exposure group. Also as previously reported, the percent of litters with fetuses having reduced ossification of the skull bones was lower in the 3000-ppm exposure group than in any of the other treatment groups or in the controls. [No fetal weight data were given in this report, nor was reference made to such data.]

In summary, the findings of these two teratology studies on MEK in the Sprague-Dawley rat are in basic agreement. Although there was no evidence of frank teratogenicity or embryotoxicity in either study, the results did not establish that MEK was free from fetotoxic or teratogenic potential in this rodent species. The decrease in the incidence of reduced ossification of the skull bones with increasing exposure concentration coupled with a parallel increase in the incidence of reduced vertebral ossification may be indicative of a toxic effect on development. Although a reduction in the incidence of reduced ossification of the skull bones, if taken alone, would not appear to be indicative of developmental toxicity, the fact that it is coincident with an increase in reduced vertebral ossification is suspicious. Since no data are available for other test species, further examination of the potential of MEK to cause developmental toxicity is warranted.

The developmental toxicity of 2-butanol, a known metabolite of MEK (Figure 1), was investigated by Brightwell et al. (1987) in Sprague-Dawley rats. Pregnant females were exposed in inhalation chambers to 3500, 5000, or 7000 ppm 2-butanol, 7 h/day, throughout gestation until sacrifice on 20 dg. There was evidence of maternal toxicity in the highest exposure group, manifested by a reduction in weight and food intake; however, there was no increase in the incidence of fetal malformations for any exposure group. A reduction in mean fetal weight was observed for the 7000-ppm exposure group; however, since this coincided with maternal toxicity (the author's considered) it was not indicative of developmental toxicity. [No comments were made regarding the number of live offspring or resorptions.]

Epidemiological Studies

Alderson and Rattan (1980) performed an historical perspective study on 446 men who had worked in two MEK dewaxing plants to determine the effect, if any, of occupational exposure to MEK on mortality or the incidence of malignant disease. MEK exposure was not found to have an effect on the number of observed deaths in this group; furthermore, the number of deaths due to neoplasms in this group was less than predicted. Although not considered to be clear evidence of a cancer hazard, significantly more deaths due to buccal

cavity and pharynx cancers were detected in this group than had been predicted.

Considerable concern exists regarding the exposure of women of child-bearing age to industrial solvents and the subsequent potential for adverse effects on reproductive and developmental processes. Holmberg and Nurminen (1980) reported a statistically significant increase in the incidence of children born with central nervous system (CNS) 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 report that no significant difference in the incidence of children with CNS defects was found when occupational exposures to metals, pesticides, dyes, noise, temperature extremes, fumes, or radiation were used as the analysis variable.

SUMMARY

MEK has a low acute and subchronic toxicity in experimental animals and apparently in humans. However, results of both rodent studies and human epidemiological findings suggest that there is cause for concern over the potential of this compound to cause developmental toxicity. Consequently, a standard inhalation teratology study in Swiss (CD-1) mice was recommended to further define the potential for MEK to cause developmental toxicity.

MATERIALS AND METHODS

Four groups of female Swiss (CD-1) mice (12 wk; Charles River, Raleigh, NC), were exposed to 0 (filtered air), 400, 1000, or 3000 ppm MEK vapors, 7 h/day, 7 days/week. Each of the 4 exposure groups consisted of 10 virgin and 33 plug-positive female mice; all groups were randomly selected using body weight as a blocking variable. The virgin mice were included to assess maternal toxic effects which may result solely from the state of pregnancy. Virgin and plug-positive female mice were exposed concurrently for 10 consecutive days (6-15 dg for mated mice). The day of plug detection in mice was designated as 0 dg. The animals were removed from the exposure chambers

on the morning after the last day of exposure and held in a holding chamber in the exposure room for 16-17 dg. All four treatment groups were placed in a single holding chamber, each treatment group on a different cage-rack level. Pregnant mice were killed on 18 dg, and virgin females were killed 3 days after the last day of exposure. Control animals (0 ppm) were housed in an exposure chamber in the same room, and were handled in the same manner as the mice that were exposed to the test chemical. Animals remained in the exposure chambers and were supplied with fresh filtered air and food when MEK exposures were not in progress. Water was provided *ad libitum* at all times.

MEK exposure concentrations 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.

EXPOSURE SYSTEM

Inhalation exposures were conducted in Battelle-designed inhalation exposure chambers (Harford System; Lab Products, Inc., Aberdeen, MD). The 2.3-m³ stainless-steel chamber (1.7-m³ active mixing volume) contained three levels of caging, each of which was split into two offset tiers. The drawer-like stainless-steel cage units accommodated individual animal cages, feed troughs and automatic waterers. Stainless-steel catch pans designed to aid in maintaining a uniform concentration of vapor throughout the chamber, as well as for the collection of urine and feces, were suspended below each cage unit. Air (HEPA- and charcoal-filtered) containing a uniform mixture of MEK flowed through the chamber at approximately 15 ft³/min (CFM) which was equivalent to approximately 15 air changes per hour. The uniform mixture was diverted along the inner surfaces of the chamber and a portion of the flow was "peeled off" by each catch pan, thus creating mixing eddies. Exhaust from each tier was cleared through the space between the tiers. See Appendix B.

The MEK exposures were conducted using an automated data acquisition and control system in an exposure suite. This system monitored and controlled the basic inhalation test system functions including chamber air flow, vacuum,

temperature, relative humidity, and test chemical concentrations at $\approx$ 4-h intervals. Conditions which may have been a threat to the health of the animals or constituted an explosion hazard triggered alarms to personnel who were on call 24 h/day. All data acquisition and exposure control originated from an executive computer which contained the exposure protocols and controlled a multiplexing-interface system.

MEK vapor was generated by a rotary evaporation system (Büchi Rotavapor, Model EL-131S) which produced high purity MEK vapor (Figure 2). Low pressure nitrogen (4-6 psi) was introduced into the inlet of a 5-gal pressurized delivery container, forcing liquid MEK out at a steady, controlled rate which was adjusted with a metering valve and monitored with a flowmeter. The liquid was delivered to a rotating flask immersed in a hot water bath. The resulting vapor was forced out of the mouth of the flask into a chilled water condenser where much of the vapor was recondensed and returned to the evaporator flask. Nitrogen was metered into the bottom of the condenser and flowed out the top saturated with MEK vapor. The temperature of the MEK-saturated nitrogen was monitored using a sensor at the top of the condenser. The vapor entered a short distribution manifold where individual delivery lines carried a metered amount of vapor to the exposure chambers. Injection of the nitrogen/vapor mix into the conditioned airstream entering the chamber occurred at a point sufficiently removed from the chamber to allow for proper mixing. This assured uniformity of chemical-laden atmosphere within the chamber. Normal operation called for approximately 20% excess vapor to be exhausted from the manifold through a flowmeter. This caused a slight positive pressure in the manifold and allowed independent adjustment of the chamber flow rates.

Generation proceeded in stages: warmup, generation and shutdown. During warmup, filling of the evaporator flask and heating of the water bath proceeded together. During this time, some evaporation occurred but all vapor was exhausted from the distribution manifold through the excess flowmeter and at each chamber through pneumatic 3-way valves. When the bath temperature and fluid level reached the correct values, computer-controlled startup of the

exposure was initiated by rotation of the pneumatic 3-way valves to the chamber position.

Shutdown at the end of the generation stage was normally initiated by the computer which closed the valves at the chambers, stopped flask rotation, and turned off the water bath heater. The operator then dumped additional cooling water into the water bath. The remaining MEK in the evaporator flask was transferred to a waste bottle. Nitrogen continuously purged the generation system until preparation for the next day's generation.

In order to determine the persistence of the chemical in the chamber following exposure, the concentration of MEK in the 3000-ppm chamber was monitored overnight following shutoff of the chemical flow to the chamber. Overnight monitoring was performed once during the prestart activities without animals, and again during the study when animals were present. Concentration of MEK in the chamber with or without animals was less than 1% of the initial concentration within 20 min following shutdown of the vapor generation system.

Exposure chambers without animals, and the exposure room, were monitored for particles during one day of test generation with a particle detector (Gardner Associates, Type CN, Schnectedy, NY). Particle monitoring was also conducted once during the exposure with animals in the chambers. No particles were detected in the control chamber or in any of the exposure chambers during any of the pre-exposure tests. The 1000-ppm chamber, with animals present, was found to contain <200 particle/cm³.

The time for the concentration to build up to 90% of the final, stable concentration following the start of generation (T_{90}), and the time for the vapor concentration to decay to 10% of the stable concentration following the cessation of generation (T_{10}), were determined before and after animals were placed in the chambers (Figure 3). The experimental value for T_{90} without animals present ranged from 10 to 12 min, and with animals present from 7 to 10 min. At a chamber air flow rate of 15 air changes per hour, the theoretical value for T_{90} was ≈ 12.5 min. Since there could have been variability in experimental buildup times due to fluctuations in chamber flow

rates and sampling accuracy, a T_{90} of 12 min was chosen for this study. The value of T_{10} ranged from 9 to 12 min without animals present, and decreased to 8 to 10 min with animals present.

Uniformity of vapor concentration in the exposure chambers was measured prior to the start of, and once during, the study. The vapor concentrations for these determinations were measured using the on-line GC with the automatic sampling valve disabled to allow continuous monitoring from a single input line. Prior to animal loading, 12 chamber positions were measured. The second set of MEK concentration measurements was taken from the front and back positions of the chamber only where cage units contained animals. Uniformity in all chambers was acceptable.

Chamber and room temperatures were measured with an accuracy of 0.5°F by calibrated resistance temperature detectors (RTD) which were located at the measurement site, and were multiplexed to a digital thermometer interfaced to the computer. Chamber temperature was controlled primarily by adjusting the temperature of the exposure room. Percent relative humidity (%RH) was determined by pulling an air sample through a Teflon® tube into a dew point hygrometer located in the control center. Measurements were taken from different chambers using a valving system which multiplexed the sampling tubes to the hygrometer. Values for %RH were calculated by the executive computer from temperature and dew point measurements with an accuracy of ±6%.

Chamber air flow was calculated with an accuracy of ±15 l/min by measuring the pressure drop across calibrated orifices located at the inlet and exhaust of each chamber. Leaks in the chambers could be detected by comparison of the inlet flow rate with exhaust flow rate. Flow was established by a gate valve in the exhaust line of each chamber. Chamber vacuum, relative to the control center, was measured with an accuracy of ±0.2 cm H₂O using the same pressure transducer system which measured chamber air flows. Chamber vacuum was maintained at approximately (-)1" H₂O, primarily by inlet resistance provided by the HEPA and charcoal filters.

ANALYTICAL CHEMISTRY

Test Material Bulk Analysis

MEK (J.T. Baker Chemical Co., Phillipsburg, N.J. 08865) was received in five 1-gallon glass bottles (5 kg/bottle) and one 55-gallon metal drum which contained 50 kg of MEK. The identity of the bulk material was confirmed by infrared spectroscopy, and the initial percent purity was found to be >99.9% by determining the percent of the total peak area that was represented by the MEK peak. Purity analyses were performed by gas chromatography on a Hewlett Packard (HP) 5890 gas chromatograph (GC) equipped with a 4 ft x 2 mm glass column packed with Porapack Q 80/100. (See Appendix A for further detail.) MEK was stored at room temperature prior to use. The teratology study consumed approximately 4.3 kg/day, a total of 52 kg.

Exposure Chamber Monitoring

The concentrations of MEK vapor in the chambers were monitored with an HP5840 GC system. This instrument was equipped with an 8-port stream select valve, and measured vapor levels in the three exposure chambers, the control chamber, the holding chamber, the exposure room, the on-line standard, and the nitrogen blank. In order to confirm values generated by the on-line monitor, bubbler grab samples were collected from the chamber and analyzed on an HP5840 GC. An on-line, certified gas standard, 1000 ppm MEK in nitrogen, was used to check instrument drift throughout the exposure day. Analytical precision was estimated to be within $\pm 1\%$ and the estimated detection limit was 0.5 ppm. Accuracy of the on-line GC was assured by calibrating it against a gravimetrically calibrated GC. (See Appendix A.)

Degradation and Stability Studies

The stability of MEK vapor in occupied and unoccupied chambers was determined for 400- and 3000-ppm chambers as well as for the distribution line. In addition, samples of liquid MEK from the generator reservoir and from the evaporator flask were collected and analyzed for purity. All samples

were analyzed for methanol, ethanol, acetone, isopropyl alcohol, MEK, and 2-butanol. These analyses were accomplished using gas chromatography-headspace analysis. The presence of less volatile impurities and degradation products in the unoccupied and occupied 400- and 3000-ppm chambers, and in the distribution line was also investigated by collection of samples onto charcoal adsorbent tubes. Materials trapped on the adsorbent tubes were desorbed in carbon disulfide and analyzed by gas chromatography. The distribution line, chamber atmosphere, and bulk material were also analyzed for MEK peroxide (MEKP) using a colorimetric method based on the oxidation of diphenylcarbazide by MEKP to form an intensely colored dye.

ANIMAL HUSBANDRY

Upon receipt, all animals were housed in quarantine rooms for 4 weeks prior to the start of exposure. Males and females were housed separately on stainless steel wire racks equipped with automatic waterers (10 mice per cage). During the quarantine period six males and four females were killed and examined for gross and microscopic lesions. Nasopharyngeal washes from these animals were cultured for bacterial pathogens. Serum from each animal was tested for antibodies to selected pathogens (Appendix D). Another check for antibodies to selected pathogens was performed on serum obtained at the final sacrifice from five females in the 0-ppm group and from five females in the highest exposure group. All results were negative for significant pathogens and lesions. Study animals were observed daily for mortality, morbidity, and overt signs of toxicity.

Food, pelleted NIH-07 diet (Ziegler Bros., Inc., Gardner, PA), was provided *ad libitum* during the entire time the animals were in the test facility except during the 7-h/day exposure period when it was removed to prevent contamination and oral ingestion of the test material. Water was provided *ad libitum* with automatic waterers throughout the study. Room lighting was maintained on a 12-h on-off cycle (0600-1800 h for the light phase). During the quarantine period animal room temperature was maintained at 75±3°F and the percent relative humidity was maintained at 50±15.

Mean chamber temperatures during the study were maintained within the limits of $75 \pm 3^\circ\text{F}$. Daily chamber temperature means for all exposure days were within the specified limits. Mean percent relative humidity in all exposure chambers was within the specified limits of $55 \pm 15\%$. The average air flow in all chambers for the study was within the specified limits of 12-18 CFM. A complete summary of the daily chamber environmental data can be found in Appendix B.

DEVELOPMENTAL TOXICOLOGY

Female mice were weighed and individually identified by eartags 1 week prior to mating. At this time 40 virgin females were randomly selected using body weight as the blocking variable. The remaining females were available for breeding by caging 2-3 females overnight with each male. A positive mating was established on the following morning if a vaginal plug was present. This day was designated as 0 dg and positively mated females were weighed and randomly assigned to exposure groups using body weight as the blocking variable. Mating was conducted for 3 consecutive nights to obtain 132 positively mated female mice (33/group). The virgins were individually caged in an open exposure chamber 10 days prior to exposure for the purposes of acclimation. Three days before exposure, virgin female mice were randomly assigned to one of the four exposure groups by using body weight as the blocking variable.

Mice were exposed to MEK vapors from 6-15 dg, then caged in a holding chamber supplied with filtered air from 16-17 dg, and sacrificed on 18 dg. Virgin mice were exposed for 10 consecutive days concurrently with mated animals, and were sacrificed 3 days after their last exposure day. Mated female mice were weighed on 0, 6, 9, 12, 15 and 18 dg. Virgin mice were weighed 3 days prior to the start of exposure, and on exposure days 1, 5, and 10, and at sacrifice.

At the time of sacrifice, mice were killed with CO_2 , weighed and examined grossly for signs of maternal toxicity. Maternal liver and kidney weights were obtained, and both ovaries were saved for later sectioning and

quantitative follicle counts (these tissues will be archived and shipped to the NTP). 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 unless abnormal.

Live fetuses were weighed, examined for gross defects, and their sex was determined by internal examination of the gonads after a lethal injection of Nembutal® (sodium pentobarbital). Fifty percent of the live fetuses and any fetuses with gross external abnormalities were examined for visceral defects by dissection of fresh tissue. The heads of fifty percent 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, with and without heads, 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 calculated with SAS statistical software on a VAX 11/780 computer. Mean body weights (as a mean of litter means for fetal data) were analyzed using the SAS General Linear Models (GLM) Procedure (SAS, 1985) with an analysis of variance (ANOVA) model for unbalanced data. Response variables, either body weight or the arc-sin transformations of proportional incidence data, were analyzed against the class variable, "treatment", in a one-way ANOVA 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 determined by means of an orthogonal trend test (Winer, 1971). In the case of proportional data the t-tests and trend analyses were performed on transformed variables. The litter was used as the basis for analysis of fetal variables.

RESULTS

EXPOSURE AND CHEMISTRY

Test material stability studies indicated that the materials and techniques used to generate MEK vapor for inhalation exposures did not affect its stability. The major volatile impurity observed in the unoccupied chamber samples of MEK atmospheres was 2-butanol, present at $\approx 0.5\%$ by weight. Since this compound was also present at $\approx 0.5\%$ by weight in the original test material it was not considered to represent a degradation product. However, since the amount of 2-butanol found was near the detection limit for that compound, the relative degree of uncertainty associated with the reported concentration is larger than it would have been for larger concentrations. 2-Butanol was not detected in the samples taken from the occupied chambers or from the distribution line during the first week of exposures. Methanol, ethanol, acetone, and isopropanol, potential contaminants or degradation products, were below detection limits in all samples collected from both unoccupied and occupied chambers. A very small amount of acetone, $< 0.1\%$, was detected in the distribution line during animal exposures. An unknown impurity of approximately 0.05% (area percent) was also observed in both the occupied and unoccupied chambers. The average purity of MEK in the unoccupied chambers and the distribution line was 99.4% during test generation and 99.9% in occupied chambers during the animal exposures.

The analyses of samples obtained from the generator reservoir were in good agreement with each other and with samples obtained from the chambers and distribution line. The samples taken from the evaporation flask at the end of the day during test generation indicated that the 2-butanol concentration was enriched by approximately a factor of two during generation. However, this degree of enrichment was not observed in chamber atmospheres.

Analyses for less volatile species was accomplished by collecting samples onto carbon adsorbent tubes, and did not indicate the presence of any species except MEK in the unoccupied 400- and 3000-ppm chambers. Minor peaks

were observed in the carbon tube samples taken from the distribution line during test generation, but these were all present at less than 0.1 area percent and were not observed during the animal exposures.

Analyses for MEK peroxide (MEKP) during test generation indicated no detectable quantities of this compound in the vapor distribution line, exposure chambers, or the bulk material. Measurable quantities were found in the evaporator flask after generation; however, they were very small ($\leq 0.1\%$). This small amount of MEKP could have been present as an impurity in the test material that became enriched during generation, or could have formed from reaction with trace amounts of oxygen in the generation system.

The test material concentration uniformity data for each chamber, with no animals present during prestart testing, and after animals were in place was acceptable in all chambers (Table 1). To provide easier interpretation of the uniformity measurement results, the concentration reading at each port is expressed as a percentage of the mean measurement at all ports measured. The possible variation of test chemical concentration measured from one sample port to another during the measurement procedure is termed the Total Port Variability (TPV) and consists of both spatial and temporal variations. Two factors contribute to the TPV. The first, the Between Port Variability (BPV), is the factor of interest as it represents the spatial variation of test chemical distribution within the chamber. The second factor, the Within Port Variability (WPV), represents the temporal fluctuation of the average chemical concentration within the chamber during the time the measurements were taken. This temporal factor includes variations in vapor generation as well as variation of the measurement instrument itself.

The WPV was determined from a minimum of three measurements taken at the on-line monitor port before, during and after all other ports were measured. The TPV was determined from measurements from, at the minimum, the front and back ports at each level on which animals were housed. The BPV was determined by applying the following equation:

$$BPV = \sqrt{(TPV)^2 - (WPV)^2}$$

Summaries (Table 2) of the MEK concentration data showed that the grand means for each chamber were between 100% and 101% of the target, with relative standard deviations of 2-3%, for all three exposure concentrations. More than 98% of all individual concentration measurements were within $\pm 10\%$ of the specified operating limits for the target levels. The maximum concentration observed in the control chamber, the holding chamber, and in the room were 0.08, 0.04 and 0.70 ppm MEK, respectively. Chamber air flow, temperature and relative humidity data for the mouse exposures were all within specified limits (Appendix B).

DEVELOPMENTAL TOXICOLOGY

The mean pregnancy rate of the plug-positive females was satisfactory, 81.8%. A total of 5 mated mice were removed from the study; one because of premature delivery and four others due to small litter size (≤ 2 implants)¹. There were no deaths and no overt signs of toxicity evident in the plug-positive or virgin mice.

Mean body weights and weight gains for maternal and virgin female mice were not affected by exposure to MEK at any time during the study when compared to the 0-ppm group (Figure 4; Tables 3 and 4). Increases in mean percent liver to body weight ratios (%LBWR) of pregnant mice (organ weights were not obtained for virgin mice) were significantly correlated with increasing MEK exposure concentration (Table 5), and the %LBWR for the 3000-ppm group was significantly greater than for the 0-ppm group. The percent kidney to body weight ratio (%KBWR) for the 3000-ppm group was also significantly greater than for the 0-ppm group. However, since the %KBWR's were nearly the same for the 400-ppm group and the 3000-ppm group, and lower for the 1000-ppm group, these changes were probably not biologically significant.

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¹ The small litter size was not treatment related; 1 of the 4 litters was in the 0-ppm group, 2 litters were in the 400-ppm group, and 1 was in the 3000-ppm group.

Maternal uterine weights and the extragestational weight gains were not affected when compared to the 0-ppm group (Table 4). Exposure of pregnant mice to MEK vapors on 6-15 dg did not affect the number of implantations, or the percent of live fetuses or intrauterine deaths per litter as compared to those for the 0-ppm group (Table 6).

Fetal body weight reductions for both male and female fetuses were significantly correlated with increasing exposure concentrations; however, the correlation was due to an abrupt decrease in fetal body weight at the 3000-ppm exposure concentration and not to a true exposure-related trend (Table 7). Mean fetal body weights were significantly reduced for males, but not for females, in the 3000-ppm group, although both groups were lower than the 0-ppm group by the same relative amount, ~4%.

The incidence of fetal malformations was not significantly increased by gestational exposure of mice to MEK vapors, nor was the percent of live fetuses with malformations per litter¹ affected (Tables 8 and 9). However, there were four malformations observed in exposed groups that were not present in either the 0-ppm group or in the contemporary control data² (Table 8); These malformations consisted of: 1) three fetuses with cleft palate—two in the 400-ppm group and one in the 1000-ppm group; 2) two with fused ribs—one in the 1000-ppm groups and one in the 3000-ppm group; 3) one with missing vertebrae—in the 1000-ppm group; and 4) five with syndactyly—all from a single litter in the 3000-ppm group. Although there was not a significant trend in the increase of malformations with respect to increasing exposure concentration, the 3000-ppm group did have a higher combined incidence of malformations than did either of the two lower exposure groups.

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¹ The mean percent incidence per litter was calculated based on the number of live fetuses examined for a given malformation or variation per litter, i.e. the incidence of visceral defects was based on the number of fetuses in each litter that received a visceral exam.

² Contemporary control data were obtained from Swiss (CD-1) mice in the 0-ppm exposure groups of recently completed inhalation teratology studies. These data are presented in Appendix C.

Gestational exposure to MEK resulted in a significant, treatment-correlated increase in the incidence of misaligned sternebrae, a variation, with respect to the 0-ppm group (Tables 9 and 10). There was also an increase, not significant, in the mean percent per litter of total variations and reduced ossifications which was mostly due to the increase in the incidence of misaligned sternebrae. Another sternebral variation, ossification sites between sternebrae, which had not been previously observed in the contemporary control data, was found in all four groups in this study. Other sites examined for reduced ossifications included the pelvis, phalanges and vertebrae; however, there were no treatment-related reductions in the ossification of these areas.

DISCUSSION

Exposure of pregnant Swiss (CD-1) mice to 0, 400, 1000, or 3000 ppm MEK vapors did not result in apparent maternal toxicity, although an exposure-correlated increase in percent liver to body weight ratios was present at higher exposure levels, and became significant at 3000 ppm MEK. Developmental toxicity, present as a decrease in fetal body weight, was evident at the 3000-ppm exposure level and was further substantiated by an exposure-correlated increase in the incidence of misaligned sternebrae, a variation.

The ability of MEK to induce the P₄₅₀-monooxygenase system as reported for rats (Toftgard, Nilsen and Gustafsson 1981) may also be true for mice if one assumes that the treatment-correlated increase in the maternal liver to body weight ratios was due to P₄₅₀ induction. This increase became significantly different from the 0-ppm group at 3000-ppm MEK. However, without histopathology data it is not possible to specifically identify the increase in maternal liver to body weight ratios as a sign of toxicity.

The incidence of fetal malformations in the MEK-exposed groups, although not statistically significant, may be of some concern since several malformations were present which had not been observed in unexposed animals. The percent 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 the Swiss (CD-1) mouse are reminiscent of those reported previously in the Sprague-Dawley rat (Schwetz, Leong and Gehring 1974; Deacon et al. 1981) where major malformations were found in only the 3000-ppm group. The results of this study also indicate that the Swiss (CD-1) mouse may be somewhat less sensitive to the toxic effects of MEK than the Sprague-Dawley rat since a reduction in the fetal weight of exposed mice was observed only at the 3000-ppm level. Fetal rat weights were reported to have been reduced at the 1000-ppm level (Schwetz, Leong and Gehring 1974). Apparently MEK begins to induce developmental toxicity in rodents at about the same level that maternal effects are observed—a weight reduction in maternal body weight in rats (Deacon et al. 1981) and a significant increase in maternal liver to body weight ratios in mice [not measured in rats].

Developmental toxicity was observed in Swiss (CD-1) mice at 3000 ppm MEK along with mild maternal effects. Neither maternal nor developmental toxicity was observed at an exposure concentration of 1000 ppm or below.

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FIGURE 1. Proposed Metabolic Pathway of Methyl Ethyl Ketone in Mammals.

FIGURE 2. Methyl Ethyl Ketone Generation and Delivery System

MEK IRT: 400 ppm Chamber

MEK IRT: 1000 ppm Chamber

MEK IRT: 3000 ppm Chamber

FIGURE 3. Buildup and Decay of Methyl Ethyl Ketone Concentrations in 400, 1000, and 3000 ppm Exposure Chambers (With and Without) Animals Present

FIGURE 4. Cumulative Weight Gain for Pregnant Mice (6-18 Days of Gestation) Exposed to Methyl Ethyl Ketone Vapors During Gestation

TABLE 1. Methyl Ethyl Ketone Teratology Study: Summary of Chamber Uniformity Data Obtained Before and During Exposure of Mice

Chamber	TPV (%RSD)		WPV (%RSD)		BPV (%RSD)	
	Pre	Post	Pre	Post	Pre	Post
400 ppm	2.1	0.5	2.2	0.1	*	0.5
1000 ppm	0.4	0.6	1.2	0.5	*	0.3
3000 ppm	1.3	0.5	1.8	0.3	*	0.5

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* Indistinguishable from WPV.

Chamber Uniformity Limits

WPV $\leq$ 5% RSD

BPV $\leq$ 5% RSD

TPV $\leq$ 7% RSD

TPV = Total Port Variability

WPT = Within Port Variability

BPV = Between Port Variability

TABLE 2. Methyl Ethyl Ketone Mouse Teratology Study: Average Daily Exposure Chamber Concentrations for Mouse Exposures.

0 ppm Methyl Ethyl Ketone Vapor						
Exposure Day	Mean $\pm$ SD (ppm)	Max (ppm)	Min (ppm)	Number Samples	Number in Range (b)	Percent in Range
1	<MDL (a)	0.08	<MDL	19	19	100
2	<MDL	0.07	<MDL	26	26	100
3	<MDL	<MDL	<MDL	19	19	100
4	<MDL	<MDL	<MDL	15	15	100
5	<MDL	<MDL	<MDL	11	11	100
6	<MDL	<MDL	<MDL	14	14	100
7	<MDL	<MDL	<MDL	15	15	100
8	<MDL	<MDL	<MDL	26	26	100
9	<MDL	<MDL	<MDL	26	26	100
10	<MDL	<MDL	<MDL	23	23	100
11	<MDL	<MDL	<MDL	25	25	100
12	<MDL	<MDL	<MDL	24	24	100
Summary	<MDL	0.08	<MDL	243	243	100

(a) Minimum Detectable Limit (MDL)=0.04 ppm Methyl Ethyl Ketone.

(b) Range=0-5 ppm Methyl Ethyl Ketone.

400 ppm Methyl Ethyl Ketone Vapor						
Exposure Day	Mean $\pm$ SD (ppm)	Max (ppm)	Min (ppm)	Number Samples	Number in Range (a)	Percent in Range
1	399 $\pm$ 10	420	384	20	20	100
2	396 $\pm$ 12	408	369	22	22	100
3	400 $\pm$ 13	439	373	23	23	100
4	388 $\pm$ 11	399	352	17	16	94
5	399 $\pm$ 7	410	384	18	18	100
6	400 $\pm$ 7	413	390	12	12	100
7	393 $\pm$ 9	412	369	22	22	100
8	399 $\pm$ 4	409	392	21	21	100
9	400 $\pm$ 5	409	383	20	20	100
10	401 $\pm$ 8	413	384	19	19	100
11	399 $\pm$ 5	411	387	22	22	100
12	406 $\pm$ 5	420	398	21	21	100
Summary	398 $\pm$ 9	439	352	237	236	100

(a) Range = $\pm$ 10% target.

TABLE 2. (contd)

1000 ppm Methyl Ethyl Ketone Vapor						
Exposure Day	Mean $\pm$ SD (ppm)	Max (ppm)	Min (ppm)	Number Samples	Number in Range (a)	Percent in Range
1	1010 $\pm$ 27	1070	973	21	21	100
2	992 $\pm$ 28	1020	921	23	23	100
3	1010 $\pm$ 36	1100	894	23	22	96
4	1020 $\pm$ 30	1140	991	18	17	94
5	1020 $\pm$ 13	1050	994	19	19	100
6	1000 $\pm$ 18	1040	979	11	11	100
7	1010 $\pm$ 25	1050	965	21	21	100
8	1010 $\pm$ 10	1040	994	20	20	100
9	1000 $\pm$ 7	1020	994	19	19	100
10	1010 $\pm$ 15	1020	975	19	19	100
11	1040 $\pm$ 34	1130	1010	22	20	91
12	1040 $\pm$ 9	1060	1030	22	22	100
Summary	1010 $\pm$ 28	1140	894	238	234	98

(a) Range = $\pm$ 10% target.

3000 ppm Methyl Ethyl Ketone Vapor						
Exposure Day	Mean $\pm$ SD (ppm)	Max (ppm)	Min (ppm)	Number Samples	Number in Range (a)	Percent in Range
1	3020 $\pm$ 83	3190	2910	21	21	100
2	2960 $\pm$ 50	3020	2830	23	23	100
3	2990 $\pm$ 135	3260	2490	23	22	96
4	3100 $\pm$ 24	3130	3030	18	18	100
5	3070 $\pm$ 39	3150	3010	18	18	100
6	3010 $\pm$ 46	3120	2920	11	11	100
7	2980 $\pm$ 84	3160	2900	22	22	100
8	3000 $\pm$ 21	3040	2970	21	21	100
9	3020 $\pm$ 46	3130	2970	20	20	100
10	3010 $\pm$ 40	3060	2910	20	20	100
11	3000 $\pm$ 28	3050	2930	22	22	100
12	3100 $\pm$ 92	3340	3030	22	20	91
Summary	3020 $\pm$ 79	3340	2490	241	238	99

(a) Range = $\pm$ 10% target.

TABLE 3. Methyl Ethyl Ketone Mouse Teratology Study: Mean Body Weights for Virgin Mice (g $\pm$ SD).

Exposure Concentration	N	Exposure Day 1	Exposure Day 5	Exposure Day 10	Sacrifice
0 ppm	10	26.3 $\pm$ 1.2	26.7 $\pm$ 1.3	27.5 $\pm$ 1.0	25.9 $\pm$ 0.9
400 ppm	10	26.4 $\pm$ 1.1	26.9 $\pm$ 1.0	27.2 $\pm$ 1.2	25.9 $\pm$ 1.3
1000 ppm	10	26.3 $\pm$ 1.1	27.2 $\pm$ 1.5	28.1 $\pm$ 1.5	28.2 $\pm$ 1.8
3000 ppm	10	26.3 $\pm$ 0.9	26.6 $\pm$ 1.0	27.4 $\pm$ 1.0	27.0 $\pm$ 1.4

TABLE 4. Methyl Ethyl Ketone Mouse Teratology Study: Mean Body, Uterine, and Extra-gestational Weights of Pregnant Mice (g $\pm$ SD).

Exposure Concentration	N	DG 0	DG 6	DG 9	DG 12	DG 15	DG 18	Uterine	Extra-gestational Weight gain
0 ppm	26	26.4 $\pm$ 1.6	28.8 $\pm$ 1.7	31.5 $\pm$ 1.8	36.8 $\pm$ 2.5	44.7 $\pm$ 3.4	53.3 $\pm$ 5.1	20.1 $\pm$ 3.6	6.9 $\pm$ 1.4
400 ppm	23	26.3 $\pm$ 1.8	28.4 $\pm$ 1.9	31.2 $\pm$ 2.1	36.4 $\pm$ 2.7	44.2 $\pm$ 3.6	52.2 $\pm$ 5.1	19.3 $\pm$ 3.7	6.5 $\pm$ 1.6
1000 ppm	26	26.7 $\pm$ 1.6	28.8 $\pm$ 1.8	31.4 $\pm$ 2.1	36.8 $\pm$ 2.4	44.0 $\pm$ 3.3	51.9 $\pm$ 4.1	18.8 $\pm$ 2.7	6.5 $\pm$ 1.9
3000 ppm	28	26.3 $\pm$ 1.4	28.7 $\pm$ 1.9	31.8 $\pm$ 2.0	37.2 $\pm$ 2.7	45.0 $\pm$ 3.8	53.0 $\pm$ 4.9	19.1 $\pm$ 2.7	7.6 $\pm$ 2.0

TABLE 5. Methyl Ethyl Ketone Mouse Teratology Study: Mean Organ Weights of Pregnant Mice (Mean $\pm$ SD).

Exposure Concentration	N	Liver (a) (grams)	Percent LBWR (a,b)	Kidney (grams)	Percent KBWR (a,c)
0 ppm	26	2.8 $\pm$ 0.4	5.28 $\pm$ 0.61	0.43 $\pm$ 0.03	0.82 $\pm$ 0.07
400 ppm	23	2.7 $\pm$ 0.3	5.16 $\pm$ 0.62	0.45 $\pm$ 0.04	0.87 $\pm$ 0.11
1000 ppm	26	2.8 $\pm$ 0.3	5.41 $\pm$ 0.36	0.44 $\pm$ 0.05(e)	0.85 $\pm$ 0.05
3000 ppm	28	3.0 $\pm$ 0.3	5.67 $\pm$ 0.41(d)	0.46 $\pm$ 0.05	0.87 $\pm$ 0.07(d)

(a) Significantly correlated with exposure concentration, $p < 0.05$.

(b) Percent LBWR=Percent Liver to Body Weight Ratio (body weight at sacrifice).

(c) Percent KBWR=Percent Kidney to Body Weight Ratio (body weight at sacrifice).

(d) Significantly different than control, $p < 0.05$.

(e) One kidney inadvertently not weighed, therefore N = 25.

TABLE 6. Methyl Ethyl Ketone Mouse Teratology Study: Reproductive Measures for Mice (Mean $\pm$ SD).

	Methyl Ethyl Ketone Chamber Concentration (ppm)			
	0	400	1000	3000
Plug-positive Females	33	33	33	33
Number Pregnant	27	26	26	29
Pregnant (%)	81.8	78.8	78.8	87.9
Pregnancies Examined	26 (a)	23 (b)	26	28 (a)
Implantations/Dam	12.4 $\pm$ 2.3	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
Early	0.3 $\pm$ 0.7	0.5 $\pm$ 0.8	0.7 $\pm$ 1.0	0.3 $\pm$ 0.5
Late	0.2 $\pm$ 0.4	0.4 $\pm$ 0.7	0.4 $\pm$ 0.8	0.4 $\pm$ 0.7
Dead Fetuses/Litter	0	0.0 $\pm$ 0.2	0	0.1 $\pm$ 0.3
Litters with Resorptions	9	12	16	16
PERCENTAGE OF:				
Live Fetuses/Litter	95.8 $\pm$ 7.3	92.4 $\pm$ 9.1	91.5 $\pm$ 8.2	93.6 $\pm$ 6.8
Resorptions/Litter	4.2 $\pm$ 7.3	7.2 $\pm$ 8.9	8.5 $\pm$ 8.2	5.8 $\pm$ 6.0
Early	3.0 $\pm$ 6.7	4.0 $\pm$ 7.0	5.8 $\pm$ 8.2	2.4 $\pm$ 3.6
Late	1.2 $\pm$ 2.9	3.3 $\pm$ 5.8	2.7 $\pm$ 4.9	3.3 $\pm$ 5.5
Dead Fetuses/Litter	0	0.3 $\pm$ 1.6	0	0.7 $\pm$ 2.5
Litters with Resorptions	34.6	52.2	61.5	57.1

(a) One litter <2 implants

(b) Two litters <2 implants and one had premature delivery.

TABLE 7. Methyl Ethyl Ketone Mouse Teratology Study: Average Fetal Mouse Weights (Mean of Litter Means; g $\pm$ SD) and Percent Male Fetuses.

	Methyl Ethyl Ketone Chamber Concentration (ppm)			
	0	400	1000	3000
Litters Examined	26	23	26	28
Live Fetuses Examined	310	260	291	323
Fetal Weight (a)	1.35 $\pm$ 0.07	1.35 $\pm$ 0.06	1.33 $\pm$ 0.07	1.29 $\pm$ 0.08 (b)
Male (a)	1.38 $\pm$ 0.07	1.38 $\pm$ 0.06	1.34 $\pm$ 0.10	1.31 $\pm$ 0.08 (b)
Female (a)	1.32 $\pm$ 0.08	1.33 $\pm$ 0.08	1.31 $\pm$ 0.06	1.27 $\pm$ 0.08
Percent Male Fetuses	50 $\pm$ 12	47 $\pm$ 13	43 $\pm$ 15	51 $\pm$ 18

(a) Significantly correlated with exposure concentration, $p < 0.05$.

(b) Significantly different than control, $p < 0.05$.

TABLE 8. Methyl Ethyl Ketone Mouse Teratology Study: Malformations Observed in Live Mouse Fetuses.

		Fetuses (a)				Litters (a)			
Methyl Ethyl Ketone (ppm)		0	400	1000	3000	0	400	1000	3000
Total Examined (b)		310	260	291	323	26	23	26	28
Heads Examined (c)		153	131	147	162	26	23	26	28
Skulls Examined (d)		157	129	144	161	26	23	26	28
Viscera Examined (e)		157	130	144	163	26	23	26	28
Malformations:									
Cleft Palate	NO. (%)		2 (0.8)	1 (0.3)			2 (8.7)	1 (3.8)	
Fused Ribs	NO. (%)			1 (0.3)	1 (0.3)			1 (3.8)	1 (3.6)
Limb Flexure	NO. (%)	1 (0.3)	1 (0.4)		3 (0.9)	1 (3.8)	1 (4.3)		3 (10.7)
Missing Vertebrae	NO. (%)			1 (0.3)				1 (3.8)	
Syndactyly	NO. (%)				5 (1.5)				1 (3.6)
Total Malformations	NO.	1	3	3	9	--	--	--	--
Total Fetuses (Litters) with Malformations	NO. (%)	1 (0.3)	3 (1.2)	3 (1.0)	9 (2.8)	1 (3.8)	3 (13.0)	3 (11.5)	5 (17.9)

- (a) A single fetus or litter may be represented more than once in this table.
(b) All fetuses examined for external and skeletal defects. One-half had heads removed prior to skeletal staining.
(c) Heads fixed in Bouin's solution for soft-tissue craniofacial evaluations.
(d) Heads remaining on the fetuses for skeletal examination; see (b).
(e) Viscerals performed on approx. 50% of live fetuses and all fetuses with external defects.

TABLE 9. Methyl Ethyl Ketone Mouse Teratology Study: Mean Percent of Live Mouse Fetuses Affected per Litter (Mean $\pm$ SD).

	Methyl Ethyl Ketone Concentration (ppm)			
	0	400	1000	3000
Number Litters	26	23	26	28
Live Fetuses/Litter	11.9 $\pm$ 2.3	11.3 $\pm$ 2.5	11.2 $\pm$ 1.6	11.5 $\pm$ 1.9
Malformations:				
Cleft Palate	0	0.7 $\pm$ 2.2	0.3 $\pm$ 1.6	0
Fused Ribs	0	0	0.3 $\pm$ 1.8	0.4 $\pm$ 1.9
Limb Flexure	0.3 $\pm$ 1.4	0.4 $\pm$ 1.9	0	0.8 $\pm$ 2.5
Missing Vertebrae	0	0	0.3 $\pm$ 1.8	0
Syndactyly	0	0	0	1.6 $\pm$ 8.6
Total Malformations	0.3 $\pm$ 1.4	1.1 $\pm$ 2.8	1.0 $\pm$ 2.9	2.8 $\pm$ 8.9
Variations:				
Misaligned Sternebrae (a)	9.7 $\pm$ 10.4	9.8 $\pm$ 11.2	17.4 $\pm$ 16.7	17.5 $\pm$ 14.9
Fused Sternebra	0	0.3 $\pm$ 1.4	0.4 $\pm$ 2.0	0.3 $\pm$ 1.3
Kinked Tail	0.5 $\pm$ 2.8	0	0	0
Ossification Site Between Sternebrae	4.8 $\pm$ 12.7	3.1 $\pm$ 8.8	1.8 $\pm$ 6.2	2.0 $\pm$ 5.5
Supernumerary Rib	17.9 $\pm$ 20.1	18.5 $\pm$ 22.3	20.2 $\pm$ 27.2	19.9 $\pm$ 20.4
Reduced Ossification				
Sternebrae	2.0 $\pm$ 4.5	2.3 $\pm$ 5.6	5.9 $\pm$ 8.2	4.6 $\pm$ 11.6
Skull	1.8 $\pm$ 7.0	2.8 $\pm$ 10.7	1.7 $\pm$ 6.2	3.3 $\pm$ 12.8
Total Variations and Reduced Ossifications	30.9 $\pm$ 22.0	30.6 $\pm$ 22.5	36.1 $\pm$ 26.5	38.2 $\pm$ 22.3

(a) Significantly correlated with exposure concentration, $p < 0.05$.

TABLE 10. Methyl Ethyl Ketone Mouse Teratology Study: Variations Observed in Live Mouse Fetuses.

		Fetuses (a)				Litters (a)			
Methyl Ethyl Ketone (ppm)		0	400	1000	3000	0	400	1000	3000
Total Examined (b)		310	260	291	323	26	23	26	28
Heads Examined (c)		153	131	147	162	26	23	26	28
Skulls Examined (d)		157	129	144	161	26	23	26	28
Viscera Examined (e)		157	130	144	163	26	23	26	28
Variations:									
Misaligned Sternebrae	NO. (%)	31 (10.0)	27 (10.4)	49 (16.8)	58 (18.0)	18 (69.2)	14 (60.9)	18 (69.2)	21 (75.0)
Fused Sternebra	NO. (%)		1 (0.4)	1 (0.3)	1 (0.3)		1 (4.3)	1 (3.8)	1 (3.6)
Kinked Tail	NO. (%)	1 (0.3)				1 (3.8)			
Ossification Site Between Sternebrae	NO. (%)	14 (4.5)	7 (2.7)	5 (1.7)	6 (1.9)	8 (30.8)	4 (17.4)	3 (11.5)	4 (14.3)
Supernumerary Rib	NO. (%)	56 (18.1)	44 (16.9)	58 (19.9)	65 (20.1)	17 (65.4)	13 (56.5)	15 (57.7)	22 (78.6)
Reduced Ossifications:									
Sternebrae	NO. (%)	6 (1.9)	6 (2.3)	16 (5.5)	14 (4.3)	5 (19.2)	4 (17.4)	11 (42.3)	7 (25.0)
Skull	NO. (%)	3 (1.9)	3 (2.3)	2 (1.4)	5 (3.1)	2 (7.7)	2 (8.7)	2 (7.7)	2 (7.1)
Total Variations and Reduced Ossifications	NO.	111	88	131	149	---	---	---	---
Total Fetuses (Litters) with Variations or Red. Ossif.	NO. (%)	95 (30.6)	76 (29.2)	103 (35.4)	123 (38.1)	25 (96.2)	20 (87.0)	24 (92.3)	27 (96.4)

(a) A single fetus or litter may be represented more than once in this table.

(b) All fetuses examined for external and skeletal defects. One-half had heads removed prior to skeletal staining.

(c) Heads fixed in Bouin's solution for soft-tissue craniofacial evaluations.

(d) Heads remaining on the fetuses for skeletal examination; see (b).

(e) Viscerals performed on approx. 50% of live fetuses and all fetuses with external defects.

APPENDIX A

**ANALYTICAL CHEMISTRY NARRATIVE AND DATA FOR
METHYL ETHYL KETONE**

Test Chemical Analysis, Storage and Disposition

Test Material Receipt, Storage and Usage

Receipt

Methyl ethyl ketone (MEK), manufactured by J.T. Baker Chemical Co., was received from Research Triangle Institute (RTI), Research Triangle Park, North Carolina. Five gallons (BNW 52713-12, RTI Lot No. 5765-154-01, Manufacturer's Lot No. N/A) of test material were received 5/13/88. Test material was packaged in one-gallon glass bottles. An additional shipment of 50 gallons of MEK packaged in a 55 gallon metal drum (BNW 52713-28, RTI Lot No. 5598-136-01, Manufacturer's Lot No. N/A) was received 5/19/88.

Storage Conditions

The bulk chemical was stored in its original shipping containers at room temperature in the chemical storage building adjacent to the LSL-II laboratory.

Usage

An average of 4.3 kg MEK was consumed per exposure day. A total of ~52 kg were required for the IRT study exposures.

Transfer Procedures

Bulk chemical was transferred to the generator reservoir under a nitrogen blanket to avoid the introduction of air. The generator reservoir was filled every two days.

Waste Disposal

Excess used test material was volatilized in a chemical hood by sparging with a nitrogen stream.

Surplus Disposal

Residual test material was returned to Research Triangle Institute at the direction of the Inhalation Reproductive Toxicology Program after completion of the MEK studies.

Chemical Analysis

Analysis at Research Triangle Institute

Chemical characterization of the MEK test material was presented in the February 1, 1988 RTI report. Bulk chemical (RTI assigned Lot No. 5598-136-03, Manufacturer's Lot No. A25623) was identified as MEK. Cumulative analytical data indicated a purity greater than 99% as received.

The infrared, ultraviolet/visible, low resolution mass and nuclear magnetic resonance spectra were consistent with the structure of MEK and available literature references.

High resolution mass spectrometry gave an observed mass of 72.0574 for the molecular ion and an empirical formula of C_4H_8O . Gas chromatography on a DB1 fused silica column showed one major peak and four impurities (0.049, 0.060, 0.23 and 0.021% of the total area). Gas chromatography on a GS-Q fused silica column showed one major peak and three impurities (0.078, 0.057 and 0.22% of the total area). The water content as determined by Karl Fischer analysis was <0.3%.

Reanalysis at Battelle Pacific Northwest Laboratories

Identity of bulk chemical was confirmed during initial bulk analysis by infrared spectroscopy. Bulk purity analysis was performed by gas chromatography using a Porapak Q 80/100 glass column. No reference material was retained for relative purity determinations. Bulk test material BNW Lot No. 52713-28 was 100.0% pure by area percent on 6/14/88 and 99.90% pure by area percent on 8/16/88. Test material purity was acceptable for the study exposures.

BULK CHEMICAL REANALYSIS

COMPOUND:	METHYL ETHYL KETONE
CAS#:	78-93-3
LOT#:	BNW 52713-28-1
APPEARANCE:	Colorless Liquid
RECEIPT DATE:	5-16-88
ANALYSIS PERIOD:	Initial Purity
STORAGE TEMPERATURE:	65° - 72°F
SAMPLE ANALYSIS DATE:	6-14-88
ANALYSIS PROCEDURE:	ØB-AC-3A1J-ØØ
NOTEBOOK REFERENCE:	BNW 52713-63,64

IDENTITY: Infrared spectroscopy is performed using a 10 cm gas cell with silver chloride windows and scanning from 4000 cm^{-1} to 600 cm^{-1}

Instrument: Beckman Acculab 8 Infrared Spectrometer

RESULTS: The spectrum was similar to that found in "Hazardous Gases and Vapors: Infrared Spectra and Physical Constants", Beckman Instruments (1974).

ASSAY: Gas chromatography using a 4 ft x 2 mm glass column packed with Porapak Q 80/100 was used to determine the purity of a solution of 1%(v/v) methyl ethyl ketone in methanol by major peak comparison. Instrument: HP5890

RESULTS: Bulk % Purity

100.0	Average
100.0	100.0 SD=±0.00
100.0	

No impurities greater than 0.01% of the total test material sample area were observed. Methyl ethyl ketone eluted at ~5.3 minutes.

ASSAY: Gas chromatography using a 4 ft x 2 mm glass column packed with Porapak Q 80/100 was used to determine the purity of the neat bulk chemical by major peak comparison. Instrument: HP5890

RESULTS: Impurity Profile

A major peak of 99.9% area was observed at a retention time of ~4.9 minutes for a neat injection of sample BNW 52713-28-1. Impurity peaks eluted at ~1.0, ~2.8, ~4.4 and ~11.7 minutes with average peak area percentages of 0.01, 0.04, 0.04 and 0.04 respectively.

Conclusion: Infrared spectroscopy confirms the gross purity and identity of lot BNW# 52713-28-1. Gas chromatography shows Lot BNW 52713-28-1 to be 100.0% pure by area %. The impurity profile showed test samples contained four impurities greater than 0.01% but not exceeding 0.05%.

Signature of Technician David J. Anderson Date 7/5/88

Signature of Chemist A. J. [Signature] Date 7/5/88

Methyl Ethyl Ketone: Initial Purity

Methyl Ethyl Ketone: Initial Purity

A.5

A.6

RUN # 1 JUN 16, 1988 14:10:14
 323.7

STOP

Closing signal file A1069000.D.BNC

RUN 1 JUN 16, 1988 14:10:14

SAMPLE NAME: 52713-63-3 SAMPLE 1

Methanol Blank

SIGNAL FILE: A1069000.D.BNC

AREA: RT AREA TYPE WIDTH AREA
 .558 1.20221480 SPE .070 100.00000

TOTAL AREA=1.2022E+08
 MUL FACTOR=1.0000E+00

Methyl Ethyl Ketone: Purity.
 6-14-88
 Method: ϕ B-AC-3A1J- ϕ ϕ
 Solvent: Methanol
 Injection: 1 μ l
 GC: HP5890 BNW52642-145

Column: 4ft x 2mm glass, Porapak Q 80/100
 Notebook: BNW52713-63
 Technician: D.J. Anderson

A.7

RUN # 2 JUN 14, 1988 14:30:03
STRT

STOP

Closing signal file H:\069091EC.BNC

RUNS 2 JUN 14, 1988 14:30:03

SAMPLE NAME: 52712-63-1 SAMPLE 2
1% Methyl Ethyl Ketone (in Methanol)

SIGNAL FILE: H:\069091EC.BNC

RT	AREA	TYPE	WIDTH	AREA%
5.222	123792220	SEB	.069	97.85895
5.222	2580674	PE	.222	3.14105

TOTAL AREA=1.2647E+08
MUL FACTOR=1.0000E+00

Methyl Ethyl Ketone: Purity
6-14-88
Method: ØB-AC-3A1J-ØØ
Solvent: Methanol
Test MEK: BNW52713-28-1
GC: HP5890 BNW52642-145

Column: 4ft x 2mm glass, Porapak Q 80/100
Notebook: BNW52713-63
Technician: D.J. Anderson

Methyl Ethyl Ketone: Purity

6-14-88

Method: ϕ B-AC-391J- ϕ

Solvent: Methanol

Test MEK: BNW52713-28-1

GC: HP5890 BNW52642-145

Column: 4 ft x 2mm glass, Porapak Q 80/100

Notebook: BNW52713-63

Technician: D.J. Anderson

A.9

610400372.2
JUN 9 14.1988
16:53:03
ST-ET

Methyl Ethyl Ketone: Impurity Profile
6-14-88

Method: DB-AC - 3A1J- $\phi\phi$

1ul Neat Injection

Test MEK: Bmw52713-28-1

Reference MEK: Bmw52713-10-1

GC: HP5890 Bmw52642-145

Column: 4 ft x 2mm glass, Porapak Q 80/100

Notebook: Bmw52713-63

Technician: D.J. Anderson

END OF SIGNAL

Closing signal file 610400372.2.Bna

RUN# 9 JUN 14. 1988 16:53:03

SAMPLE NAME: 52713-28-2 SAMPLE 3
Neat Reference Methyl Ethyl Ketone

SIGNAL FILE: 610400372.2.Bna

RT	AREA	TYPE	WIDTH	AREA%
0.973	32869	FB	0.071	0.0028
2.828	127059	FB	0.179	0.0003
4.410	163461	PP	0.192	0.0017
4.876	2915160	FB	0.218	99.9738
11.722	129621	BB	0.282	0.00204

TOTAL AREA=2.9234E+08

MUL FACTOR=1.0000E+00

A.10

01195151 1981 JUN 14 11:54:10
 JUN 9 9 200:2510640011 use

END OF SIGNAL

Closing signal file: a1069d352.BNA

RUN 2 JUN 14, 1981 13:54:10

SAMPLE NAME: 52713-28-1
 Neat Test Methyl Ethyl Ketone

SIGNAL FILE: a1069d352.BNA

PT	AREA	TYPE	WIDTH	AREA%
.992	26047	PE	.075	.00662
2.274	148829	PE	.180	.02766
4.430	156594	PP	.191	.04015
4.893	526461760	PD	.218	99.88192
11.740	131010	SE	.277	.03328

TOTAL AREA=3.8932E+08
 MUL FACTOR=1.0000E+00

Methyl Ethyl Ketone: Impurity Profile

6-14-88

Method: ϕ B-AC-3A1J- $\phi\phi$

1ul Neat Injection

Test MEK: BNW52713-28-1

Reference MEK: BNW52713-10-1

GC: HP5890 BNW52642-145

Column: 4ft x 2mm glass, Porapak Q 80/100

Notebook: BNW52713-63

Technician: D.J. Anderson

BULK CHEMICAL REANALYSIS

COMPOUND	METHYL ETHYL KETONE
CAS#	78-93-3
LOT#	BNW52713-28 (RTI Lot No. 5598-136-01)
APPEARANCE	Colorless liquid
RECEIPT DATE	5-19-88
ANALYSIS PERIOD	3 months after initial purity
STORAGE TEMPERATURE	~25°C
SAMPLE ANALYSIS DATE	8-16-88
ANALYSIS PROCEDURE	ØB-AC-3A1J-ØØ
NOTEBOOK REFERENCE	BNW 52713-101

Assay: Gas chromatography using a 4 ft x 2 mm glass column packed with Porapak Q 80/100 was used to determine the purity of a solution of 1% (v/v) methyl ethyl ketone in methanol by major peak area %.

Instrument: HP5890

Results: % Purity

99.99	
99.78	Average = 99.90% SD= ±0.11
99.93	

No impurities greater than 0.20% of the total test material sample area were observed. Methyl ethyl ketone eluted at ~5.2 minutes.

Conclusion: Gas chromatography shows lot BNW 52713-28 (RTI Lot No. 5598-136-01) to be 99.90% pure by area %.

Signature of Technician: N.B. Allentree Date 8-30-88

Reviewed by: K.H. Stoney Date 8-30-88

Signature of Chemist: R. J. DeLong Date 9/1/88

* ATT 2-9 W
 +HH A106FICCOA.BMCBNC
 RUN # 621 AUG 16, 1988 11:48:25
 START

Methanol Blank

Closing signal file A106FICCOA.BNA

RUN# 621 AUG 16, 1988 11:48:25

SAMPLE NAME# 52713-101-3 SAMPLE# 1
 METHANOL BLANK

SIGNAL FILE# A106FICCOA.BNA

RT	AREA	TYPE	WIDTH	AREA*
.155	1100	PH	.016	.00010
.389	1083	PH	.053	.00010
.434	1.099E+09	SHB	.163	99.81501
2.792	31588	TSS	.208	.00287
5.377	10501	BP	.214	.00095
7.928	10622	VV	.393	.00097
11.942	576248	VV	1.873	.05235
15.947	1485853	I VH	3.234	.12773

TOTAL AREA=1.1087E+09
 MUL FACTOR=1.0000E+00

Purity analysis of Methyl Ethyl Ketone BNV 52713-100-1.
 (was BNV 52713-28-1) three months after initial purity analysis.
 Solvent: Methanol, "B & J" Lot # AR513
 GC: Hp5890, BNV 52642-149
 Column: 4ft x 2mm glass, Poropak Q 80/100
 Method: 08-AC-3A-1J-00
 Date: 8/16/88
 Sample to be analyzed will be prepared as a 1% (V/V) solution.
 Linearity: A 0.5% (V/V) solution will be used
 Technician: N.B. Valerine

7/10/88 N.B. Valerine 8:25 PM

+AM A106F1DCF5.BMC
 RUN # 622 AUG 16, 1988 13:00:36
 START

Closing signal file A106F1DCF5.BNA

RUN# 622 AUG 16, 1988 13:00:36

SAMPLE NAME: 52713-101-1 SAMPLE# 2
 1%V/V MEK

SIGNAL FILE: A106F1DCF5.BNA
 AREA#

RT	AREA	TYPE	WIDTH	AREA%
.154	1876	PS	.016	.00010
.432	1.086E+09	SHB	.162	96.56563
2.788	47340	TSS	.209	.00421
5.234	36836864	BB	.273	3.27568
6.552	3305	PV	.243	.00029
12.058	596367	PV	2.005	.05303
15.569	1138060	1 VM	2.849	.10120

TOTAL AREA=1.1246E+09
 MUL FACTOR=1.0000E+00

A.13

Purity analysis of Methyl Ethyl Ketone BNV 52713-100-1,
 (was BNV 52713-20-1) three months after initial purity analysis.
 Solvent: Methanol, B & J Lot # AR513
 GC: Hp5890, BNV 52842-149
 Column: 4m x 2mm glass, Porapak Q 80/100
 Method: DB-AC-3A13-00
 Date: 8/16/88
 Sample to be analyzed will be prepared as a 1% (V/V) solution.
 Linearity: A 0.5% (V/V) solution will be used
 Technician: N.B. Valentine

N.B. Valentine 8-25-88

***H AT06F1ECEE.BHC
 RUN # 625 AUG 16, 1988 14:08:46
 START

Closing signal file AT06F1ECEE.BHA

RUN# 625 AUG 16, 1988 14:08:46

SAMPLE NAME: 52713-101-2 SAMPLE# 3
 0.5%V/V MEK

SIGNAL FILE: AT06F1ECEE.BHA
 AREA%

RT	AREA	TYPE	WIDTH	AREA%
.153	1195	PH	.217	.00011
.303	3097	BH	.048	.00020
.438	1.099E+09	SHB	.162	98.38832
2.785	40347	TBB	.212	.00364
5.265	18549872	VB	.269	1.67379
11.985	62259	PV	.388	.00562
15.358	91989	I BH	1.090	.00838

TOTAL AREA=1.1003E+09
 MUL FACTOR=1.0000E+00

Purity analysis of Methyl Ethyl Ketone BNW 52713-100-1,
 (was BNW 52713-26-1) three months after initial purity analysis.
 Solvent: Methanol, "B & J" Lot # AR513
 GC: Hp5890, BNW 52642-149
 Column: 4ft x 2mm, 5%ss, Porapak Q 80/100
 Method: DB-AC-3A, 1.00
 Date: 8/16/88
 Sample to be analyzed will be prepared as a 1% (V/V) solution.
 Linearity: A 0.5% (V/V) solution will be used
 Technician: N.B. Valerline

7/8/88 M. Valerline 8-25-88

Test Chemical Stability Studies

Introduction

A report provided by Research Triangle Institute (Comprehensive Analysis Report, Methyl Ethyl Ketone, AO3, February 1, 1988) indicated the presence of four unidentified impurities in the test chemical (JT Baker, Lot/Batch #A25623), all exhibiting chromatographic peak areas of $\leq 0.22\%$ relative to the total peak area. In another MEK toxicity study (ECETOC, 1983) the impurities in commercially available test chemical were identified and quantified; methyl ethyl ketone 99.7%, isopropanol, and C4-C5 alkanes 0.046%, acetone 0.018%, secondary butyl ether 0.002%, probably C5 alcohols 0.022%, 2-butanol 0.205%, and C5 ketones 0.030% (Table 1).

Saturated ketones are not generally susceptible to attack by nucleophilic agents; therefore, degradation by hydrolysis, oxidation, or reduction is unlikely (ECETOC, 1983). However, MEK is susceptible to photochemical decomposition (Levy et al., 1969; Laity et al., 1973), probably via a combination of direct photolysis and free radical reactions. Under conditions approximating urban atmospheres, low concentrations (~ 10 ppm) of MEK exhibited a photochemical degradation half-life of approximately 5-10 hours (ECETOC, 1983; Dilling et al., 1976; Winer et al., 1976). However, in this study photochemical degradation of MEK was not expected because of the high concentrations and low residence time of the test chemical in the chambers.

The presence of volatile impurities or degradation products in the unoccupied and occupied 400- and 3000-ppm chambers, and in the distribution line was investigated. Chamber and distribution line samples were collected in water-filled bubblers. In addition, samples of liquid MEK from the generator reservoir and from the generator (flask) were collected and analyzed for MEK purity. All samples were analyzed for methanol, ethanol, acetone, isopropyl alcohol, MEK, and 2-butanol, as well for other unknown species. These analyses were accomplished using gas chromatography-headspace analysis.

The presence of less volatile impurities and degradation products in the unoccupied and occupied 400- and 3000-ppm chambers, and in the distribution line was also investigated by collection of samples onto charcoal adsorbent tubes. Materials trapped on the adsorbent tubes were desorbed in carbon disulfide and analyzed by gas chromatography.

Oxidation of MEK can result in the formation of methyl ethyl ketone peroxide (2-butanone peroxide) according to the following reaction.

Because the generation method employs vaporization of MEK at elevated temperature, formation of MEK peroxide (MEKP) is possible. However, nitrogen (rather than air) is employed for removal of vapors from the generator, and formation of MEKP in the absence of oxygen is unlikely. MEKP could also be present as a trace impurity in the bulk material which has been exposed to air. Although no data is available on the boiling point of MEKP, the relatively high molecular weight of MEKP (176.2 g/mol) should make this compound considerably less volatile than MEK. If MEK peroxide is present in the generator flask, its lower volatility could prevent significant vaporization of this compound, and consequently, MEKP could become enriched in the generator flask during generation.

Because of this potential for MEK peroxide formation or enrichment in the generator, measurements were performed to determine this compound in the unoccupied 400- and 3000-ppm chambers, the vapor distribution line, and in samples of MEK from the generator (flask). This was accomplished using a colorimetric method based on the oxidation of diphenylcarbazide by MEKP to form an intensely colored dye (NIOSH, 1987). MEK did not present a substantial interference in the measurement of MEKP. Commercial 50% MEKP in

dimethyl pthalate was standardized via titration with sodium thiosulfate, and dilutions of this solution were used to generate a standard curve for colorimetric quantitation of MEKP. Exposure chamber and distribution line samples were collected in bubblers filled with dimethyl pthalate. Aliquots from the bubblers and the generator flask were treated with diphenylcarbazine and the absorbance of the solutions was measured at 565 nanometers.

Experimental and Results

Determination of Volatile Impurities by Gas Chromatography-Headspace Analysis

Samples were collected from the unoccupied and occupied control chamber, 400 ppm chamber, 3000 ppm chamber, and the vapor distribution line using water-filled bubblers packed in ice (BNW 52713-67). Samples were collected using a calibrated critical orifice at approximately 1.0 liter per minute with two bubblers connected in series to assess sample breakthrough. Samples (~10 ml each) were collected from the generator reservoir at the beginning and end of the generation period, and from the generator (flask) at the end of generation (Table 2).

Gravimetric standards were prepared for methanol, ethanol, acetone, isopropanol and 2-butanol in deionized water (water purified using the Millipore Milli-Q® System). All standards contained MEK in approximately the same amounts expected in samples collected from the chambers and distribution line.

Samples from the generator flask and generator reservoir were diluted with water prior to analysis. Five milliliter aliquots of all standards and samples were pipetted into headspace analyzer vials, placed in the headspace analyzer, and analyzed using the conditions shown in Table 3. In this method, the vials are equilibrated at elevated temperature and volatile species are partitioned into the vial headspace. The vials are pressurized and the headspace gases are backflushed onto a sample loop and flushed onto the chromatographic column for GC analysis (Figure 1).

All results shown are corrected for breakthrough during sample collection (Tables 4-7). No methanol, ethanol, or isopropanol was observed in any of the samples. Acetone and 2-butanol were observed in quantifiable amounts in some of the samples, reported as weight percent. The "less than" values reported in Tables 4-7 for the different compounds were calculated as the quotient of the peak area for the most dilute standard to the peak area for MEK in the sample ($\times 100\%$). The most dilute standards contained approximately 5 mg of each of these components and approximately 600 mg of MEK. Note, however, that the peak areas for the low standard for each of these species were all easily quantifiable, and that no peak was observed for any of these compounds in any of the samples. Thus, the "less than" values reported for these compounds represents a very conservative estimate of detection limit.

Determination of Less Volatile Impurities by Collection on Carbon Adsorbent Tubes and Gas Chromatographic Analysis

Samples were collected from the unoccupied and occupied 400- and 3000-ppm chambers and the distribution line using ORBO-32 charcoal adsorbent traps. Samples were obtained by drawing known volumes of air through the tubes using a calibrated orifice at a flow-rate of approximately 0.25 liter per minute, two tubes per location (Table 8).

Each charcoal tube contained a front and rear charcoal bed, with the rear bed being employed to trap material that escaped collection on the front bed. The front and rear adsorbent beds from each tube were placed in separate vials, and 1.0 ml carbon disulfide was added. The vials were capped and sonicated for about 10 minutes prior to analysis. Gravimetric standards of approximately 700 and 1400 mg/ml MEK were prepared in the presence and absence of the charcoal adsorbent. Recovery of MEK from the adsorbent averaged $81.4 \pm 1.5\%$. A calibration curve for MEK was generated from the blanks and standards that contained the charcoal adsorbent. Samples and standards were analyzed using the chromatographic conditions shown in Table 9. Sample chromatograms are shown in Figure 2. The results of the analyses are summarized in Table 10.

As shown in Table 10 and Figure 2, only one peak was observed in the analyses of the carbon tube samples from the unoccupied 400 and 3000 ppm chambers, and that peak corresponded to MEK. No compounds other than MEK and solvent peaks were observed in either of these samples samples.

Three small peaks in addition to MEK were observed in one of the distribution line samples during test generation. These occurred at retention times of 1.4, 1.5, and 5.7 minutes. The total area for all three of these peaks was only 0.12 area percent. Only one of these three peaks was present in the second distribution line sample collected (retention time 1.5 minutes, 0.04 area %). Tube samples collected during the first week of animal exposures contained only MEK with no impurities detected.

Colorimetric Determination of MEK Peroxide

The method used to quantify MEK peroxide was adapted from a NIOSH (1987) colorimetric method. Sodium thiosulfate (0.1 N) was standardized using a common volumetric titration. Iodate is reacted with a known amount of iodide in acidic solution to form molecular iodine, and the molecular iodine is titrated with thiosulfate using a starch indicator. Sodium thiosulfate standardized in this fashion was used to standardize a solution of MEKP using a similar titration. A known amount of iodide is reacted with MEKP in glacial acetic acid and isopropanol solution to quantitatively form molecular iodine. This solution is titrated with sodium thiosulfate until the yellow iodine color disappears.

Samples were collected from the unoccupied 400- and 3000-ppm chambers and the vapor distribution line. Samples were collected for 1 h using a calibrated critical orifice at a flow rate of approximately 1 liter per minute and bubblers filled with dimethyl phthalate. All glassware used in the collection and preparation of MEK samples was silanized to eliminate contamination from metal ions which cause catalytic decomposition of MEKP. A 1.0 ml sample from the generator flask (collected at the end of the generation day) was diluted to 15 ml with dimethyl phthalate and treated in the same manner as the bubbler samples. To evaluate any interference from MEK, a 1.0 ml sample of bulk MEK from the generator reservoir at the

beginning of the day was analyzed in the same manner as the sample from the generator reservoir.

Serial dilutions of the standardized MEKP solution in dimethyl phthalate were treated with the color forming reagent (0.25% diphenyl carbazide) and the absorbances measured at 565 nanometers using a Cary 219 uv-visible spectrophotometer. Absorbances were measured against a blank containing all reagents except MEKP. The calibration curve generated in this fashion covered the range from 34-340 ug of MEKP (Figure 3). The detection limit specified in the NIOSH procedure for MEKP determination is approximately 25 micrograms MEKP.

MEK peroxide was below the detection limit in all samples collected from the exposure chambers and the vapor distribution line (Table 11). The "less than" amounts shown in Table 11 represent the ratio of the detection limit for MEKP (in micrograms) to the micrograms of MEK collected ($\times 100\%$). Similarly, MEKP was below the detection limit in the sample of bulk MEK taken from the generator flask at the beginning of generation. However, MEKP was observed in measurable quantities in the sample from the generator flask collected at the end of generation, and the amount in units of weight percent is 0.009 (See Table 11).

Discussion

The major volatile impurity observed in the unoccupied chamber samples was found to be 2-butanol at approximately 0.5% by weight. This compound was present at about 0.5% by weight in the original test material, and thus, is not considered to represent a degradation product. Note, however, that this amount of 2-butanol is only slightly above the detection limit for that compound, and a considerable degree of uncertainty is associated with the reported concentration. Butanol was not detected in the samples taken from the occupied chambers or the distribution line during the first week of exposures. Methanol, ethanol, acetone, and isopropanol were below the detection limit in all samples collected from both the unoccupied and occupied chambers. A very small amount of acetone was detected in the distribution line sample during animal exposures, although the amount was

less than 0.1%. An unknown impurity of approximately 0.05% (area percent) was also observed in both the occupied and unoccupied chambers. The average purity of MEK in the unoccupied chambers and the distribution line was 99.4 % during test generation and 99.9% during the animal exposures.

The analysis of samples from the generator reservoir were in good agreement with each other and with samples obtained from the chambers and distribution line. The sample taken from the generator (flask) at the end of the day during test generation indicated that the 2-butanol concentration was enriched by approximately a factor of two during generation. However, this degree of enrichment was not observed during animal exposures. The results of this study indicated no sample degradation products occurred at or above the 0.1% concentration level.

Analyses for less volatile species with sample collection onto carbon adsorbent tubes did not indicate the presence of any species except MEK in the unoccupied 400 and 3000 ppm chambers. Minor peaks were observed in the carbon tube samples taken from the distribution line during test generation, but these were all present at less than 0.1 area percent, and were not observed during the animal exposures.

Analyses for MEK peroxide during test generation indicated no detectable quantities of this compound in the vapor distribution line, exposure chambers, or the bulk material. Measurable quantities were found in the generator flask after generation; however, they were very small ($\leq 0.1\%$). This small amount of MEKP could have been present as an impurity in the test material that became enriched during generation, or could have formed from trace amounts of oxygen in the generation system.

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Table 1. Typical Composition of Commercial Methyl Ethyl Ketone (ECETOC, 1983)

Compound	Weight %
methyl ethyl ketone	99.7
low boiling substances (isopropanol, C4-C5 alkanes)	0.046
acetone	0.018
secondary butyl ether	0.002
intermediate boiling unknowns (probably C5 alcohols)	0.022
secondary butyl alcohol (2-butanol)	0.205
higher boiling unknowns (C5 ketones)	0.030

Table 2. Summary of Samples Collected from the Unoccupied Chambers, Distribution Line, Generator Reservoir and Generator (Samples Collected in Water Filled Bubblers for Gas Chromatography - Headspace Analysis)

Sample Location	Flow Rate Liters/Min.	Total Volume Liters	Chamber Concentration (from monitor)	Micrograms MEK Collected

Phase 1 (Prestart Test Generation):

Unoccupied Chambers:

Control Chamber	0.907	19	0.8 ppm ^b	b
400 ppm Chamber	0.907	19	442 ppm	24718
3000 ppm Chamber	0.907	2.72	3038 ppm	24330
Distribution Line	0.907	0.23	80,000 ppm ^a	54156

Generator Reservoir:

10 ml liquid MEK at 0925 hours

10 ml liquid MEK at 1500 hours

Generator (flask):

10 ml liquid MEK at 1500 hours

Phase 2 (First Week of Exposures):

Occupied Chambers:

Control Chamber	0.97	21	0.0 ppm	0
400 ppm Chamber	0.97	21	384 ppm	23019
3000 ppm Chamber	0.97	3.0	2951 ppm	25272
Distribution Line	0.97	0.25	80,000 ppm ^a	57091

Generator Reservoir:

10 ml liquid MEK at 1600 hours

Generator (flask):

10 ml liquid MEK at 1600 hours

a. Amount shown is calculated from chemical usage and sample volume.

b. This amount of MEK probably represents memory effects in the sampling for the on-line gas chromatograph.

The amount of MEK collected in water bubblers from the control chamber did not differ significantly from the amount of MEK observed in the water blank (see Figure 1). Thus, the concentration of MEK in the control chamber is effectively zero.

Table 3. Gas Chromatography-Headspace Analysis Method for Determining Volatile Species

Conditions	Description
Gas Chromatograph:	Hewlett-Packard 5890
Column:	10' x 1/8" nickel with 1% SP-1000 1500 on 60/80 mesh Carbopack B
Carrier:	He at total flow of 24 cc/min (8 cc/min provided by the gc and 16 cc/min provided by the headspace analyzer)
Detector:	FID
Detector Temperature:	275°C
Injector Temperature:	240°C
Initial Temperature:	40°C
Initial Time:	10.0 min
Temperature Ramp:	10°C/min
Final Temperature:	200°C
Hold Time:	10.0 min
Injection Volume:	1 ml
Headspace Analyzer:	Hewlett-Packard 19395A
Bath Equilibration Time:	120 minutes
Bath Temperature:	90°C
Valve/Loop Temperature:	95°C
Carrier Flow:	16 cc/min He
Aux. Pressure	1.7 bar
Servo Air Pressure	3.6 Bar
Time Table:	0:01 min, probe down 0:03 min, pressure on 0:23 min, pressure off 0:33 min, vent through loop on 0:38 min, vent through loop off 0:40 min, inject on 1:40 min, inject off 1:42 min, probe up

Table 4. Results of GC-Headspace Analysis of Samples from the 400 ppm Unoccupied and Occupied Chamber

Retention Time (Minutes)	Identification	% Breakthrough	Relative Amount (%)*
<u>Phase 1 (Prestart Test Generation):</u>			
<u>Unoccupied 400 ppm Chamber:</u>			
4.1	Methanol	ND	<0.09
13.2	Ethanol	ND	<0.1
15.6	Acetone	ND	<0.3
17.2	2-propanol	ND	<0.2
20.0	unknown	0	0.05
21.3	MEK	38.5	99.4
22.0	2-butanol	0	0.53*
<u>Phase 2 (First Week of Exposures):</u>			
<u>Occupied 400 ppm Chamber:</u>			
4.7	Methanol	ND	<0.3
13.9	Ethanol	ND	<0.4
16.1	Acetone	ND	<0.9
17.7	2-propanol	ND	<0.6
20.4	unknown	0	0.06
21.7	MEK	38.5	99.9
22.5	2-butanol	0	<1.1

* All values expressed as area % unless indicated by an asterisk. Values accompanied by an asterisk are in weight %. See text for description of "less than" values.

Table 5. Results of GC-Headspace Analysis of Samples from the 3000 ppm Unoccupied and Occupied Chamber

Retention Time (Minutes)	Identification	% Breakthrough	Relative Amount (%)*
<u>Phase 1 (Prestart Test Generation):</u>			
<u>Unoccupied 3000 ppm Chamber:</u>			
4.1	methanol	ND	<0.07
13.2	ethanol	ND	<0.1
15.6	acetone	ND	<0.3
17.2	2-propanol	ND	<0.15
20.0	unknown	0	0.05
21.3	MEK	5.2	99.5
22.0	2-butanol	0	0.43*
<u>Phase 2 (First Week of Exposures):</u>			
<u>Occupied 3000 ppm Chamber:</u>			
4.7	Methanol	ND	<0.2
13.9	Ethanol	ND	<0.2
16.1	Acetone	ND	<0.6
17.7	2-propanol	ND	<0.4
20.4	unknown	0	0.05
21.7	MEK	38.5	99.9
22.5	2-butanol	0	<0.7

* All values expressed as area % unless indicated by an asterisk. Values accompanied by an asterisk are in weight %. See text for description of "less than" values.

Table 6. Results of GC-Headspace Analysis of Samples from the Distribution Line

Retention Time (Minutes)	Identification	% Breakthrough	Relative Amount (%)*
<u>Phase 1 (Prestart Test Generation):</u>			
<u>Distribution Line:</u>			
4.1	methanol	ND	<0.09
13.2	ethanol	ND	<0.1
15.6	acetone	ND	<0.3
17.2	2-propanol	ND	<0.3
20.0	unknown	0	0.05
21.3	MEK	0.28	99.4
22.0	2-butanol	0	0.55*
<u>Phase 2 (First Week of Exposures):</u>			
<u>Distribution Line:</u>			
4.7	Methanol	ND	<0.1
13.9	Ethanol	ND	<0.1
16.1	Acetone	ND	0.07*
17.7	2-propanol	ND	<0.2
20.4	unknown	0	0.06
21.7	MEK	38.5	99.9
22.5	2-butanol	0	<0.4

* All values expressed as area % unless indicated by an asterisk. Values accompanied by an asterisk are in weight %. See text for description of "less than" values.

Table 7. Results of Analyses from Generator Reservoir and Generator Flask and Generator Reservoir

Retention Time (Minutes)	Identity	Area % ^a
<u>Phase 1 (Prestart Test Generation):</u>		
Generator Reservoir Before Generation:		
20.0	unknown	0.0
21.2	MEK	99.3
22.1	2-butanol	0.61
Generator Reservoir After Generation:		
20.0	unknown	0.05
21.2	MEK	99.4
22.1	2-butanol	0.59
Generator Flask After Generation:		
20.0	unknown	0.05
21.2	MEK	98.7
22.1	2-butanol	1.21
<u>Phase 2 (First Week of Exposures):</u>		
Generator Reservoir After Generation:		
20.4	unknown	0.05
21.7	MEK	99.9
Generator Flask After Generation:		
20.4	unknown	0.05
21.7	MEK	99.4
22.5	2-butanol	0.24
29.5	unknown	0.11

a. All values expressed as area % except 2-butanol as wt %.

Table 8. Summary of Samples Collected from the Unoccupied Chambers and Distribution Line
(Samples Collected on Carbon Adsorbent Tubes for Gas Chromatography Analysis)

Sample Location	Flow Rate Liters/Min.	Total Volume Liters	Chamber Concentration (from monitor)	Micrograms MEK Collected ^b
<u>Phase 1 (Prestart Test Generation):</u>				
<u>Unoccupied Chambers:</u>				
Control Chamber	0.234	0.935	0.0 ppm	0
400 ppm Chamber	0.234	0.935	396 ppm	1089
3000 ppm Chamber	0.234	0.117	2953 ppm	1016
Distribution Line	0.234	0.012	80,000 ppm ^a	2751
<u>Phase 2 (First Week of Exposures):</u>				
<u>Occupied Chambers:</u>				
Control Chamber	0.326	1.304	0.0 ppm	0
400 ppm Chamber	0.326	1.304	396 ppm	1520
3000 ppm Chamber	0.326	0.163	2953 ppm	1417
Distribution Line	0.326	0.016	80,000 ppm ^a	3767

a. Calculated amount based on chemical use rate and distribution line flow rate.

b. Calculated amount based on concentration and sample volume.

Table 9. Gas Chromatograph Conditions for the Analysis of Methyl Ethyl Ketone and Potential Degradation Products in Carbon Disulfide

Parameter	Description
Chromatograph:	Hewlett-Packard 5890 with Hewlett-Packard Model 7673A Automatic Liquid Sampler
Column:	6 ft x 2 mm glass column with 20% SP 2100/0.1 % Carbowax 1500 on 100/120 mesh Supelcoport
Carrier Gas:	Helium at ~15 cc/min. flow rate
Detector:	Flame Ionization Detector operated at 300°C
Injector:	Splitless configuration at 250°C
Initial Temp:	50°C
Initial Time:	1.0 min.
Rate:	10 °C/min.
Final Temp:	150°C
Final Time:	5.0 min.
Injection Volume:	1 microliter

Table 10. Results of Analyses of Samples Collected on Carbon Adsorbent Tubes

Sample Location	Retention Time ^a	Identification	Area %
<u>Phase 1 (Prestart Test Generation):</u>			
<u>Unoccupied Chambers:</u>			
Control Chamber	2.3	MEK	100
400 ppm Chamber	2.3	MEK	100
3000 ppm chamber	2.3	MEK	100
Distribution Line	1.4	unknown	0.02
	1.5	unknown	0.04
	2.3	MEK	99.9
	5.7	unknown	0.06
<u>Phase 2 (First Week of Exposures):</u>			
<u>Occupied Chambers:</u>			
Control Chamber	2.2	MEK	100
400 ppm Chamber	2.2	MEK	100
3000 ppm chamber	2.2	MEK	100
Distribution Line	2.2	MEK	100

a. Retention time in minutes. Only those peaks not present in the blank are reported.

Table 11. Results of MEK Peroxide Determinations in the Bulk Chemical from the Generator Reservoir and in Samples from the Generator Flask, Vapor Distribution Line, and Unoccupied 400 and 3000 ppm Chambers.

Sample Location	Micrograms of MEK Collected	Weight % MEK Peroxide
Generator Reservoir	805,000	<0.003
Generator Flask	805,000	0.009
400 ppm Chamber	73,779	<0.03
3000 ppm Chamber	522,777	<0.005
Distribution Line	14,758,474	<0.0002

A. Sample from Control Chamber

B. Sample from 3000 ppm Chamber

C. Water Blank

Figure 1. Sample Chromatograms from Gas Chromatography - Headspace Analysis of Samples from: A. Control Chamber; B. 3000 ppm Chamber; C. Water Blank.

Figure 2. Example Chromatograms of Samples Taken on Charcoal Tubes: A. Solvent Blank; and B. Sample from Distribution Line.

Figure 3. Calibration Curve for Colorimetric Determination of MEK Peroxide

Test Chemical Monitoring

Monitoring System Description (SOW II.D.7.c)

An HP5840 gas chromatograph equipped with a flame ionization detector was used to monitor the exposure chambers, the control chamber, the exposure room and a certified on-line standard of MEK.

Sampling from multiple positions was accomplished by means of an automated 8 port stream select valve. An HP85B computer remotely controlled the selection of the correct sample stream and the operation of the monitor. Each analysis required about 3 minutes. The equation for the calibration curve was contained in the HP85B and applied to the data transmitted by the on-line GC monitor. The HP85B also accumulated and printed the sample values until all 8 ports of the stream select valve had been measured. These values were then sent to the executive computer for printing and storage. Each value accumulated by the HP85B was compared with limit values for that particular location. If the value was beyond the control limits, the HP85B immediately sent the information to the executive computer which took the appropriate action.

As described in the section that follows, the monitor was calibrated against gravimetrically prepared standards. These standards were related to the on-line monitor through quantitative analysis of grab samples taken from the chambers during generation.

Additionally, the operation of the chamber monitor was checked daily against an on-line standard. This check provided a measure of day-to-day instrument drift. Additional grab sampling was performed to check the monitor calibration when the concentration for the on-line standard exhibited excessive drift.

The uniformity of the distribution of test chemical in the chamber was checked before the start of the study and once during study exposure.

Calibration of the On-Line Monitor (SOW II.D.7.c)

Calibration of the on-line GC chamber monitor was based on quantitative analysis of bubbler grab samples taken directly from the exposure chambers during a routine exposure period. The normal dynamic operation of the monitor was not disrupted by the collection of these grab samples. The response of the on-line monitor during grab sampling was tied to an independent analysis of the grab sample.

Grab samples were obtained by collecting MEK in dimethylformamide (DMF) filled bubblers. Gravimetrically prepared standard solutions of MEK in DMF were used to construct a calibration curve on an independent GC system. The relationship between the peak area observed with the on-line GC and the concentration of MEK in the chamber was defined using chamber concentrations determined by the gravimetrically calibrated GC. A set of five standards was run for each analysis session. The concentration range of the standards bracketed the concentration range of the chamber grab samples. Two independently weighed stock solutions were used each time the standard series was prepared. The calibration was linear through the range of interest.

On-Line Standard

A certified on-line standard of 1000 ppm MEK in nitrogen was used to check instrument drift throughout the exposure day. The standard was also checked before the start of each exposure day and then monitored every 8th sample. If the on-line standard was between 5% and 10 % of the target concentration, exposure control personnel were immediately notified and recalibration of the on-line gas chromatograph was accomplished at the discretion of the chemist. Drift in the on-line standard concentration which exceeded 10% required recalibration of the on-line monitor as quickly as practical.

Specificity (SOW II.D.7.c)

One measure of chromatographic specificity is defined by determination of the analyte's partition coefficient. The retention time of methane, assumed to be non-retained, was found to be about 0.09 minutes. The retention time of MEK was 0.60 minutes. The partition coefficient was approximately 5.7.

Precision and Sensitivity (SOW II.D.7.c)

Introduction

While the generation system for methyl ethyl ketone (MEK, 2-butanone) was being developed, preliminary methods development was accomplished with the on-line gas chromatograph. This testing was performed in order to optimize chromatographic conditions, and to determine preliminary estimates of sensitivity and detection limit for the on-line monitor. Test atmospheres were generated using a laboratory scale, diffusion tube standard generator which was gravimetrically calibrated. Sensitivity and precision were estimated from repeated measurements at an MEK concentration of approximately 233 ppm. Detection limit was estimated at 0.5 ppm from repeated measurements at an MEK concentration of approximately 6 ppm. During these measurements the on-line monitor was operated in a manner identical to that employed for the inhalation teratology study. Additional measurements were performed under fully operational exposure conditions to confirm these results.

Experimental

Because the test chemical was not available when this work was initiated, methyl ethyl ketone test atmospheres were generated using commercially available MEK. Test atmospheres of MEK were generated using a diffusion tube standard generator (Thermolectron Instruments, Model 360, Franklin, MA). Four capillary vials filled with MEK were weighed and placed in the diffusion cell controlled at approximately 30°C. The MEK diffusing from the capillary vials was swept from the diffusion cell and diluted with air. After 96.5 hours the vials were reweighed and a weight loss of 4.27 grams of

MEK was determined. The dilution flow rate was determined to be 1.08 liters per minute, using a large bubble flow meter. From this information the calculated concentration of MEK from the standards generator was 233 ppm. Repetitive gas chromatograph measurements were made on the output from the standard generator using the chromatographic conditions shown in Table 1. A sample chromatogram is shown in Figure 1. The retention time for MEK was approximately 0.7 minute.

After gas chromatograph measurements were made at an MEK concentration of 233 ppm, three of the four diffusion tubes were removed and the remaining tube was reweighed. After 44.1 hours a weight loss of 0.45 g was determined and the flow was reset and recalibrated at 9.6 liters per minute to give an MEK concentration of 6 ppm. Again, repetitive gas chromatograph measurements were made on the output from the standard generator using the chromatographic conditions shown in Table 1.

From 27 measurements at the 233 ppm concentration, the average peak area was 52787 ± 211 , which represented a relative standard deviation of 0.4% and a 99% confidence interval of ± 113 area units or $\pm 0.2\%$ ($t(26, 0.005) = 2.779$ and confidence interval $= \pm t \cdot s/\sqrt{n}$). The slope of a single point calibration curve at 233 ppm was 227 area units/ppm. The analytical sensitivity, γ , was calculated as:

$$\gamma = \frac{dx/dc}{S_x}$$

where X is peak area, C is the concentration of MEK in ppm, S_x is the standard deviation in peak area, and γ has units of ppm^{-1} . The analytical sensitivity at an MEK concentration of 233 ppm was 1.07 ppm^{-1} , which indicated that the smallest concentration change that could be discriminated at this concentration was about 0.93 ppm ($1/\gamma$).

From 32 measurements at a concentration of approximately 6 ppm MEK, the average peak area was 3154 ± 83 area units or a relative standard deviation of $\pm 2.6\%$ and a 99% confidence interval of ± 40 area units or $\pm 1.3\%$ ($t(31, 0.005) = 2.745$ and confidence interval $= \pm t \cdot s/\sqrt{n}$). The slope of a single point calibration curve at this concentration was 526 area units/ppm.

The analytical sensitivity at an MEK concentration of 6 ppm was 6.4 ppm^{-1} , which indicated that the smallest concentration change that could be discriminated at this concentration was about 0.16 ppm ($1/\gamma$). The detection limit calculated from the sensitivity as $3/\gamma$ was estimated to be 0.47 ppm of MEK.

Additional measurements were performed under fully operational exposure conditions to confirm these results. Precision for the on-line monitor was estimated from 8 repeated measurements made using the on-line standard. The on-line standard was sampled from each of the 8 sample ports. A standard deviation of 3.09 ppm was observed for a 0.3 % coefficient of variance (BNW Notebook 52714-18).

From 10 measurements at the 400 ppm concentration, the average peak area was 87940 ± 575 , which represented a relative standard deviation of 0.65% and a 99% confidence interval of ± 591 area units or $\pm 0.67\%$ ($t(9,0.005) = 3.250$ and confidence interval = $\pm t \cdot s/\sqrt{n}$). The slope of a single point calibration curve at 400 ppm was 220 area units/ppm. The analytical sensitivity at an MEK concentration of 400 ppm was 0.38 ppm^{-1} , which indicated that the smallest concentration change that could be discriminated at this concentration was about 2.61 ppm ($1/\gamma$).

From 14 measurements at the 3000 ppm concentration, the average peak area was 655900 ± 3100 , which represented a relative standard deviation of 0.47% and a 99% confidence interval of ± 2495 area units or $\pm 0.38\%$ ($t(13,0.005) = 3.012$ and confidence interval = $\pm t \cdot s/\sqrt{n}$). The slope of a single point calibration curve at 3000 ppm was 219 area units/ppm. The analytical sensitivity at an MEK concentration of 3000 ppm was 0.07 ppm^{-1} , which indicated that the smallest concentration change that could be discriminated at this concentration was about 14.2 ppm ($1/\gamma$).

Discussion

The test chemical atmospheres generated by the standards generator were apparently quite stable over time, as indicated by excellent precision of the measurements. Although these measurements were made at concentrations

somewhat less than the actual exposure concentrations, the analytical precision was within $\pm 1\%$ during prestart exposures. However, it should be noted that precision estimates measured during exposures contain uncertainties that arise from any minor fluctuations in the generated test atmospheres, and are thus not true estimates of the precision of the analytical measurement process.

The method used for determining and calculating detection limits is superior to less rigorous methods, since it accounts for the sensitivity of the measurement as well as the precision. Proper use of this method requires that measurements be made at or near the detection limit. However, this is not always easily accomplished with the full-scale generation systems used for exposures. Thus, the laboratory scale generator provides a useful tool for obtaining measurements of analytical figures of merit.

The NTP April 1987 Statement of Work (SOW) required that the vapor concentration monitoring methodology developed by the study laboratory be sensitive down to a level of 1% the target concentration. Since the estimated detection limit was 0.47 ppm and the lowest target concentration is 400 ppm, the measurement technique easily meets this criteria (detection limit was 0.1% of the lowest target concentration). In addition, the SOW required that the chemical monitor provide measurements that are precise to within $\pm 10\%$. The results reported above indicate that the chosen method was easily capable of this goal.

Linearity and Absolute Recovery

Linearity of the on-line monitor was assured by indirectly calibrating the on-line monitor against a gravimetrically calibrated GC (see "Calibration of the On-Line Monitor" section). The calibration was linear through the range of interest.

Recovery of the bubbler grab sample method was measured by determining breakthrough. Breakthrough was measured every time samples were collected by collection of back-up bubblers from the high concentration chamber. With the 1 liter sample size selected for the study, no breakthrough was

encountered. Grab samples were analyzed by the calibration method before and after being spiked with additional test material. Results indicated 100% recovery of the spiked test material from the bubbler grab samples at the 400 and 1000 ppm levels.

Monitoring for Methyl Ethyl Ketone in Building Exhaust

Introduction

A NIOSH method (NIOSH Manual of Analytical Methods, Third Edition, P. M. Eller, Editor, 1984, Method 1300) for the determination of ketones in air was adapted for measurement of methyl ethyl ketone (MEK) in the building exhaust of LSL-II during chemical generation periods. The method was based on collection of the sample by drawing building exhaust air through a tube filled with a charcoal adsorbent. The MEK was desorbed from the adsorbent with carbon disulfide and determined by gas chromatography. In this work the method was evaluated for breakthrough during sampling and recoveries of MEK from the adsorbent using carbon disulfide. The approximate sensitivity and the detection limit of the measurement method were determined. The approximate concentration of MEK in the building exhaust was calculated on the basis of estimated chemical use rate and building exhaust rate, and this information was used to obtain appropriate sampling times for actual measurements of MEK in the building exhaust.

Experimental

Because the test chemical was not available when this work was initiated, methyl ethyl ketone test atmospheres were generated using commercially available MEK. Test atmospheres of MEK were generated using a diffusion tube standards generator (Thermoelectron Instruments, Model 360, Franklin, MA). Four capillary vials filled with MEK were weighed and placed in the diffusion cell controlled at approximately 30°C. The MEK diffusing from the capillary vials was swept from the diffusion cell and diluted with air. After 48 hours the vials were reweighed and a weight loss of 2.03 grams of MEK was determined. The dilution flow rate was determined to be 7.06 lpm,

using a large bubble flow meter. From this information the calculated concentration of MEK from the standard generator was ~34 ppm.

Samples were drawn from the diffusion tube generator through ORBO-32 charcoal adsorbent tubes. These tubes contain a front and rear portion of adsorbent, with the rear portions being used to collect material that escapes collection on the front portion. Flow rate was controlled using a calibrated critical orifice, and samples were drawn at two different flow rates (0.36 lpm and 1.11 lpm) for varying periods of time.

Adsorbent from the front and rear portion of each tube was desorbed with 1.0 ml of carbon disulfide in automatic liquid sampler vials. Standards of MEK in carbon disulfide were prepared gravimetrically in the 10-1000 ug MEK/ml range. These standards were analyzed in the presence and absence of unexposed charcoal adsorbent (front portion of tube). In order to account for less than quantitative desorption, calibration curves for the analysis of tube samples were derived from standards containing the charcoal adsorbent from the front portion of unexposed tubes. Samples and standards were sonicated for 10 minutes and analyzed using the gas chromatographic conditions shown in Table 2. An example chromatogram is shown in Figure 2.

Table 3 contains data on the percent recovery of MEK using carbon disulfide as the solvent. As shown in Table 3, the percent recovery increased slightly with increasing MEK concentration. Over the range of concentrations studied, recoveries averaged $75 \pm 2\%$. Table 4 contains a summary of analyses of tube samples of the test atmospheres collected from the standard generator. The determined amounts of MEK shown in Table 4 were in good agreement with the amounts expected based on gravimetric calibration of the standard generator (~34 ppm). No breakthrough of MEK was observed in any of the samples, indicating that the collection efficiency for MEK under the sampling conditions was essentially 100%.

Methyl ethyl ketone was detected in standards containing 9 ug/ml of test chemical, but did not show peak areas large enough for good quantitative results under the chromatographic conditions shown in Table 2. Using

duplicate measurements of the 47 ug/ml standard measured on two separate days, the sensitivity, γ , was calculated as:

$$\gamma = \frac{dx/dc}{S_x}$$

where X is peak area, C is the amount of MEK in micrograms, and S_x is the standard deviation in peak area, and γ has units of ug^{-1} . From the value of γ , the detection limit is determined as:

$$\text{Detection Limit} = 3/\gamma.$$

Using these definitions, the sensitivity was calculated to be 1.69 ug^{-1} and the detection limit was calculated to be approximately 1.78 ug. It was expected that acceptable quantitation would require an amount of MEK equal to approximately 25 times the detection limit, or about 45 ug of MEK. This was in good agreement with the experimental observation that peak areas for the 47 ug/ml standard were sufficiently large to yield reliable quantitative information.

The use rate of MEK by the generation system was expected to be approximately 11.4 ml/minute. Given a building exhaust flow of 80,000 cfm, the calculated concentration of MEK in the building exhaust was approximately 1.5 ppm. At this concentration, sampling at a flow rate of 1 lpm for about 10 minutes would yield a sample of about 45 ug of MEK.

An additional test was performed to ensure that collection of larger sample volumes does not adversely effect the collection efficiency of the charcoal adsorbent for MEK. Samples were drawn from the standard generator at 1 lpm for 2 minutes. The adsorbent tubes were disconnected from the standard generator and lab air was drawn through the tubes at 1 lpm for about 30 minutes. The front and rear portions of these tubes were desorbed in carbon disulfide and analyzed by gas chromatography. The results are shown in Table 5. No breakthrough of MEK into the rear portion of the tubes was observed, which showed that larger sample volumes did not reduce collection efficiencies to any observable extent. Note that the samples that were

exposed to 30 liters of room air exhibited larger concentrations of MEK than those that were not exposed. This was possibly due to collection of ambient MEK in the laboratory air, or may have been due to the collection of a different compound that coelutes with MEK under the conditions of the analysis.

MEK was determined in the LSL-II building exhaust using the method described above. Samples were drawn at approximately 0.44 liters per minute (for 20 minutes) from three different locations in the exhaust plenum. Under these conditions, measurable amounts of MEK were collected from each of these locations in the exhaust plenum. No breakthrough was observed in any of the samples. The average concentrations of MEK in samples collected from different ports in the plenum were 0.54 ppm in port #1, 1.38 ppm in port #2, and 1.49 ppm in port #3. The concentration of MEK averaged over all three sampling ports was 1.14 ± 0.46 ppm. Based on a chemical use rate of 11.4 ml/min and a building exhaust flow rate of 80,000 CFM, the calculated concentration of MEK in the building exhaust is 1.5 ppm. The Threshold Limit Value (TLV) for MEK was 200 ppm.

Discussion

The collection efficiency of the charcoal adsorbent was found to be essentially 100% for collection of approximately 30-200 micrograms of MEK from test atmospheres containing approximately 30 ppm MEK. Sample volumes as large as 30 liters did not noticeably reduce the collection efficiency. Using carbon disulfide for desorbing MEK from the adsorbent produced recoveries in the range of approximately 72-78%, and recoveries increased somewhat as increasing amounts of MEK were collected. However, provided that standards contain the charcoal adsorbent and bracket the MEK concentration of the samples, this small dependence of recovery on sample size should be of little consequence.

The detection limit was found to be approximately 1.78 micrograms MEK, although standards containing 47 micrograms of MEK were required to give peak areas large enough to provide reliable concentration estimates. Based on chemical use rate and building exhaust flow rate, the concentration of

MEK in the building exhaust was calculated to be approximately 1.5 ppm. Thus, a minimum sampling time of 10 minutes, at a sampling flow rate of 1 lpm was required to obtain samples sufficiently large to determine MEK in the building exhaust. Precisions of 5-10% relative standard deviation could be expected from replicate analyses.

MEK measurements in the LSL-II building exhaust indicated different concentrations of MEK in samples obtained from different portions of the exhaust plenum. The sample from two of the plenum ports gave concentrations of 1.4 and 1.5 ppm MEK, which were in good agreement with the calculated MEK concentration; the third sample gave a level below the calculated concentration.

Table 1. Chromatographic Conditions for the On-line Gas Chromatograph Used to Monitor MEK

Parameter	Description
Gas Chromatograph:	Hewlett-Packard Model 5840
Detector:	Flame Ionization Detector at 150°C
Valves and Plumbing:	8-port stream select valve and sampling valve (Hastelloy-C) with 0.25 ml nickel sample loop, valves thermostated at 130°C and all transfer lines stainless steel.
Column:	20 inch x 1/8 inch (od) nickel with Porapak PS packing.
Oven Temperature:	130 °C (isothermal)
Attenuation:	8 (233 ppm MEK) or 3 (6 ppm MEK)

Table 2. Gas Chromatograph Conditions for the Analysis of Methyl Ethyl Ketone in Carbon Disulfide

Parameter	Description
Chromatograph:	Hewlett-Packard 5890 with Hewlett-Packard Model 7673A Automatic Liquid Sampler
Column:	6 ft x 2 mm glass column with 20% SP 2100/0.1 % Carbowax 1500 on 100/120 mesh Supelcoport
Carrier Gas:	Helium at ~15 cc/min. flow rate
Detector:	Flame Ionization Detector operated at 300°C
Injector:	Splitless configuration at 250°C
Initial Temp:	50°C
Initial Time:	1.0 min.
Rate:	10 °C/min.
Final Temp:	150°C
Final Time:	0.0 min.
Injection Volume:	1 microliter

Table 3. Recovery of Methyl Ethyl Ketone from Charcoal Adsorbent with Carbon Disulfide

Concentration of MEK (micrograms per milliliter)	% Recovery ^a
47	72.7 73.1
94	74.1 74.8
472	75.2 75.4
943	78.1 78.3

a. % Recovery = (MEK peak area with charcoal/MEK peak area without charcoal) x100%

Table 4. Results of Analyses of Charcoal Tube Samples Collected from the Output of the MEK Standard Generator.

Sample#	Sampling Flow Rate (liters/min)	Volume (liters)	Average µg of MEK Collected	MEK Vapor Conc. (Average ppm)
BNW52713-19-1	1.11	1.11	84	26
BNW52713-19-2	1.11	1.11	90	27
BNW52713-19-3	1.11	1.67	115	23
BNW52713-19-4	0.36	0.36	32	31
BNW52713-19-5	0.36	0.71	56	27
BNW52713-10-6	0.36	0.89	69	26
Average:				27 ± 2

Table 5. Effect of Large Sample Volumes on Sample Breakthrough Using Charcoal Tubes^a

Sample#	Sampling Flow Rate (liters/min)	Volume (liters)	Average μg of MEK Collected	MEK Vapor Conc. (Average ppm)
BNW52713-33-1 ^b	1.11	2.22	216	33
BNW52713-33-2 ^b	1.11	2.22	196	30
BNW52713-33-3 ^b	1.11	2.22	192	29
			Average:	31 $\pm$ 2
BNW52713-33-4	1.11	2.22	152	23
BNW52713-33-5	1.11	2.22	156	24
BNW52713-33-6	1.11	2.22	146	22
			Average:	23 $\pm$ 1

a. Based on the analysis of the rear adsorbent bed in each tube, no breakthrough of sample was observed in any of the samples.

b. Approximately 30 liters of room air was drawn through the samples after the samples were collected from the output of the standard generator.

Figure 1. Chromatogram of MEK at Approximately 233 ppm Concentration Using the Conditions Shown in Table 1.

Figure 2. Sample Chromatogram of 47 $\mu\text{g/ml}$ of MEK in Carbon Disulfide.

FIGURE 1. Sample of a drawing of a mechanical part.

APPENDIX B

EXPOSURE NARRATIVE AND DATA FOR
METHYL ETHYL KETONE

EXPOSURE DATA AND NARRATIVE FOR METHYL ETHYL KETONE

Animal Exposure Chamber

The Battelle-designed inhalation exposure chamber (commercially available from Harford Systems/Lab Products, Inc., Aberdeen, MD) was used for the inhalation exposures. The 2.3 m³ (1.7 m³ active mixing volume) stainless steel chamber contained three levels of caging, each level split into two offset tiers (Figure B.1). The drawer-like stainless steel cage units comprised individual animal cages, feed troughs and automatic waterers. Stainless steel catch pans for the collection of urine and feces were suspended below each cage unit.

The catch pans, which remained in the chamber during exposure, were designed to aid in maintaining uniform concentrations of aerosol, dust or vapors throughout the chamber. Incoming air was HEPA and charcoal filtered before addition of the test article. Following the addition of the test article the uniform mixture was diverted along the inner surfaces of the chamber. A portion of the flow was "peeled off" by each catch pan thus creating mixing eddies. Exhaust from each tier was cleared through the space between the tiers.

Exposure Suite System Description

The methyl ethyl ketone (MEK) exposures were conducted using an automated data acquisition and control system in an exposure suite (Figures B.2 and B.3). This system monitored and controlled the basic inhalation test system functions including chamber air flow, vacuum, temperature, relative humidity and test chemical concentration. The system computers, printers, magnetic data storage devices, interface equipment, and monitoring instruments were located in a central control room and interfaced with monitoring and control elements in three exposure rooms. All data acquisition and control originated from an executive computer which controlled a multiplexing interface system. All experimental protocols related to data acquisition and control resided in this computer and were entered into software tables accessed by menus.

Data from each exposure was stored in the exposure control center on separate micro-floppy diskettes. Data and comments from each exposure room were printed on separate printers. Data was printed and stored immediately upon completion of the measurement. At the end of the 24 hour period, the daily data was analyzed and summary and data outlier reports were printed.

A dual point alarm system with user-defined set points was available for each parameter measured. Action taken upon alarm depended on the cause and severity of the alarm and ranged from audio/visual alert to automatic shutoff of the exposure generator. Alarm conditions which might be a threat to the health of the animals alerted a building power operator who was on duty 24 hours per day.

FRONT VIEW

SIDE VIEW

FIGURE B.1. Inhalation Exposure Chamber

FIGURE B.2. Methyl Ethyl Ketone Exposure Suite

FIGURE B.3. Data Acquisition System for Methyl Ethyl Ketone Exposures

COMPUTER SYSTEM

Chamber and room temperatures were measured by Resistance Temperature Detectors (RTDs) located at the measurement site. The RTDs were multiplexed to a digital thermometer which was interfaced to the computer. Chamber temperature was controlled primarily by controlling the temperature of the room housing the chambers. Prior to the start of the study RTDs were calibrated to within $\pm 0.5^{\circ}\text{F}$ of a certified mercury thermometer in a temperature controlled water bath.

Relative humidity (RH) was determined by pulling a sample from the measurement location through a Teflon® tube into a dew point hygrometer located in the control center. Measurements were made from different locations by a valving system which multiplexed the tubes to the hygrometer. Percent RH was calculated by the executive computer from temperature and dew point measurements with an accuracy of $\pm 6\%$. Chamber %RH was maintained by a "wet/dry" air source supplied to each chamber. The ratio of "wet" to "dry" air, determined by a manually-controlled mixing valve, determined the chamber %RH.

Chamber air flow was calculated with an accuracy of ± 15 l/min by measurement of the pressure drop across calibrated orifices located at the inlet and exhaust of each chamber. The desired flow orifice was attached by means of a multiplexed valve system to a calibrated pressure transducer located in the control center. Leaks in the chambers could be detected by comparison of the measurement of inlet flow with that of the exhaust. Flow was maintained by a manually-controlled gate valve in the exhaust line of each chamber.

Chamber vacuum, relative to the control center, was measured with an accuracy of ± 0.2 cm H₂O using the same pressure transducer system which measured chamber air flows. Chamber vacuum was maintained at approximately (-)1" H₂O primarily by inlet resistance provided by the HEPA and charcoal filters.

Methyl Ethyl Ketone Generation System

A schematic diagram of the methyl ethyl ketone generation and delivery system is shown in Figure B.4. The MEK generator was housed in a vented cabinet located in the Suite Control Center.

The vapor generator employed a rotary evaporation system (Büchi Rotavapor, Model EL-131S) to produce high purity MEK vapor. The bulk MEK was transferred to a 5-gallon pressurized delivery container where low pressure nitrogen (4 - 6 psi) was introduced into the inlet of the vessel, forcing liquid MEK out at a steady rate. Chemical flow rate was adjusted with a stainless steel metering valve and monitored with a Teflon® flowmeter. The liquid was delivered to a rotating flask immersed in a hot water bath. Nitrogen was also metered into this flask. MEK vapor was carried out of the mouth of the flask by the nitrogen into a chilled water condenser where much of the vapor was recondensed, returning to the evaporator flask. As nitrogen moved through the condenser, it cooled and became saturated with MEK vapor. The temperature of the saturated nitrogen was monitored at the top of the condenser using a sensor. The saturation vapor pressure was calculated and used to determine the output (ppm of MEK and flow rate of saturated nitrogen) of the generator. The vapor entered a short distribution manifold from which individual delivery lines carried a

metered amount of vapor to the exposure chambers. Vacuum transducer pumps at the chamber end of each line generated the negative pressure needed to move the MEK vapor. Within the chemical storage cabinet, each line was connected to the distribution manifold through a fine metering valve and flowmeter. Adjustment of chamber concentration was done with the metering valves and/or adjustment of compressed air pressure to the pumps. Injection of the nitrogen/vapor mix into the conditioned airstream entering the chamber occurred at a point sufficiently removed from the chamber to allow for proper mixing. This assured uniformity of chemical-laden atmosphere within the chamber.

To prevent degradation of the vapor before delivery to the chamber inlet, the vapor was generated and delivered in nitrogen. In the high dose chamber, this resulted in a reduction in the oxygen content of the chamber to 20.1% from the normal level of 20.9%.

Normal operation called for approximately 20% excess vapor to be exhausted from the manifold through a flowmeter. This caused a slight positive pressure in the manifold and allowed independent adjustment of the chamber flow rates. However, there was the possibility of creating a negative pressure in the manifold and generator which could draw air into the nitrogen/MEK atmosphere since the vacuum transducer pumps were withdrawing vapor from the manifold. This would occur if nitrogen delivery was interrupted or the pump delivery rates were grossly misadjusted. To monitor for this situation, a pressure transducer (Photohelic) measured the pressure drop across the excess vapor flowmeter. A drop in pressure to below 2 cm of water resulted in a shutdown of the generation system.

Generation proceeded in stages: warmup, generation and shutdown. During warmup, filling of the evaporator flask and heating of the water bath proceeded together. During this time, some evaporation occurred but all vapor was exhausted from the distribution manifold through the excess flowmeter and at each chamber through pneumatic 3-way valves. These valves allowed for a faster buildup of vapor concentration at startup as well as a more rapid diversion of chemical flow from chambers in the event rapid shutdown was necessary. After stabilization of the vapor temperature and possible fine adjustments of the vapor delivery and nitrogen flow rates, the generator was in its normal operating stage. At this time, computer-controlled startup of the exposure was initiated by rotation of the pneumatic 3-way valves to the chamber position. During this stage, the generator operated under computer and exposure operator supervision. The exposure operator monitored the fluid level in the flask as well as other operating parameters. The operator adjusted the overall generator output by changing the flow rate of cooling water to the condenser. This affected the temperature of the vapor leaving the condenser and hence, the concentration of chemical in the nitrogen/vapor. Overall generator output could also be controlled by adjusting the flow rate of dilution nitrogen. Individual chamber concentration adjustments were generally done by changing the air pressure to the pressure transducer pumps which were withdrawing vapor from the distribution manifold.

FIGURE B.4. Methyl Ethyl Ketone Generation and Delivery System

The computer was able to initiate a shutdown of the generator output under certain conditions by stopping flask rotation and turning off the bath heater. Further reduction in the generator output was then initiated by the operator by reducing the nitrogen flow and opening a valve which introduced chilled water into the water bath.

Shutdown at the end of the generation stage was similar to a computer-initiated shutdown. Following closure of the valves at the chambers and discontinuation of flask rotation, the operator dumped additional cooling water into the bath. The remaining MEK in the evaporator flask was removed to a waste bottle. Nitrogen continuously purged the generation system until preparation for the next day's generation.

A Gardner Inc. Type CN small particle detector was used to check the chambers for particles during generation before animals were placed in the chambers and with animals in the chambers. No particles were found in the control chamber or any of the exposure chambers before animals were brought to the chambers. A count of <200 particles/cm³ was found in the 1000 ppm chamber during exposure to animals.

The time (T_{90}), following the start of generation, for the concentration to build up to 90% of the final stable concentration in the chamber and the time (T_{10}), following the stop of generation for the vapor concentration to decay to 10% of the stable concentration were determined before animals were placed in the chambers prior to the start of the study. The resulting curves for all chambers are shown in Figure B.5. The value of T_{90} was found to range from approximately 10 to 12 minutes. At a chamber air flow rate of 15 air changes per hour, the theoretical value for T_{90} is approximately 12.5 minutes. A T_{90} of 12 minutes was chosen for this study. The value of T_{10} ranged from 9 to 12 minutes.

The buildup and decay of concentration with mice present in all the chambers were also checked during the exposure (Figure B.5). The values of T_{90} ranged from 7 to 10 minutes. The decay time, T_{10} , ranged between 8 and 10 minutes.

In order to determine the persistence of the chemical in the chamber following exposure, the concentration of MEK in the 3000 ppm chamber was monitored overnight following shutoff of the chemical flow to the chamber. Monitoring was performed once during the prestart activities without animals, and again during the study when animals were present. Concentration of MEK in the chamber without animals was below 1% of the initial concentration approximately 20 minutes following shutdown of the vapor generation system compared with approximately 19 minutes with animals in the chambers.

MEK IRT: 400 ppm Chamber

MEK IRT: 1000 ppm Chamber

MEK IRT: 3000 ppm Chamber

FIGURE B.5. Buildup and Decay of Vapor Concentrations With and Without Animals Present.

Vapor Concentration Uniformity in Chambers

Uniformity of vapor concentration in the exposure chambers was measured prior to the start of and once during the study. The vapor concentration was measured using the on-line GC with the automatic 8-port sample valve disabled to allow continuous monitoring from a single input line. Prior to animal loading, 12 chamber positions (two positions, one in front and one in back, for each of the six possible animal cage unit positions per chamber) were measured. The second set of gas concentration measurements was taken from the front and back positions of the chamber only where cage units contained animals.

The sample point was just above and about 10 cm in from the front or back center of each cage unit. The uniformity data for each chamber during prestart testing and after animals were in place in the chambers are summarized in Table B.1. Complete data are found later in this appendix. Uniformity in all chambers was found acceptable. The possible variation of test chemical concentration measured from one sample port to another during the measurement procedure is termed the Total Port Variability (TPV) and consists of both spatial and temporal variations. Two factors contribute to the TPV. The first, the Between Port Variability (BPV), is the factor of interest as it represents the spatial variation of test chemical distribution within the chamber. The second factor, the Within Port Variability (WPV), represents the temporal fluctuation of the average chemical concentration within the chamber during the time the measurements were taken. This temporal factor includes variations in vapor generation as well as variation of the measurement instrument itself.

The WPV was determined from a minimum of three measurements taken at the on-line monitor port (1B or 2B) before, during and after all other ports were measured.

The TPV was determined from measurements, at the minimum, from the front and back ports at each level on which animals are housed.

The BPV was determined by applying the following equation:

$$BPV = \sqrt{(TPV)^2 - (WPV)^2}$$

Since the WPV is often determined from fewer measurements than the TPV, statistically it is possible for the WPV to be greater than the TPV. In these cases, the BPV is very small, but it cannot be distinguished from the WPV. The BPV can't be determined using the above equation as it yields the square root of a negative number. In this case, it is reported as unresolvable from the WPV.

TABLE B.1. Teratology Study of Methyl Ethyl Ketone in Mice -
Summary of Chamber Uniformity Data Obtained before
Exposure (Pre) and During Exposure with Mice Present
(Post).

Chamber	TPV (%RSD)		WPV (%RSD)		BPV (%RSD)	
	Pre	Post	Pre	Post	Pre	Post
400 ppm	2.1	0.5	2.2	0.1	*	0.5
1000 ppm	0.4	0.6	1.2	0.5	*	0.3
3000 ppm	1.3	0.5	1.8	0.3	*	0.5

Chamber Uniformity Limits

WPV $\leq$ 5% RSD

BPV $\leq$ 5% RSD

TPV $\leq$ 7% RSD

* Indistinguishable from WPV.

Environmental Data During Exposure

Summations of chamber air flow, temperature and relative humidity data for the study are shown in Table B.2. This includes the mean, standard deviation, mean expressed as a percentage of the target, the percent relative standard deviation (SD/Mean), maximum, minimum readings, number of readings and the percent of readings for which the value was within the specified operating range.

The mean value of temperature in each chamber for the entire study was between 73.7 and 75.5°F, all within the specified limits of 72 to 78°F. Temperature extremes (considering all chambers) ranged from 71.1 to 78.3°F. The percent of temperature readings within the operating range were greater than or equal to 99% for all chambers except for the hold chamber, where 92% of the readings were within the operating range.

The mean value of relative humidity in each chamber for the entire study was between 53.9 and 57.2%, all within the specified limits of 40 to 70%. Relative humidity extremes (considering all chambers) ranged from 44 to 68%. All readings were within the normal operating range.

The mean value of chamber air flow in each chamber was between 15.0 and 15.6 CFM (1 CFM = 1 air change per hour), all within the specified limits of 12 to 18 CFM. Flow extremes (considering all chambers) ranged from 14.9 to 15.7 CFM. All readings were within normal operating limits.

A complete summary of the daily chamber environmental data and notations on any readings which exceeded critical limits follows.

TABLE B.2. Inhalation Teratology Study of Methyl Ethyl Ketone in Mice—
Summation of Environmental Data for the Period when Animals
were Housed in the Exposure Chambers. Acceptable ranges are
also shown.

Temperature (°F)
Acceptable Range = 72 to 78 °F

Target Chamber Conc. (ppm)	Mean ± SD	Percent of Target ±RSD	Maximum	Minimum	Number of Samples	% Samples in Range
Room	73.8 ± 0.7	103 ± 1%	75.0	71.1	101	100 ¹
0	75.2 ± 0.8	100 ± 1%	76.6	72.4	96	100
Hold	75.5 ± 1.4	101 ± 2%	78.3	73.5	61	92
400	73.7 ± 0.6	98 ± 1%	74.8	71.1	98	99
1000	74.1 ± 0.7	99 ± 1%	75.0	71.4	97	99
3000	74.3 ± 0.7	99 ± 1%	75.8	71.4	97	99

¹ Range for room: 69 to 75°F

Relative Humidity (% RH)
Acceptable Range = 40 to 70 %RH

Target Chamber Conc. (ppm)	Mean ± SD	Percent of Target ±RSD	Maximum	Minimum	Number of Samples	% Samples in Range
0	56.7 ± 2.9	103 ± 5%	68	49	94	100
Hold	57.2 ± 5.0	104 ± 9%	65	46	60	100
400	54.4 ± 4.6	99 ± 8%	62	44	95	100
1000	54.8 ± 3.9	100 ± 7%	62	46	94	100
3000	53.9 ± 4.6	98 ± 8%	62	44	93	100

Air Flow (CFM)
Acceptable Range = 12 to 18 CFM

Target Chamber Conc. (ppm)	Mean ± SD	Percent of Target ±RSD	Maximum	Minimum	Number of Samples	% Samples in Range
0	15.6 ± 0.1	104 ± 0%	15.7	15.5	92	100
Hold	15.3 ± 0.1	102 ± 1%	15.4	15.1	59	100
400	15.3 ± 0.1	102 ± 0%	15.4	15.1	93	100
1000	15.2 ± 0.1	101 ± 1%	15.0	15.0	93	100
3000	15.0 ± 0.1	100 ± 1%	15.1	14.9	93	100

Exposure Data

A summary of the concentration data for the study for all chambers and the exposure room are included in Table B.3. Summaries of concentration by exposure day follow in this appendix along with graphic illustrations of the daily mean and standard deviation for each chamber.

The grand means of the concentrations in each chamber for the entire study were between 100 and 101% of the target, with relative standard deviations in the range of 2 to 3%. The daily mean concentrations ranged from 98 to 104% of target (the daily protocol required the daily means to be within $\pm 10\%$ of the target concentrations) and % RSD's were less than 10%. At least 98% of all individual concentration measurements were within $\pm 10\%$ of the target levels, the specified operating limits. The maximum concentration observed in the control chamber was 0.08 ppm and 0.04 ppm in the hold chamber. The maximum concentration observed in the room was 0.7 ppm.

A complete discussion of all concentration excursions is included in this appendix.

TABLE B.3. Inhalation Teratology Study of Methyl Ethyl Ketone in Mice—
Summation of Concentration Data for the Period when Animals
were Housed in the Exposure Chambers.

Concentration (PPM)							
Acceptable Range = Target $\pm 10\%$							
Target Conc. (ppm)	Mean $\pm$ SD	Percent Target $\pm$ RSD	Max	Min	Number Samples	Number In Range	% Samples in Range
Room	0.03 $\pm$ 0.06	-----	0.7	0	235	*235	*100
0	0.00 $\pm$ 0.01	-----	0.08	0	243	*243	*100
Hold	0.00 $\pm$ 0.01	-----	0.04	0	80	*80	*100
400	398 $\pm$ 9.4	100 $\pm$ 2%	439	352	237	236	>99
1000	1010 $\pm$ 28	101 $\pm$ 3%	1140	894	238	234	98
3000	3020 $\pm$ 79	101 $\pm$ 3%	3340	2490	241	238	99
St. Gas	1100 $\pm$ 48	101 $\pm$ 4%	1110	310	273	272	>99

* Samples with concentration less than 5 ppm

CHAMBER UNIFORMITY DATA SHEET

COMPOUND: IRT Methyl Ethyl Ketone

EXPOSURE ROOM NUMBER: 436

TPV MEASUREMENTS

CHAMBER: #8 / 3000 ppm			#7 / 1000 ppm			#6 / 400 ppm						
DATE: 6/6/88			6/6/88			6/6/88						
SAMPLE PORT	MONITOR READING	% of Mean	MONITOR READING	% of Mean	MONITOR READING	% of Mean	MONITOR READING	% of Mean	MONITOR READING	% of Mean	MONITOR READING	% of Mean
BACK:	1B	586000.0	102.8%	80000.0	100.9%	133400.0	100.9%					
	2B	547900.0	96.2%	79340.0	100.1%	133800.0	101.2%					
	3B	576400.0	101.2%	78700.0	99.3%	133800.0	101.2%					
	4B	583600.0	102.4%	79240.0	100.0%	133800.0	101.2%					
	5B	575400.0	101.0%	78920.0	99.6%	133900.0	101.3%					
	6B	578400.0	101.5%	79140.0	99.8%	133800.0	101.2%					
FRONT:	1F	580800.0	101.9%	79480.0	100.3%	131400.0	99.4%					
	2F	562200.0	98.7%	79360.0	100.1%	131900.0	99.7%					
	3F	558600.0	98.0%	79180.0	99.9%	130800.0	98.9%					
	4F	563400.0	98.9%	79560.0	100.4%	130500.0	98.7%					
	5F	564700.0	99.1%	78840.0	99.5%	129900.0	98.2%					
	6F	560300.0	98.3%	79360.0	100.1%	129800.0	98.2%					
MEAN:		569808.3	100.0%	79260.0	100.0%	132233.3	100.0%					
TPV:		11842.87	2.1%	348.92	0.4%	1683.79	1.3%					
BPV:		//////////	*	//////////	*	//////////	*	//////////	//////////	//////////	//////////	//////////

* Indistinguishable from WPV

WPV MEASUREMENTS

IN-LINE	1st	547900.0	97.7%	80000.0	100.1%	133400.0	100.6%			
	2nd	561800.0	100.2%	78920.0	98.7%	134500.0	101.4%			
	3rd	572300.0	102.1%	80880.0	101.2%	130000.0	98.0%			
MEAN:		560666.7	100.0%	79933.3	100.0%	132633.3	100.0%			
WPV:		12239.42	2.2%	981.70	1.2%	2345.92	1.8%			

MONITOR TYPE: HP5840A

SERIAL # : N809422

MONITOR DATA LOCATION: Data is kept with prestart records.

COMMENTS: Without animals in chambers.

ENTERED BY: LL TrentDATE: 6/7/88REVIEWED BY: RJ Weigel *RJW*DATE: 8/29/88

CHAMBER UNIFORMITY DATA SHEET

COMPOUND IRT Methyl Ethyl Ketone

EXPOSURE ROOM NUMBER: 436

TPV MEASUREMENTS

CHAMBER: #6/400 ppm			#7/1000 ppm			#8/3000 ppm						
DATE: 7/23/88			7/23/88			7/24/88						
SAMPLE PORT	MONITOR READING	% of Mean	MONITOR READING	% of Mean		MONITOR READING	% of Mean		MONITOR READING	% of Mean	MONITOR READING	% of Mean
BACK: 1B	85580.0	99.8%	223800.0	99.1%								
2B	85260.0	99.4%	225200.0	99.7%	669000.0	100.0%						
3B	85280.0	99.4%	224900.0	99.5%	673800.0	100.7%						
4B	86360.0	100.7%	226600.0	100.3%	672400.0	100.5%						
5B												
6B												
FRONT: 1F												
2F	85740.0	100.0%	226800.0	100.4%	667600.0	99.8%						
3F	85940.0	100.2%	227700.0	100.8%	667400.0	99.8%						
4F	86180.0	100.5%	226600.0	100.3%	663800.0	99.2%						
5F												
6F												
MEAN:	85762.9	100.0%	225942.9	100.0%	669000.0	100.0%						
TPV:	424.65	0.5%	1348.90	0.6%	3637.58	0.5%						
BPV:	//////////	0.5%	//////////	0.3%	//////////	0.5%	//////////		//////////		//////////	

WPV MEASUREMENTS

IN-LINE 1st	85580.0	100.0%	223800.0	99.5%	669000.0	99.7%			
2nd	85500.0	99.9%	225000.0	100.0%	672200.0	100.1%			
3rd	85720.0	100.1%	226200.0	100.5%	672400.0	100.2%			
MEAN:	85600.0	100.0%	225000.0	100.0%	671200.0	100.0%			
WPV:	111.36	0.1%	1200.00	0.5%	1907.88	0.3%			

INLET AND EXHAUST MEASUREMENTS

Inlet	82220.0		225500.0		672400.0			
Exhaust	84260.0		215700.0		663000.0			
% Difference:	-2.5%		4.3%		1.4%			

MONITOR TYPE: GC

SERIAL # : N809422

MONITOR DATA LOCATION: Data found with daily data file.

COMMENTS: With animals

ENTERED BY: Lynn Trent

DATE: 7/26/88

REVIEWED BY: RJ Weigel

DATE: 8/29/88

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: Room

/Concentration

Range=0.00E+0 to 5.00E+0

Date	Mean	Std Dev	Maximum	Minimum	N	N in	% N in
20 Jul 1988	6.59E-02	4.258E-02	1.46E-01	0.00E+00	23	23	100.0%
21 Jul 1988	4.55E-02	4.062E-02	1.28E-01	0.00E+00	20	20	100.0%
22 Jul 1988	1.73E-02	3.810E-02	1.37E-01	0.00E+00	26	26	100.0%
23 Jul 1988	3.73E-02	4.845E-02	1.37E-01	0.00E+00	16	16	100.0%
24 Jul 1988	1.87E-02	3.852E-02	1.05E-01	0.00E+00	9	9	100.0%
25 Jul 1988	0.00E+00	0.000E+00	0.00E+00	0.00E+00	13	13	100.0%
26 Jul 1988	0.00E+00	0.000E+00	0.00E+00	0.00E+00	9	9	100.0%
27 Jul 1988	2.75E-02	1.347E-01	6.88E-01	0.00E+00	26	26	100.0%
28 Jul 1988	5.64E-03	1.832E-02	7.29E-02	0.00E+00	21	21	100.0%
29 Jul 1988	2.73E-02	5.079E-02	1.59E-01	0.00E+00	22	22	100.0%
30 Jul 1988	3.44E-02	6.552E-02	2.46E-01	0.00E+00	25	25	100.0%
31 Jul 1988	3.83E-03	1.113E-02	4.55E-02	0.00E+00	25	25	100.0%
Summary	2.57E-02	6.068E-02	6.88E-01	0.00E+00	235	235	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 0 ppm chamber

/Concentration

Range=0.00E+0 to 5.00E+0

Date	Mean	Std Dev	Maximum	Minimum	N	N in	% N in
20 Jul 1988	1.10E-02	2.323E-02	7.74E-02	0.00E+00	19	19	100.0%
21 Jul 1988	7.18E-03	1.818E-02	7.29E-02	0.00E+00	26	26	100.0%
22 Jul 1988	1.20E-03	3.340E-03	1.37E-02	0.00E+00	19	19	100.0%
23 Jul 1988	1.21E-03	3.637E-03	1.37E-02	0.00E+00	15	15	100.0%
24 Jul 1988	0.00E+00	0.000E+00	0.00E+00	0.00E+00	11	11	100.0%
25 Jul 1988	0.00E+00	0.000E+00	0.00E+00	0.00E+00	14	14	100.0%
26 Jul 1988	0.00E+00	0.000E+00	0.00E+00	0.00E+00	15	15	100.0%
27 Jul 1988	1.40E-03	4.949E-03	1.82E-02	0.00E+00	26	26	100.0%
28 Jul 1988	0.00E+00	0.000E+00	0.00E+00	0.00E+00	26	26	100.0%
29 Jul 1988	0.00E+00	0.000E+00	0.00E+00	0.00E+00	23	23	100.0%
30 Jul 1988	0.00E+00	0.000E+00	0.00E+00	0.00E+00	25	25	100.0%
31 Jul 1988	0.00E+00	0.000E+00	0.00E+00	0.00E+00	24	24	100.0%
Summary	1.95E-03	9.492E-03	7.74E-02	0.00E+00	243	243	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 18 Jul 1988 through 31 Jul 1988

Summary Data for: Hold chamber

/Concentration

Range=0.00E+0 to 5.00E+0

Date	Mean	Std Dev	Maximum	Minimum	N	N in	% N in
18 Jul 1988							
19 Jul 1988							
20 Jul 1988	8.20E-03	1.197E-02	3.64E-02	0.00E+00	20	20	100.0%
21 Jul 1988	1.63E-03	2.264E-03	4.55E-03	0.00E+00	14	14	100.0%
22 Jul 1988	No animals present in the chamber.						
23 Jul 1988							
24 Jul 1988							
25 Jul 1988							
26 Jul 1988							
27 Jul 1988							
28 Jul 1988							
29 Jul 1988							
30 Jul 1988	0.00E+00	0.000E+00	0.00E+00	0.00E+00	21	21	100.0%
31 Jul 1988	0.00E+00	0.000E+00	0.00E+00	0.00E+00	25	25	100.0%
Summary	2.33E-03	6.873E-03	3.64E-02	0.00E+00	80	80	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 400 ppm chamber

/Concentration

Range=3.60E+2 to 4.40E+2

Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	3.99E+02	99.8%	9.694E+00	2.4%	4.20E+02	3.84E+02	20	20	100.0%
21 Jul 1988	3.96E+02	98.9%	1.217E+01	3.1%	4.08E+02	3.69E+02	22	22	100.0%
22 Jul 1988	4.00E+02	100.1%	1.296E+01	3.2%	4.39E+02	3.73E+02	23	23	100.0%
23 Jul 1988	3.88E+02	97.1%	1.117E+01	2.9%	3.99E+02	3.52E+02	17	16	94.1%
24 Jul 1988	3.99E+02	99.7%	6.699E+00	1.7%	4.10E+02	3.84E+02	18	18	100.0%
25 Jul 1988	4.00E+02	100.0%	6.608E+00	1.7%	4.13E+02	3.90E+02	12	12	100.0%
26 Jul 1988	3.93E+02	98.3%	9.242E+00	2.4%	4.12E+02	3.69E+02	22	22	100.0%
27 Jul 1988	3.99E+02	99.7%	4.484E+00	1.1%	4.09E+02	3.92E+02	21	21	100.0%
28 Jul 1988	4.00E+02	100.1%	5.292E+00	1.3%	4.09E+02	3.83E+02	20	20	100.0%
29 Jul 1988	4.01E+02	100.4%	7.854E+00	2.0%	4.13E+02	3.84E+02	19	19	100.0%
30 Jul 1988	3.99E+02	99.7%	5.282E+00	1.3%	4.11E+02	3.87E+02	22	22	100.0%
31 Jul 1988	4.06E+02	101.4%	5.263E+00	1.3%	4.20E+02	3.98E+02	21	21	100.0%
Summary	3.98E+02	99.6%	9.397E+00	2.4%	4.39E+02	3.52E+02	237	236	99.6%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 1000 ppm chamber

/Concentration

Range=9.00E+2 to 1.10E+3

Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	1.01E+03	101.2%	2.737E+01	2.7%	1.07E+03	9.73E+02	21	21	100.0%
21 Jul 1988	9.92E+02	99.2%	2.828E+01	2.9%	1.02E+03	9.21E+02	23	23	100.0%
22 Jul 1988	1.01E+03	101.2%	3.584E+01	3.5%	1.10E+03	8.94E+02	23	22	95.7%
23 Jul 1988	1.02E+03	102.4%	2.992E+01	2.9%	1.14E+03	9.91E+02	18	17	94.4%
24 Jul 1988	1.02E+03	102.1%	1.343E+01	1.3%	1.05E+03	9.94E+02	19	19	100.0%
25 Jul 1988	1.00E+03	100.3%	1.843E+01	1.8%	1.04E+03	9.79E+02	11	11	100.0%
26 Jul 1988	1.01E+03	100.5%	2.480E+01	2.5%	1.05E+03	9.65E+02	21	21	100.0%
27 Jul 1988	1.01E+03	100.6%	9.854E+00	1.0%	1.04E+03	9.94E+02	20	20	100.0%
28 Jul 1988	1.00E+03	100.2%	6.578E+00	.7%	1.02E+03	9.94E+02	19	19	100.0%
29 Jul 1988	1.01E+03	100.6%	1.450E+01	1.4%	1.02E+03	9.75E+02	19	19	100.0%
30 Jul 1988	1.04E+03	104.0%	3.433E+01	3.3%	1.13E+03	1.01E+03	22	20	90.9%
31 Jul 1988	1.04E+03	103.9%	9.058E+00	.9%	1.06E+03	1.03E+03	22	22	100.0%
Summary	1.01E+03	101.4%	2.754E+01	2.7%	1.14E+03	8.94E+02	238	234	98.3%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 3000 ppm chamber

/Concentration

Range=2.70E+3 to 3.30E+3

Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	3.02E+03	100.8%	8.252E+01	2.7%	3.19E+03	2.91E+03	21	21	100.0%
21 Jul 1988	2.96E+03	98.6%	5.040E+01	1.7%	3.02E+03	2.83E+03	23	23	100.0%
22 Jul 1988	2.99E+03	99.6%	1.347E+02	4.5%	3.26E+03	2.49E+03	23	22	95.7%
23 Jul 1988	3.10E+03	103.4%	2.400E+01	.8%	3.13E+03	3.03E+03	18	18	100.0%
24 Jul 1988	3.07E+03	102.2%	3.898E+01	1.3%	3.15E+03	3.01E+03	18	18	100.0%
25 Jul 1988	3.01E+03	100.4%	4.591E+01	1.5%	3.12E+03	2.92E+03	11	11	100.0%
26 Jul 1988	2.98E+03	99.5%	8.351E+01	2.8%	3.16E+03	2.90E+03	22	22	100.0%
27 Jul 1988	3.00E+03	100.1%	2.051E+01	.7%	3.04E+03	2.97E+03	21	21	100.0%
28 Jul 1988	3.02E+03	100.7%	4.586E+01	1.5%	3.13E+03	2.97E+03	20	20	100.0%
29 Jul 1988	3.01E+03	100.4%	3.959E+01	1.3%	3.06E+03	2.91E+03	20	20	100.0%
30 Jul 1988	3.00E+03	100.1%	2.845E+01	.9%	3.05E+03	2.93E+03	22	22	100.0%
31 Jul 1988	3.10E+03	103.2%	9.193E+01	3.0%	3.34E+03	3.03E+03	22	20	90.9%
Summary	3.02E+03	100.7%	7.936E+01	2.6%	3.34E+03	2.49E+03	241	238	98.8%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: Standard Gas

/Concentration

Range=9.79E+2 to 1.20E+3

Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	1.08E+03	98.9%	1.380E+02	12.8%	1.11E+03	3.10E+02	33	32	97.0%
21 Jul 1988	1.10E+03	101.1%	1.465E+00	.1%	1.10E+03	1.10E+03	24	24	100.0%
22 Jul 1988	1.10E+03	101.1%	1.090E+00	.1%	1.10E+03	1.10E+03	22	22	100.0%
23 Jul 1988	1.10E+03	101.1%	1.167E+00	.1%	1.10E+03	1.10E+03	16	16	100.0%
24 Jul 1988	1.10E+03	101.1%	2.144E+00	.2%	1.10E+03	1.10E+03	19	19	100.0%
25 Jul 1988	1.10E+03	100.9%	2.290E+00	.2%	1.10E+03	1.10E+03	12	12	100.0%
26 Jul 1988	1.10E+03	100.9%	1.604E+00	.1%	1.10E+03	1.10E+03	23	23	100.0%
27 Jul 1988	1.10E+03	101.1%	1.270E+00	.1%	1.10E+03	1.10E+03	22	22	100.0%
28 Jul 1988	1.10E+03	101.1%	1.005E+00	.1%	1.10E+03	1.10E+03	20	20	100.0%
29 Jul 1988	1.10E+03	101.1%	1.890E+00	.2%	1.10E+03	1.10E+03	36	36	100.0%
30 Jul 1988	1.10E+03	101.1%	1.592E+00	.1%	1.10E+03	1.10E+03	23	23	100.0%
31 Jul 1988	1.10E+03	100.9%	1.602E+00	.1%	1.10E+03	1.09E+03	23	23	100.0%
Summary	1.10E+03	100.8%	4.800E+01	4.4%	1.11E+03	3.10E+02	273	272	99.6%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 0 ppm chamber

/Exhaust Air Flow

Range= 12.0 to 18.0

Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	15.6	104.0%	.04	.3%	15.7	15.5	7	7	100.0%
21 Jul 1988	15.7	104.4%	.03	.2%	15.7	15.6	7	7	100.0%
22 Jul 1988	15.6	104.3%	.03	.2%	15.7	15.6	8	8	100.0%
23 Jul 1988	15.6	104.2%	.04	.3%	15.7	15.5	8	8	100.0%
24 Jul 1988	15.7	104.4%	.02	.1%	15.7	15.6	8	8	100.0%
25 Jul 1988	15.7	104.5%	.03	.2%	15.7	15.6	7	7	100.0%
26 Jul 1988	15.7	104.5%	.02	.2%	15.7	15.6	8	8	100.0%
27 Jul 1988	15.6	103.8%	.05	.3%	15.7	15.5	8	8	100.0%
28 Jul 1988	15.6	104.0%	.05	.3%	15.6	15.5	8	8	100.0%
29 Jul 1988	15.7	104.4%	.03	.2%	15.7	15.6	8	8	100.0%
30 Jul 1988	15.6	103.7%	.02	.2%	15.6	15.5	8	8	100.0%
31 Jul 1988	15.5	103.5%	.04	.2%	15.6	15.5	7	7	100.0%
Summary	15.6	104.1%	.06	.4%	15.7	15.5	92	92	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 18 Jul 1988 through 2 Aug 1988

Summary Data for: Hold chamber		/Exhaust Air Flow			Range= 12.0 to 18.0				
Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
18 Jul 1988	15.4	102.7%	.01	.1%	15.4	15.4	6	6	100.0%
19 Jul 1988	15.3	102.1%	.06	.4%	15.4	15.2	8	8	100.0%
20 Jul 1988	15.2	101.5%	.07	.4%	15.3	15.2	8	8	100.0%
21 Jul 1988	15.2	101.1%	.03	.2%	15.2	15.1	7	7	100.0%
22 Jul 1988	No animals present in the chamber.								
23 Jul 1988									
24 Jul 1988									
25 Jul 1988									
26 Jul 1988									
27 Jul 1988									
28 Jul 1988									
29 Jul 1988									
30 Jul 1988	15.2	101.4%	.03	.2%	15.2	15.2	7	7	100.0%
31 Jul 1988	15.2	101.7%	.02	.1%	15.3	15.2	8	8	100.0%
1 Aug 1988	15.2	101.5%	.04	.3%	15.3	15.2	7	7	100.0%
2 Aug 1988	15.2	101.5%	.02	.2%	15.3	15.2	8	8	100.0%
Summary	15.3	101.7%	.08	.5%	15.4	15.1	59	59	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 400 ppm chamber /Exhaust Air Flow					Range= 12.0 to 18.0				
Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	15.3	101.8%	.04	.3%	15.3	15.2	7	7	100.0%
21 Jul 1988	15.3	102.0%	.04	.3%	15.4	15.2	7	7	100.0%
22 Jul 1988	15.3	101.9%	.05	.3%	15.4	15.2	8	8	100.0%
23 Jul 1988	15.3	101.8%	.03	.2%	15.3	15.2	8	8	100.0%
24 Jul 1988	15.3	102.0%	.03	.2%	15.3	15.3	8	8	100.0%
25 Jul 1988	15.3	102.1%	.04	.3%	15.4	15.3	7	7	100.0%
26 Jul 1988	15.3	101.9%	.05	.3%	15.4	15.2	8	8	100.0%
27 Jul 1988	15.2	101.3%	.05	.3%	15.3	15.1	8	8	100.0%
28 Jul 1988	15.2	101.4%	.05	.3%	15.3	15.1	8	8	100.0%
29 Jul 1988	15.2	101.5%	.03	.2%	15.3	15.2	8	8	100.0%
30 Jul 1988	15.2	101.3%	.03	.2%	15.2	15.1	8	8	100.0%
31 Jul 1988	15.2	101.3%	.03	.2%	15.2	15.1	8	8	100.0%
Summary	15.3	101.7%	.06	.4%	15.4	15.1	93	93	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 1000 ppm chamber /Exhaust Air Flow					Range= 12.0 to 18.0				
Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	15.1	100.9%	.06	.4%	15.2	15.1	7	7	100.0%
21 Jul 1988	15.2	101.3%	.05	.3%	15.3	15.1	7	7	100.0%
22 Jul 1988	15.2	101.2%	.08	.5%	15.3	15.1	8	8	100.0%
23 Jul 1988	15.2	101.1%	.06	.4%	15.2	15.0	8	8	100.0%
24 Jul 1988	15.2	101.5%	.04	.3%	15.3	15.1	8	8	100.0%
25 Jul 1988	15.2	101.6%	.08	.6%	15.3	15.2	7	7	100.0%
26 Jul 1988	15.2	101.3%	.07	.5%	15.3	15.1	8	8	100.0%
27 Jul 1988	15.1	100.9%	.03	.2%	15.2	15.1	8	8	100.0%
28 Jul 1988	15.2	101.2%	.04	.3%	15.2	15.1	8	8	100.0%
29 Jul 1988	15.2	101.1%	.05	.3%	15.2	15.1	8	8	100.0%
30 Jul 1988	15.1	100.7%	.05	.3%	15.2	15.0	8	8	100.0%
31 Jul 1988	15.1	100.7%	.05	.3%	15.2	15.0	8	8	100.0%
Summary	15.2	101.1%	.07	.5%	15.3	15.0	93	93	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 3000 ppm chamber /Exhaust Air Flow					Range= 12.0 to 18.0				
Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	15.0	99.8%	.07	.5%	15.1	14.9	7	7	100.0%
21 Jul 1988	15.0	100.2%	.07	.5%	15.1	15.0	7	7	100.0%
22 Jul 1988	15.0	100.1%	.07	.5%	15.1	14.9	8	8	100.0%
23 Jul 1988	15.0	99.9%	.05	.3%	15.1	14.9	8	8	100.0%
24 Jul 1988	15.0	100.3%	.07	.5%	15.1	15.0	8	8	100.0%
25 Jul 1988	15.1	100.4%	.06	.4%	15.1	15.0	7	7	100.0%
26 Jul 1988	15.0	100.2%	.06	.4%	15.1	15.0	8	8	100.0%
27 Jul 1988	14.9	99.6%	.04	.3%	15.0	14.9	8	8	100.0%
28 Jul 1988	15.0	100.0%	.07	.5%	15.1	14.9	8	8	100.0%
29 Jul 1988	15.0	99.7%	.06	.4%	15.0	14.9	8	8	100.0%
30 Jul 1988	14.9	99.4%	.04	.3%	15.0	14.9	8	8	100.0%
31 Jul 1988	14.9	99.6%	.03	.2%	15.0	14.9	8	8	100.0%
Summary	15.0	99.9%	.07	.5%	15.1	14.9	93	93	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 0 ppm chamber

/Relative Humidity

Range= 40.0 to 70.0

Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	58.1	105.7%	4.74	8.2%	68.0	54.0	7	7	100.0%
21 Jul 1988	56.1	102.1%	3.18	5.7%	60.0	52.0	7	7	100.0%
22 Jul 1988	55.9	101.6%	3.18	5.7%	61.0	52.0	8	8	100.0%
23 Jul 1988	54.0	98.2%	2.14	4.0%	57.0	51.0	8	8	100.0%
24 Jul 1988	54.4	98.9%	2.67	4.9%	58.0	50.0	8	8	100.0%
25 Jul 1988	55.7	101.3%	3.15	5.6%	58.0	49.0	7	7	100.0%
26 Jul 1988	57.9	105.2%	3.00	5.2%	62.0	53.0	8	8	100.0%
27 Jul 1988	58.4	106.1%	1.60	2.7%	61.0	56.0	8	8	100.0%
28 Jul 1988	59.0	107.3%	1.51	2.6%	61.0	57.0	8	8	100.0%
29 Jul 1988	57.2	104.0%	1.86	3.2%	59.0	54.0	9	9	100.0%
30 Jul 1988	57.4	104.3%	1.77	3.1%	60.0	55.0	8	8	100.0%
31 Jul 1988	56.6	103.0%	1.60	2.8%	60.0	55.0	8	8	100.0%
Summary	56.7	103.2%	2.90	5.1%	68.0	49.0	94	94	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 18 Jul 1988 through 2 Aug 1988

Summary Data for: Hold chamber /Relative Humidity					Range= 40.0 to 70.0				
Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
18 Jul 1988	57.4	104.4%	6.66	11.6%	64.0	48.0	5	5	100.0%
19 Jul 1988	58.3	105.9%	4.40	7.6%	63.0	51.0	8	8	100.0%
20 Jul 1988	54.4	98.9%	3.58	6.6%	61.0	50.0	8	8	100.0%
21 Jul 1988	50.6	92.0%	2.77	5.5%	54.0	47.0	8	8	100.0%
22 Jul 1988	No animals present in the chamber.								
23 Jul 1988									
24 Jul 1988									
25 Jul 1988									
26 Jul 1988									
27 Jul 1988									
28 Jul 1988									
29 Jul 1988									
30 Jul 1988	54.9	99.7%	5.64	10.3%	61.0	46.0	7	7	100.0%
31 Jul 1988	59.9	108.9%	1.81	3.0%	61.0	56.0	8	8	100.0%
1 Aug 1988	61.1	111.1%	2.75	4.5%	65.0	58.0	8	8	100.0%
2 Aug 1988	61.0	110.9%	2.27	3.7%	65.0	58.0	8	8	100.0%
Summary	57.2	104.0%	5.06	8.8%	65.0	46.0	60	60	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 400 ppm chamber

/Relative Humidity

Range= 40.0 to 70.0

Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	46.4	84.4%	.53	1.2%	47.0	46.0	7	7	100.0%
21 Jul 1988	50.4	91.6%	2.00	4.0%	53.0	47.0	8	8	100.0%
22 Jul 1988	53.0	96.4%	2.14	4.0%	56.0	50.0	8	8	100.0%
23 Jul 1988	51.7	94.0%	2.87	5.6%	56.0	48.0	7	7	100.0%
24 Jul 1988	50.3	91.4%	3.41	6.8%	54.0	44.0	8	8	100.0%
25 Jul 1988	55.9	101.6%	4.63	8.3%	60.0	47.0	7	7	100.0%
26 Jul 1988	56.3	102.3%	2.96	5.3%	61.0	52.0	8	8	100.0%
27 Jul 1988	55.0	100.0%	3.46	6.3%	59.0	49.0	9	9	100.0%
28 Jul 1988	58.9	107.0%	2.23	3.8%	62.0	55.0	8	8	100.0%
29 Jul 1988	59.3	107.9%	2.55	4.3%	62.0	56.0	9	9	100.0%
30 Jul 1988	57.9	105.2%	2.64	4.6%	61.0	53.0	8	8	100.0%
31 Jul 1988	55.7	101.4%	2.55	4.6%	60.0	51.0	8	8	100.0%
Summary	54.4	98.9%	4.58	8.4%	62.0	44.0	95	95	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 1000 ppm chamber /Relative Humidity					Range= 40.0 to 70.0				
Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	54.4	99.0%	3.15	5.8%	58.0	50.0	7	7	100.0%
21 Jul 1988	55.0	100.0%	3.38	6.1%	59.0	50.0	8	8	100.0%
22 Jul 1988	54.4	98.9%	2.77	5.1%	58.0	50.0	8	8	100.0%
23 Jul 1988	53.0	96.4%	3.61	6.8%	58.0	50.0	7	7	100.0%
24 Jul 1988	52.0	94.5%	3.96	7.6%	58.0	46.0	8	8	100.0%
25 Jul 1988	53.4	97.1%	3.60	6.7%	59.0	49.0	7	7	100.0%
26 Jul 1988	53.7	97.7%	5.34	9.9%	62.0	46.0	8	8	100.0%
27 Jul 1988	54.0	98.2%	5.04	9.3%	60.0	46.0	8	8	100.0%
28 Jul 1988	57.5	104.5%	2.78	4.8%	61.0	53.0	8	8	100.0%
29 Jul 1988	57.2	104.0%	2.73	4.8%	61.0	54.0	9	9	100.0%
30 Jul 1988	57.0	103.6%	3.21	5.6%	60.0	51.0	8	8	100.0%
31 Jul 1988	55.2	100.5%	3.77	6.8%	62.0	49.0	8	8	100.0%
Summary	54.8	99.7%	3.86	7.1%	62.0	46.0	94	94	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 3000 ppm chamber /Relative Humidity				Range= 40.0 to 70.0					
Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	53.0	96.4%	3.27	6.2%	56.0	48.0	7	7	100.0%
21 Jul 1988	50.1	91.2%	4.06	8.1%	54.0	44.0	7	7	100.0%
22 Jul 1988	52.1	94.8%	3.52	6.8%	57.0	47.0	8	8	100.0%
23 Jul 1988	50.7	92.2%	4.15	8.2%	56.0	45.0	7	7	100.0%
24 Jul 1988	50.1	91.1%	3.83	7.6%	57.0	46.0	8	8	100.0%
25 Jul 1988	51.1	93.0%	3.18	6.2%	54.0	45.0	7	7	100.0%
26 Jul 1988	53.4	97.0%	4.75	8.9%	58.0	46.0	8	8	100.0%
27 Jul 1988	55.6	101.1%	4.96	8.9%	62.0	47.0	8	8	100.0%
28 Jul 1988	59.3	107.7%	2.43	4.1%	62.0	56.0	8	8	100.0%
29 Jul 1988	56.3	102.4%	1.32	2.3%	58.0	55.0	9	9	100.0%
30 Jul 1988	59.1	107.5%	2.85	4.8%	62.0	54.0	8	8	100.0%
31 Jul 1988	54.6	99.3%	2.50	4.6%	60.0	52.0	8	8	100.0%
Summary	53.9	98.1%	4.55	8.4%	62.0	44.0	93	93	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: Room		/Temperature			Range= 69.0 to 75.0					
Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in	
20 Jul 1988	72.6	100.8%	.98	1.3%	73.8	71.1	9	9	100.0%	
21 Jul 1988	73.7	102.4%	.98	1.3%	74.9	71.8	8	8	100.0%	
22 Jul 1988	74.4	103.3%	.41	.6%	75.0	73.7	8	8	100.0%	
23 Jul 1988	73.5	102.1%	1.12	1.5%	74.5	71.4	8	8	100.0%	
24 Jul 1988	74.3	103.2%	.36	.5%	74.7	73.7	9	9	100.0%	
25 Jul 1988	73.9	102.7%	.24	.3%	74.3	73.7	8	8	100.0%	
26 Jul 1988	73.9	102.6%	.32	.4%	74.4	73.5	9	9	100.0%	
27 Jul 1988	73.7	102.3%	.40	.5%	74.2	72.8	9	9	100.0%	
28 Jul 1988	73.8	102.5%	.31	.4%	74.2	73.1	9	9	100.0%	
29 Jul 1988	73.9	102.7%	.33	.4%	74.3	73.2	9	9	100.0%	
30 Jul 1988	73.9	102.6%	.27	.4%	74.3	73.4	8	8	100.0%	
31 Jul 1988	74.1	102.9%	.16	.2%	74.2	73.8	7	7	100.0%	
Summary	73.8	102.5%	.71	1.0%	75.0	71.1	101	101	100.0%	

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 0 ppm chamber

/Temperature

Range= 72.0 to 78.0

Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	73.6	98.2%	.79	1.1%	74.9	72.4	7	7	100.0%
21 Jul 1988	74.9	99.9%	.98	1.3%	76.2	73.4	8	8	100.0%
22 Jul 1988	75.9	101.2%	.23	.3%	76.2	75.6	8	8	100.0%
23 Jul 1988	75.8	101.0%	.54	.7%	76.3	75.0	8	8	100.0%
24 Jul 1988	75.8	101.1%	.52	.7%	76.6	75.0	9	9	100.0%
25 Jul 1988	75.3	100.5%	.52	.7%	76.0	74.6	7	7	100.0%
26 Jul 1988	74.9	99.8%	.61	.8%	76.0	74.1	8	8	100.0%
27 Jul 1988	75.2	100.2%	.59	.8%	76.0	74.4	8	8	100.0%
28 Jul 1988	75.4	100.5%	.36	.5%	75.9	75.0	8	8	100.0%
29 Jul 1988	75.4	100.5%	.49	.7%	76.0	74.8	9	9	100.0%
30 Jul 1988	75.4	100.5%	.25	.3%	75.9	75.2	8	8	100.0%
31 Jul 1988	75.1	100.1%	.08	.1%	75.2	75.0	8	8	100.0%
Summary	75.2	100.3%	.76	1.0%	76.6	72.4	96	96	100.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 18 Jul 1988 through 2 Aug 1988

Summary Data for: Hold chamber		/Temperature		Range= 72.0 to 78.0					
Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
18 Jul 1988	74.0	98.7%	.49	.7%	74.7	73.5	6	6	100.0%
19 Jul 1988	74.0	98.7%	.28	.4%	74.5	73.7	8	8	100.0%
20 Jul 1988	75.1	100.2%	.98	1.3%	76.0	73.6	9	9	100.0%
21 Jul 1988	74.9	99.8%	.90	1.2%	76.3	73.8	8	8	100.0%
22 Jul 1988	No animals present in the chamber.								
23 Jul 1988									
24 Jul 1988									
25 Jul 1988									
26 Jul 1988									
27 Jul 1988									
28 Jul 1988									
29 Jul 1988									
30 Jul 1988	75.7	101.0%	.20	.3%	76.1	75.5	7	7	100.0%
31 Jul 1988	77.8	103.8%	.64	.8%	78.3	76.4	8	4	50.0%
1 Aug 1988	77.0	102.7%	.59	.8%	78.2	76.5	7	6	85.7%
2 Aug 1988	75.0	100.0%	.72	1.0%	76.6	74.5	8	8	100.0%
Summary	75.5	100.6%	1.42	1.9%	78.3	73.5	61	56	91.8%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 400 ppm chamber /Temperature					Range= 72.0 to 78.0				
Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	72.4	96.5%	.62	.9%	73.1	71.1	7	6	85.7%
21 Jul 1988	73.5	98.0%	.72	1.0%	74.5	72.3	8	8	100.0%
22 Jul 1988	74.2	99.0%	.18	.2%	74.4	74.0	8	8	100.0%
23 Jul 1988	74.1	98.8%	.37	.5%	74.6	73.6	8	8	100.0%
24 Jul 1988	74.1	98.8%	.38	.5%	74.8	73.6	9	9	100.0%
25 Jul 1988	73.9	98.5%	.22	.3%	74.2	73.6	8	8	100.0%
26 Jul 1988	73.7	98.3%	.38	.5%	74.3	73.2	9	9	100.0%
27 Jul 1988	73.6	98.2%	.42	.6%	74.4	73.3	8	8	100.0%
28 Jul 1988	73.7	98.3%	.25	.3%	74.0	73.4	8	8	100.0%
29 Jul 1988	73.9	98.5%	.29	.4%	74.3	73.5	9	9	100.0%
30 Jul 1988	73.9	98.6%	.34	.5%	74.4	73.4	8	8	100.0%
31 Jul 1988	73.7	98.2%	.17	.2%	74.0	73.4	8	8	100.0%
Summary	73.7	98.3%	.57	.8%	74.8	71.1	98	97	99.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 1000 ppm chamber /Temperature

Range= 72.0 to 78.0

Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	72.6	96.8%	.78	1.1%	73.8	71.4	7	6	85.7%
21 Jul 1988	73.6	98.2%	.93	1.3%	75.0	72.3	8	8	100.0%
22 Jul 1988	74.5	99.4%	.29	.4%	75.0	74.1	8	8	100.0%
23 Jul 1988	74.3	99.1%	.53	.7%	75.0	73.5	8	8	100.0%
24 Jul 1988	74.3	99.0%	.49	.7%	75.0	73.6	9	9	100.0%
25 Jul 1988	73.9	98.5%	.48	.6%	74.6	73.2	7	7	100.0%
26 Jul 1988	73.8	98.4%	.56	.8%	74.6	73.1	9	9	100.0%
27 Jul 1988	74.0	98.6%	.46	.6%	74.6	73.3	8	8	100.0%
28 Jul 1988	74.6	99.5%	.22	.3%	74.9	74.4	8	8	100.0%
29 Jul 1988	74.6	99.5%	.27	.4%	75.0	74.2	9	9	100.0%
30 Jul 1988	74.5	99.3%	.36	.5%	75.0	74.0	8	8	100.0%
31 Jul 1988	74.2	98.9%	.17	.2%	74.5	74.0	8	8	100.0%
Summary	74.1	98.8%	.71	1.0%	75.0	71.4	97	96	99.0%

Daily Summation For IRT - Methyl Ethyl Ketone (Mice)

From 20 Jul 1988 through 31 Jul 1988

Summary Data for: 3000 ppm chamber

/Temperature

Range= 72.0 to 78.0

Date	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	N	N in	% N in
20 Jul 1988	72.8	97.1%	.82	1.1%	74.0	71.4	7	6	85.7%
21 Jul 1988	74.0	98.7%	1.00	1.4%	75.4	72.6	8	8	100.0%
22 Jul 1988	74.9	99.9%	.35	.5%	75.5	74.4	8	8	100.0%
23 Jul 1988	74.7	99.6%	.65	.9%	75.4	73.8	8	8	100.0%
24 Jul 1988	74.7	99.6%	.66	.9%	75.8	73.9	9	9	100.0%
25 Jul 1988	74.2	99.0%	.51	.7%	75.0	73.6	7	7	100.0%
26 Jul 1988	73.9	98.5%	.52	.7%	75.0	73.1	9	9	100.0%
27 Jul 1988	74.4	99.2%	.64	.9%	75.4	73.6	8	8	100.0%
28 Jul 1988	74.6	99.5%	.36	.5%	75.1	74.2	8	8	100.0%
29 Jul 1988	74.7	99.6%	.41	.5%	75.3	74.2	9	9	100.0%
30 Jul 1988	74.5	99.3%	.21	.3%	74.9	74.1	8	8	100.0%
31 Jul 1988	74.4	99.3%	.16	.2%	74.7	74.1	8	8	100.0%
Summary	74.3	99.1%	.74	1.0%	75.8	71.4	97	96	99.0%

EXPOSURE OPERATION DISCUSSION SHEET

INCLUDES DISCUSSIONS AND/OR EXPLANATIONS OF PROBLEMS AFFECTING ANIMAL ENVIRONMENT AND EXPOSURES. EXPLANATIONS ARE INCLUDED FOR DATA IN WHICH THERE WERE EXCURSIONS OF DAILY MEAN OR STANDARD DEVIATION BEYOND ALLOWABLE OPERATING LIMITS OR EXCURSIONS OF INDIVIDUAL DATUM BEYOND CRITICAL LIMITS.

STUDY: IRT Methyl Ethyl Ketone Study

REPORTING PERIOD: July 18-Aug 2, 1988

NOTE: 24 Hour Data Collection Period extends from ~5:00 a.m. to ~5:00 a.m.

COMPILED BY: R.J. Weigel

RJW

DATE: 8/9/88

CHAMBER CONCENTRATION

<u>DATE</u>	<u>DISCUSSION OR EXPLANATION</u>

7/20/88	Scheduled time to reach T ₉₀ is 09:00. On this day, it was not reached until 09:10 due to problem with the executive computer.

7/28/88	Scheduled time to reach T ₉₀ is 09:00. On this day, it was not reached until 09:28 due to air leak problem with an exposure chamber.

TEMPERATURE & RELATIVE HUMIDITY

<u>DATE</u>	<u>DISCUSSION OR EXPLANATION</u>

No problems or excursions to report during this period.

CHAMBER FLOW & VACUUM

<u>DATE</u>	<u>DISCUSSION OR EXPLANATION</u>

No problems or excursions to report during this period.

APPENDIX C

DEVELOPMENTAL TOXICOLOGY DATA

----- 0 ppm Methyl Ethyl Ketone -----											
MATNO	Pre-study Wt (g)	0 dg Wt (g)	8 dg Wt (g)	9 dg Wt (g)	12 dg Wt (g)	15 dg Wt (g)	18 dg Wt (g)	Uter Wt (g)	Pregnant	Liver (g)	Kidney (g)
1103	25.8	25.6	27.1	26.5	27.2	27.2	27.674	0.127	0	1.444	0.378
1104	28.2	27.8	31.3	32.7	38.4	47.8	60.051	23.591	1	3.158	0.464
1113	25.2	23.5	26.0	28.7	34.5	40.4	48.602	17.079	1	2.281	0.417
1127	24.9	24.8	26.6	30.8	35.9	43.9	55.018	22.340	1	2.432	0.424
1135	25.9	24.9	26.0	26.6	27.5	28.0	26.397	0.109	0	1.745	0.407
1139	27.6	26.9	29.3	31.8	36.9	45.4	53.727	20.530	1	2.745	0.413
1182	24.5	25.4	27.2	27.4	27.4	27.5	27.202	0.202	0	1.696	0.424
1186	27.2	26.3	28.8	31.8	37.8	43.5	51.261	17.750	1	2.862	0.480
1189	23.6	23.9	25.6	26.5	25.4	27.0	28.081	0.108	0	1.719	0.465
1194	27.2	26.7	29.3	31.7	36.2	43.1	51.848	19.347	1	2.513	0.400
1211	28.0	27.1	29.7	33.8	39.2	45.9	54.909	20.249	1	2.535	0.490
1212	24.5	25.3	28.0	30.6	35.3	44.6	51.156	18.748	1	2.667	0.423
1226	27.8	27.3	30.9	33.0	39.4	48.6	57.736	23.337	1	3.247	0.481
1239	26.8	26.2	29.0	32.1	36.5	43.5	51.388	19.437	1	2.625	0.425
1247	22.5	24.7	27.2	29.5	33.3	40.2	47.337	17.509	1	2.415	0.421
1250	24.6	24.1	25.7	26.9	31.8	40.8	49.088	18.855	1	2.917	0.403
1256	28.2	27.6	29.8	32.3	37.7	45.6	56.234	22.266	1	3.007	0.456
1259	25.7	25.3	27.9	30.8	35.3	43.6	49.805	17.824	1	2.851	0.447
1279	28.1	27.8	31.2	34.0	42.1	52.0	62.981	25.798	1	3.305	0.433
1291	27.8	28.0	30.3	33.3	37.0	45.8	54.617	19.392	1	3.315	0.445
1297	26.0	26.6	27.1	29.1	33.9	41.8	49.441	18.050	1	2.798	0.394
1304	25.3	25.9	26.0	26.8	31.5	36.4	40.398	9.711	1	2.652	0.373
1313	28.4	25.8	28.1	30.4	35.6	42.4	50.215	18.370	1	2.684	0.390
1336	28.1	28.8	31.5	34.4	40.6	49.9	61.203	24.309	1	3.127	0.491
1354	28.9	25.6	26.2	26.3	27.4	25.8	25.844	0.150	0	1.806	0.389
1358	29.9	30.8	30.9	32.9	37.6	43.3	48.528	12.920	1	2.863	0.489
1360	25.0	23.9	28.0	31.6	38.1	46.1	53.467	21.570	1	2.211	0.406
1364	26.7	26.9	29.2	32.6	38.2	47.0	57.016	22.629	1	2.939	0.455
1382	25.2	25.5	28.1	31.7	37.7	47.2	57.050	23.899	1	3.642	0.436
1392	26.9	26.4	30.4	33.1	39.5	49.0	61.546	25.177	1	2.808	0.449
1404	28.1	26.0	26.9	28.3	28.0	28.6	28.298	0.174	0	1.567	0.430
1409	26.5	26.1	28.4	30.2	36.3	44.3	52.457	21.065	1	2.365	0.443

C.1

Pregnant: 1=Pregnant 0=Non-Pregnant

400 ppm Methyl Ethyl Ketone

MATNO	Pre-study Wt (g)	0 dg Wt (g)	6 dg Wt (g)	9 dg Wt (g)	12 dg Wt (g)	15 dg Wt (g)	18 dg Wt (g)	Uter Wt (g)	Pregnant	Liver (g)	Kidney (g)
1112	27.1	26.4	27.3	31.2	37.3	47.5	57.754	22.919	1	2.716	0.452
1119	27.4	27.0	31.3	32.4	35.9	42.0	49.306	13.543	1	2.911	0.491
1121	26.6	26.3	28.7	30.4	34.9	41.0	49.786	17.900	1	2.526	0.447
1149	25.6	26.1	28.2	31.1	36.9	45.7	55.260	21.293	1	2.856	0.497
1151	25.6	25.6	27.6	30.1	36.1	44.6	52.091	18.446	1	2.780	0.447
1166	26.2	25.1	27.3	27.0	27.3	27.5	26.097	0.125	0	1.824	0.413
1176	27.0	28.7	30.4	34.0	41.2	50.6	61.088	25.324	1	3.015	0.502
1183	26.5	26.9	29.8	33.5	39.5	47.5	59.985	24.449	1	3.172	0.392
1196	28.3	28.8	29.6	32.1	36.0	40.3	55.345	23.055	1	2.682	0.432
1207	29.4	29.1	28.9	30.3	30.4	30.5	29.246	0.151	0	1.558	0.402
1227	26.2	25.4	27.8	27.3	27.0	28.4	26.741	0.099	0	2.284	0.347
1254	27.0	26.5	27.6	29.7	29.3	30.3	28.579	0.129	0	1.824	0.431
1262	26.1	24.9	25.5	26.9	31.4	39.0	44.343	14.137	1	2.216	0.417
1299	23.4	24.5	25.2	26.3	28.5	28.3	25.298	0.140	0	1.378	0.375
1335	25.4	26.1	28.4	28.0	28.2	27.1	25.698	0.123	0	1.671	0.403
1339	26.6	27.4	29.0	33.1	37.8	46.3	55.001	22.889	1	2.393	0.412
1344	31.1	30.2	32.6	35.9	41.8	50.6	58.098	19.975	1	3.108	0.521
1352	24.7	24.8	26.9	29.6	35.4	42.9	50.432	20.339	1	2.171	0.417
1357	28.2	26.6	28.9	31.7	38.7	47.2	55.642	21.284	1	2.956	0.441
1359	28.8	28.9	30.0	32.1	37.2	44.3	51.337	17.270	1	3.373	0.477
1361	24.7	24.8	26.4	26.9	30.9	35.2	41.180	11.115	1	2.472	0.430
1368	25.3	23.7	25.6	29.1	34.4	41.5	50.125	20.449	1	2.082	0.435
1369	29.7	27.2	30.6	32.8	38.7	46.9	56.917	21.505	1	2.755	0.420
1370	25.9	26.6	28.2	31.5	36.6	44.3	52.506	21.209	1	2.144	0.420
1375	26.2	25.6	27.5	30.2	34.5	41.0	46.197	14.551	1	2.717	0.489
1376	26.2	25.7	25.7	26.1	25.1	25.3	24.373	0.260	0	1.483	0.373
1380	24.4	24.7	26.8	29.8	35.0	43.9	50.629	20.504	1	2.601	0.472
1396	24.9	24.2	26.2	28.9	33.5	41.3	45.748	15.487	1	2.664	0.387
1412	23.5	23.1	26.9	26.6	34.4	41.7	48.985	18.656	1	2.692	0.436
1430	27.0	26.8	29.7	32.9	37.4	45.1	51.240	18.568	1	2.704	0.538

Pregnant: 1=Pregnant 0=Non-Pregnant

----- 1000 ppm Methyl Ethyl Ketone -----

MATNO	Pre-study Wt (g)	0 dg Wt (g)	8 dg Wt (g)	9 dg Wt (g)	12 dg Wt (g)	15 dg Wt (g)	18 dg Wt (g)	Uter Wt (g)	Pregnant	Liver (g)	Kidney (g)
1106	28.4	25.8	27.4	28.5	33.2	39.4	48.702	18.188	1	2.318	0.391
1110	27.2	25.7	29.8	33.0	37.9	45.5	53.600	18.228	1	2.993	0.541
1118	24.8	25.3	27.4	27.2	27.1	28.0	28.528	0.081	0	1.524	0.383
1137	23.3	23.8	26.8	30.1	35.3	41.9	49.318	18.491	1	2.745	0.397
1142	28.4	24.4	27.5	27.9	29.1	27.7	27.708	0.178	0	1.837	0.384
1143	28.6	28.8	30.8	34.8	39.9	48.9	58.825	20.892	1	3.378	.
1144	28.5	28.4	28.5	28.9	28.4	27.2	28.383	0.194	0	1.937	0.478
1163	25.7	25.3	27.3	31.1	38.4	43.1	52.848	20.187	1	2.547	0.458
1164	28.1	27.1	28.9	30.8	35.5	41.9	48.295	11.983	1	2.841	0.398
1165	24.8	26.1	28.7	32.5	37.8	48.8	55.012	21.585	1	2.842	0.453
1180	28.8	27.8	32.1	34.1	40.8	50.8	58.889	22.215	1	3.179	0.484
1188	30.8	29.5	32.9	34.2	39.9	48.0	53.341	18.183	1	3.175	0.452
1197	29.8	30.8	32.7	38.8	42.4	50.8	59.128	19.798	1	3.189	0.490
1213	28.1	28.0	28.3	27.7	27.8	27.4	28.019	0.109	0	1.555	0.422
1255	28.8	27.3	28.8	28.3	32.1	37.4	43.570	14.822	1	2.590	0.383
1281	28.2	25.8	28.9	29.2	34.2	38.7	48.185	15.908	1	2.437	0.380
1270	24.2	23.9	28.3	25.7	27.2	28.4	28.108	0.232	0	1.551	0.389
1275	24.5	24.7	28.0	28.9	28.0	28.5	27.121	0.119	0	1.838	0.484
1278	25.8	26.1	29.0	31.4	38.0	42.9	51.488	17.995	1	2.928	0.434
1281	28.9	28.9	28.9	31.0	35.8	43.3	52.572	20.088	1	2.887	0.438
1293	24.0	24.8	28.8	28.8	35.2	43.5	51.092	19.392	1	2.700	0.433
1307	25.7	24.9	25.9	29.2	34.8	41.8	48.850	18.871	1	2.873	0.374
1328	24.5	25.5	29.3	31.0	38.2	43.7	52.083	18.899	1	2.754	0.458
1332	29.2	30.0	31.1	33.8	39.8	47.9	57.931	21.458	1	2.887	0.533
1343	29.7	28.3	28.9	30.3	35.8	42.0	50.080	17.899	1	2.841	0.410
1353	24.5	24.3	28.5	25.8	28.4	28.1	25.881	0.189	0	1.279	0.380
1362	25.3	26.7	28.8	30.3	38.0	43.8	52.113	20.288	1	2.713	0.475
1371	25.8	25.5	28.2	30.0	37.0	45.1	55.282	22.891	1	2.930	0.459
1373	27.3	26.4	27.8	30.7	38.7	44.0	50.812	18.898	1	2.813	0.397
1415	27.0	27.1	29.3	32.2	39.1	47.5	55.889	22.184	1	3.350	0.488
1418	25.8	28.5	28.5	31.4	36.3	41.1	48.720	15.082	1	2.505	0.423
1421	25.7	26.9	28.0	30.2	35.0	42.3	49.187	19.711	1	2.431	0.427
1431	27.9	27.8	28.3	32.7	38.7	47.3	54.758	20.807	1	2.841	0.424

Pregnant: 1=Pregnant 0=Non-Pregnant

----- 3000 ppm Methyl Ethyl Ketone -----											
MATNO	Pre-study Wt (g)	0 dg Wt (g)	6 dg Wt (g)	9 dg Wt (g)	12 dg Wt (g)	15 dg Wt (g)	18 dg Wt (g)	Uter Wt (g)	Pregnant	Liver (g)	Kidney (g)
1102	28.6	28.6	28.1	30.9	38.2	42.5	50.382	17.624	1	2.786	0.459
1107	27.7	27.2	27.8	30.9	35.8	44.8	54.930	20.348	1	3.124	0.444
1118	28.9	28.9	28.9	31.9	37.4	44.5	53.909	19.798	1	2.722	0.448
1122	24.8	24.4	28.7	30.9	37.8	46.0	55.417	19.735	1	2.885	0.510
1130	23.7	23.9	26.3	29.3	34.7	43.1	53.468	20.298	1	2.898	0.446
1138	28.6	27.5	30.4	33.9	38.2	48.0	58.084	20.728	1	3.589	0.448
1179	27.7	28.9	32.0	35.3	42.2	51.8	62.899	23.310	1	3.038	0.556
1184	28.9	25.8	30.2	32.5	36.7	42.7	50.195	18.361	1	3.147	0.454
1186	26.4	26.7	31.0	34.5	39.8	51.1	60.027	23.414	1	3.047	0.458
1187	25.9	26.2	29.1	30.2	35.8	43.8	52.205	19.174	1	3.197	0.462
1193	27.0	25.9	27.1	31.1	34.8	42.7	49.325	16.205	1	2.725	0.458
1203	28.2	28.0	30.6	33.5	38.8	45.5	63.010	18.794	1	3.255	0.412
1205	25.3	25.4	28.8	28.5	28.0	27.8	27.394	0.150	0	1.547	0.368
1208	29.0	29.0	32.5	35.9	43.8	52.7	63.235	23.613	1	3.281	0.578
1209	30.7	29.4	31.6	35.4	41.5	51.4	61.299	23.003	1	3.408	0.500
1214	29.9	29.3	29.0	28.8	30.5	29.7	29.065	0.218	0	1.891	0.477
1268	25.3	25.0	26.7	29.1	35.0	42.8	50.001	18.413	1	2.856	0.480
1290	26.2	26.0	28.8	31.4	38.0	41.1	46.631	13.989	1	2.818	0.411
1298	25.4	24.8	25.9	29.5	35.1	41.2	45.818	15.497	1	2.719	0.419
1300	27.4	26.8	28.9	30.8	36.4	43.3	49.818	17.262	1	3.125	0.397
1316	25.4	24.8	25.9	30.1	34.1	41.1	47.435	14.863	1	2.714	0.391
1317	25.5	25.9	27.3	29.5	33.8	39.5	45.990	14.994	1	2.340	0.409
1325	26.4	25.8	27.6	30.8	38.8	43.3	51.272	20.430	1	2.717	0.409
1334	28.5	27.5	28.0	32.9	38.4	46.3	52.828	19.040	1	3.008	0.497
1348	26.5	27.2	30.5	34.1	41.9	50.9	58.858	19.859	1	3.559	0.572
1368	27.6	26.2	29.0	32.4	38.3	45.5	52.805	19.569	1	3.051	0.521
1384	24.8	25.2	27.4	30.3	34.2	42.0	47.873	17.232	1	2.785	0.472
1405	26.5	25.4	27.3	27.9	27.9	27.0	28.153	0.140	0	1.711	0.409
1408	26.7	25.3	27.5	30.0	34.2	40.5	49.820	18.038	1	2.695	0.449
1428	26.8	27.0	27.1	29.5	29.0	28.6	27.162	0.222	0	1.814	0.425
1429	24.0	23.8	25.9	29.9	35.7	43.0	52.134	21.239	1	2.511	0.432
1440	26.5	27.3	30.0	33.8	39.4	48.0	58.580	22.760	1	3.180	0.485

Pregnant: 1=Pregnant 0=Non-Pregnant

Methyl Ethyl Ketone Mouse Teratology Study: Body Weights (g) for Virgin Females

----- 0 ppm Methyl Ethyl Ketone -----

MATNO	Pre-study Wt	Exposure Day1	Exposure Day5	Exposure Day10	Sacrifice Wt
1131	26.6	27.0	26.9	27.0	26.9
1241	28.5	27.9	28.7	28.6	28.2
1288	26.0	26.0	27.0	26.0	28.1
1292	26.5	26.1	26.7	26.1	25.7
1327	24.8	25.6	25.0	26.6	26.6
1331	25.0	24.6	25.5	26.7	26.5
1372	26.5	25.1	25.8	27.4	26.6
1388	24.5	25.7	25.7	27.2	27.7
1413	26.4	26.6	27.1	27.8	26.4
1439	27.9	28.4	28.9	29.5	28.6

Methyl Ethyl Ketone Mouse Teratology Study: Body Weights (g) for Virgin Females

----- 400 ppm Methyl Ethyl Ketone -----

MATNO	Pre-study Wt	Exposure Day1	Exposure Day5	Exposure Day10	Sacrifice Wt
1125	25.8	28.3	27.3	28.7	27.2
1169	28.9	25.7	28.4	28.0	28.8
1173	28.6	27.0	27.4	27.3	28.8
1221	25.2	28.0	27.5	27.6	28.2
1269	28.2	28.6	28.4	27.1	28.7
1274	28.2	28.9	29.0	29.7	31.4
1330	25.9	28.0	25.9	27.4	27.2
1341	27.8	27.0	27.4	28.5	29.4
1408	24.8	25.0	25.5	26.8	27.8
1424	24.7	25.3	26.1	25.4	25.3

Methyl Ethyl Ketone Mouse Teratology Study: Body Weights (g) for Virgin Females

----- 1000 ppm Methyl Ethyl Ketone -----

MATNO	Pre-study Wt	Exposure Day1	Exposure Day6	Exposure Day10	Sacrifice Wt
1124	25.7	28.6	28.1	28.3	28.4
1150	25.7	25.8	25.9	25.9	26.9
1210	29.7	28.4	30.4	31.2	31.8
1220	28.2	27.2	27.5	28.2	27.9
1257	26.0	27.0	27.5	28.2	28.9
1284	25.7	24.7	25.0	26.3	26.5
1298	25.0	26.0	26.4	26.9	26.2
1388	26.1	25.7	27.6	28.1	27.9
1437	25.5	25.1	26.4	27.8	26.5

Methyl Ethyl Ketone Mouse Teratology Study: Body Weights (g) for Virgin Females

----- 3000 ppm Methyl Ethyl Ketone -----

MATNO	Pre-study Wt	Exposure Day1	Exposure Day5	Exposure Day10	Sacrifice Wt
1132	28.9	27.1	27.8	27.8	29.1
1172	28.0	28.9	28.2	28.8	29.9
1181	28.8	28.1	28.3	27.9	29.5
1198	27.9	28.9	27.5	28.2	30.3
1217	29.4	28.0	27.7	28.3	30.2
1248	24.7	25.4	27.5	27.2	27.5
1249	28.2	28.8	28.9	27.8	28.0
1251	28.2	28.0	25.4	25.9	27.4
1283	25.8	25.8	25.8	28.7	28.3
1407	28.7	24.8	24.9	25.8	27.8

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 8 ppm Methyl Ethyl Ketone -----									
Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1104	1	1	1.484	1	V				
1104	2	1	1.420	2	H				
1104	3	1	1.340	2	V	LMFL			
1104	4	1	1.236	2	H				
1104	5	1	1.389	1	V				
1104	6	1	1.165	1	H				
1104	7	1	1.290	2	V				
1104	8	1	1.327	2	H	MAST			
1104	9	1	1.405	1	V				
1104	10	1	1.523	1	H				
1104	11	1	1.458	1	V				
1104	12	1	1.337	2	H	QSST			
1104	13	1	1.365	1	V				
1104	14	1	1.453	2	H				
1113	1	1	1.379	2	V				
1113	2	1	1.464	2	H	MAST			
1113	3	1	1.532	1	V	SURB			
1113	4	1	1.317	1	H				
1113	5	1	1.374	2	V				
1113	6	1	1.407	1	H				
1113	7	1	1.301	2	V				
1113	8	1	1.366	1	H				
1113	9	1	1.423	2	V				
1113	10	1	1.507	2	H				
1127	1	1	1.289	2	H	SURB			
1127	2	1	1.376	1	V	SURB			
1127	3	1	1.295	1	V				
1127	4	1	1.130	2	H	SURB			
1127	5	1	1.275	1	H	MAST			
1127	6	1	1.249	2	V				
1127	7	1	1.301	2	H				
1127	8	1	1.364	1	V	SURB			
1127	9	1	1.278	1	H	SURB			
1127	10	1	1.235	1	V				
1127	11	1	1.209	1	H	MAST			
1127	12	1	1.275	1	V	MAST			
1127	13	1	1.190	2	H	MAST			
1127	14	1	1.301	1	V				
1139	1	1	1.518	1	V	SURB			
1139	2	1	1.396	2	H	SURB			
1139	3	1	1.474	1	V	SURB			
1139	4	1	1.326	2	H				
1139	5	1	0.712	2	V				
1139	6	1	1.411	1	H	SURB			
1139	7	1	1.343	2	V	SURB			
1139	8	1	1.394	1	H	SURB			
1139	9	1	1.366	2	V	SURB			

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 0 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1139	10	1	1.436	1	H	SURB			
1139	11	1	1.402	1	V	SURB			
1139	12	1	1.416	2	H	SURB			
1185	1	1	1.374	2	H	MAST			
1185	2	1	1.222	1	V	MAST	ROST		
1185	3	1	1.177	1	H	MAST	ROST		
1185	4	1	1.203	2	V				
1185	6	1	1.201	1	H				
1185	6	4	.	.					
1185	7	1	1.217	2	V				
1185	8	1	1.260	2	H				
1185	9	1	1.279	2	V				
1185	10	1	1.363	1	H				
1185	11	1	1.416	2	V	MAST			
1185	12	1	1.360	2	H				
1194	1	1	1.320	2	V				
1194	2	1	1.301	1	H				
1194	3	1	1.213	2	V				
1194	4	1	1.303	1	H				
1194	6	1	1.263	2	V				
1194	6	1	1.323	1	H				
1194	7	1	1.236	2	V	MAST			
1194	8	1	1.139	2	H				
1194	9	1	1.344	1	V				
1194	10	1	1.349	1	H	SURB			
1194	11	1	1.438	1	V				
1194	12	1	1.301	2	H				
1211	1	1	1.461	1	H				
1211	2	1	1.352	2	V				
1211	3	1	1.178	2	H				
1211	4	1	1.398	2	V				
1211	5	1	1.325	2	H				
1211	6	1	1.398	1	V				
1211	7	1	1.402	2	H				
1211	8	1	1.481	2	V				
1211	9	1	1.576	1	H				
1211	10	1	1.296	2	V				
1211	11	1	1.467	1	H				
1211	12	1	1.307	2	V				
1212	1	1	1.299	1	V	SURB			
1212	2	1	1.236	1	H	SURB	OSST		
1212	3	1	1.290	2	V	SURB			
1212	4	1	1.310	2	H	SURB			
1212	5	2	.	.					
1212	6	1	1.145	2	V	MAST			
1212	7	1	1.440	1	H				
1212	8	1	1.601	1	V	SURB			

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

0 ppm Methyl Ethyl Ketone									
Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1212	9	1	1.410	2	H				
1212	10	1	1.445	1	V				
1212	11	1	1.363	2	H				
1212	12	1	1.523	1	V	SURB			
1226	1	1	1.203	1	H				
1226	2	1	1.333	1	V				
1226	3	1	1.286	1	H				
1226	4	1	1.271	1	V	ROSK	SURB		
1226	5	1	1.291	1	H				
1226	6	1	1.344	1	V				
1226	7	1	1.224	1	H				
1226	8	1	1.117	2	V				
1226	9	1	1.094	2	H				
1226	10	1	1.309	1	V	MAST			
1226	11	1	1.229	2	H				
1226	12	2	.	.	.				
1226	13	1	1.313	1	V				
1226	14	1	1.117	2	H	SURB			
1226	15	1	1.275	2	V	OSST	SURB		
1226	16	1	1.138	2	H				
1239	1	1	1.505	1	H				
1239	2	1	1.562	1	V	OSST			
1239	3	2	.	.	.				
1239	4	1	1.412	2	H	OSST	SURB		
1239	5	1	1.475	1	V	OSST			
1239	6	1	1.400	2	H				
1239	7	1	1.431	2	V				
1239	8	1	1.380	2	H	OSST			
1239	9	1	1.435	2	V	OSST	SURB		
1239	10	1	1.287	2	H	MAST			
1239	11	1	1.358	1	V	OSST	SURB		
1239	12	1	1.415	1	H	OSST	SURB		
1247	1	1	1.352	1	H				
1247	2	1	1.347	1	V				
1247	3	1	1.276	2	H				
1247	4	4	.	.	.				
1247	5	1	1.228	2	V				
1247	6	1	1.032	1	H				
1247	7	1	1.344	1	V				
1247	8	1	1.283	2	H				
1247	9	1	1.214	2	V				
1247	10	1	1.280	2	H	ROST			
1247	11	1	1.258	1	V	MAST			
1247	12	1	1.369	1	H				
1250	1	1	1.477	1	V	SURB			
1250	2	1	1.382	2	H				
1250	3	1	1.305	1	V				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 0 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1250	4	1	1.382	1	H				
1250	6	1	1.250	2	V				
1250	6	1	1.373	2	H				
1250	7	1	1.471	1	V				
1250	8	1	1.325	2	H	SURB			
1250	9	1	1.301	2	V				
1250	10	1	1.199	1	H	SURB			
1250	11	1	1.373	1	V				
1250	1	1	1.385	1	V				
1250	2	1	1.410	1	H				
1250	3	1	1.343	2	V				
1250	4	1	1.300	2	H	SURB			
1250	5	1	1.459	1	V	SURB			
1250	6	1	1.457	2	H	SURB			
1250	7	1	1.352	1	V				
1250	8	1	1.372	2	H				
1250	9	1	1.313	1	V				
1250	10	1	1.372	1	H				
1250	11	1	1.437	1	V				
1250	12	1	1.403	1	H				
1250	13	1	1.307	1	V				
1250	1	1	1.426	2	V				
1250	2	1	1.283	1	H				
1250	3	1	1.298	2	V	SURB			
1250	4	2	.	.	.				
1250	5	1	1.301	2	H				
1250	6	1	1.022	2	V				
1250	7	1	1.291	1	H				
1250	8	1	1.094	2	V				
1250	9	2	.	.	.				
1250	10	1	1.260	2	H				
1250	11	1	1.220	2	V				
1250	12	1	1.278	1	H				
1250	13	4	.	.	.				
1250	14	1	1.422	1	V				
1270	1	1	1.184	2	V				
1270	2	1	1.368	1	H				
1270	3	1	1.285	1	V				
1270	4	1	1.136	1	H				
1270	5	1	1.196	2	V	SURB	MAST		
1270	6	1	1.323	2	H				
1270	7	1	1.394	1	V				
1270	8	1	1.301	2	H				
1270	9	1	1.419	2	V				
1270	10	1	1.189	2	H				
1270	11	1	1.281	1	V				
1270	12	1	1.296	2	H				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

0 ppm Methyl Ethyl Ketone

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1279	13	1	1.355	1	V	SURB			
1279	14	1	1.300	2	H				
1279	15	1	1.313	2	V				
1279	16	1	1.283	2	H				
1291	1	1	1.100	2	H				
1291	2	1	1.204	2	V				
1291	3	1	1.139	1	H				
1291	4	1	1.300	1	V				
1291	5	1	0.999	2	H	MAST	ROST		
1291	6	1	1.281	2	V				
1291	7	4	.	.					
1291	8	1	1.232	2	H	MAST			
1291	9	1	1.275	2	V				
1291	10	1	1.284	1	H				
1291	11	1	1.247	2	V				
1291	12	1	1.305	1	H				
1291	13	1	1.295	1	V				
1297	1	1	1.321	1	V				
1297	2	1	1.315	2	H				
1297	3	1	1.184	1	V	ROSK	ROST	SURB	
1297	4	1	1.330	1	H				
1297	5	1	1.297	1	V	ROSK	SURB		
1297	6	1	1.192	2	H				
1297	7	1	1.248	1	V	SURB			
1297	8	1	1.260	2	H	SURB			
1297	9	1	1.345	1	V				
1297	10	1	1.353	1	H	MAST			
1297	11	1	1.389	1	V				
1304	1	1	1.523	1	V				
1304	2	1	1.381	2	H				
1304	3	1	1.501	1	V				
1304	4	1	1.339	1	H	SURB			
1304	5	2	.	.					
1304	6	2	.	.					
1304	7	1	1.347	2	V				
1313	1	1	1.207	2	V				
1313	2	1	1.414	1	H	OSST			
1313	3	1	1.252	2	V	SURB			
1313	4	1	0.991	1	H	MAST			
1313	5	1	1.385	1	V	MAST			
1313	6	1	1.304	1	H				
1313	7	1	1.318	1	V	MAST			
1313	8	1	1.424	1	H				
1313	9	1	1.382	2	V	MAST			
1313	10	1	1.391	2	H				
1313	11	1	1.303	2	V	SURB			
1338	1	1	1.458	1	H				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

0 ppm Methyl Ethyl Ketone

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1336	2	1	1.368	1	V				
1336	3	1	1.354	2	H				
1336	4	1	1.427	1	V				
1336	5	1	1.329	1	H				
1336	6	1	1.352	1	V				
1336	7	2	.	.					
1336	8	2	.	.					
1336	9	1	1.392	1	H				
1336	10	1	1.378	2	V	MAST			
1336	11	1	1.425	2	H				
1336	12	1	1.374	2	V				
1336	13	1	1.373	1	H				
1336	14	1	1.353	2	V				
1336	15	1	1.350	1	H				
1336	16	1	1.506	1	V	MAST			
1350	1	1	1.439	2	V	KITA			
1350	2	1	1.430	2	H				
1350	3	1	1.405	2	V				
1350	4	1	1.397	2	H	OSST			
1350	5	1	1.414	1	V				
1350	6	1	1.454	1	H				
1350	7	1	1.355	2	V				
1360	1	1	1.589	2	V				
1360	2	1	1.450	1	H	OSST			
1360	3	1	1.454	2	V				
1360	4	1	1.547	2	H	MAST			
1360	5	1	1.461	1	V				
1360	6	1	1.502	1	H				
1360	7	1	1.396	2	V				
1360	8	1	1.517	1	H				
1360	9	1	1.504	2	V				
1360	10	1	1.463	2	H				
1360	11	1	1.399	1	V	MAST			
1360	12	1	1.413	2	H				
1364	1	1	1.337	2	V				
1364	2	1	1.327	2	H	MAST			
1364	3	1	1.484	2	V				
1364	4	1	1.404	1	H				
1364	5	1	1.317	2	V				
1364	6	1	1.430	2	H				
1364	7	1	1.434	2	V				
1364	8	1	1.518	1	H				
1364	9	1	1.445	1	V				
1364	10	1	1.472	2	H				
1364	11	1	1.178	2	V				
1364	12	1	1.440	1	H				
1364	13	1	1.449	2	V				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 0 ppm Methyl Ethyl Ketone -----									
Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1382	1	1	1.395	2	V				
1382	2	1	1.276	2	H	SURB			
1382	3	1	1.341	2	V				
1382	4	1	1.384	1	H	SURB			
1382	5	1	1.429	2	V				
1382	6	1	1.434	1	H				
1382	7	1	1.372	1	V				
1382	8	1	1.235	2	H	MAST	SURB		
1382	9	1	1.377	1	V				
1382	10	1	1.379	1	H				
1382	11	1	1.318	2	V	SURB			
1382	12	1	1.392	1	H	MAST	ROST		
1382	13	1	1.458	1	V				
1382	14	1	1.581	1	H	OSST			
1392	1	1	1.515	1	H				
1392	2	1	1.370	1	V	SURB			
1392	3	1	1.830	2	H	SURB			
1392	4	1	1.243	2	V	MAST			
1392	5	1	1.323	1	H				
1392	6	1	1.345	2	V				
1392	7	1	1.349	1	H				
1392	8	1	1.361	2	V				
1392	9	1	1.300	1	H	SURB			
1392	10	1	1.350	1	V	SURB			
1392	11	1	1.330	1	H				
1392	12	1	1.384	1	V				
1392	13	1	1.444	1	H				
1392	14	1	1.325	2	V				
1392	15	1	1.335	1	H				
1409	1	1	1.403	2	V				
1409	2	1	1.427	2	H				
1409	3	1	1.447	1	V				
1409	4	1	1.415	1	H				
1409	5	1	1.488	1	V				
1409	6	1	1.407	2	H	SURB			
1409	7	1	1.389	2	V				
1409	8	1	1.443	1	H				
1409	9	1	1.452	1	V				
1409	10	1	1.424	2	H	SURB			
1409	11	1	1.395	2	V				
1409	12	1	1.440	1	H				

C.15

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption
 Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 400 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1112	1	1	1.4730	1	H				
1112	2	1	1.3810	2	V				
1112	3	1	1.4130	2	H				
1112	4	1	1.4900	1	V				
1112	6	1	1.4100	2	H				
1112	8	1	1.1410	1	V				
1112	7	1	1.4780	1	H				
1112	8	1	1.4210	1	V	MAST			
1112	9	1	1.4700	2	H				
1112	10	1	1.4320	2	V				
1112	11	1	1.3910	1	H				
1112	12	1	1.4030	2	V				
1112	13	1	1.4580	2	H				
1119	1	1	1.4110	1	H				
1119	2	1	1.4250	1	V				
1119	3	4	.	.	.				
1119	4	1	1.2879	2	H				
1119	5	1	1.3454	1	V				
1119	6	1	0.9839	2	H	MAST	SURB		
1119	7	1	1.4100	1	V	SURB			
1119	8	1	1.1900	1	H	SURB			
1119	9	2	.	.	.				
1119	10	2	.	.	.				
1119	11	1	1.2270	1	V	MAST			
1121	1	1	1.4620	1	H	SURB			
1121	2	1	1.3350	1	V				
1121	3	1	1.2580	2	H				
1121	4	1	1.3890	1	V				
1121	5	1	1.3330	2	H	MAST			
1121	6	1	1.4180	1	V				
1121	7	1	1.2770	2	H	SURB			
1121	8	1	1.3670	2	V				
1121	9	1	1.2710	2	H				
1121	10	1	1.3210	2	V				
1121	11	1	1.2730	2	H				
1149	1	1	1.2410	2	V				
1149	2	1	1.3670	2	H	SURB			
1149	3	1	1.2970	2	V	MAST			
1149	4	2	.	.	.				
1149	5	1	1.4280	1	H	MAST	SURB		
1149	6	1	1.2810	1	V				
1149	7	1	1.2200	1	H	MAST	SURB		
1149	8	1	1.2890	1	V	MAST			
1149	9	1	1.3900	2	H				
1149	10	1	1.3540	1	V				
1149	11	1	1.2850	1	H	MAST	ROST		
1149	12	1	1.2870	2	V				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 400 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1149	13	1	1.3540	1	H				
1149	14	1	1.1990	1	V				
1151	1	1	1.3080	2	H	OSST			
1151	2	1	1.3520	2	V				
1151	3	1	1.3000	1	H				
1151	4	1	1.4340	1	V	SURB			
1151	6	1	1.3390	2	H	SURB			
1151	8	1	1.2420	2	V	SURB			
1151	7	1	1.3020	1	H				
1151	8	1	1.2220	2	V				
1151	9	1	1.3070	1	H				
1151	10	1	1.2800	2	V	MAST	SURB		
1151	11	2	.	.	.				
1151	12	1	1.3180	2	H	SURB			
1176	1	1	1.3570	2	H				
1176	2	1	1.3980	1	V				
1176	3	1	1.3980	1	H				
1176	4	1	1.3200	2	V				
1176	6	1	1.2620	2	H				
1176	6	1	1.3000	2	V	MAST			
1176	7	1	1.4150	1	H				
1176	8	1	1.2910	1	V				
1176	9	1	1.2410	1	H				
1176	10	1	1.3280	1	V				
1176	11	1	1.3090	2	H				
1176	12	1	1.3940	2	V				
1176	13	1	1.4090	1	H				
1176	14	1	1.3540	1	V				
1176	15	1	1.4970	1	H				
1183	1	1	1.5361	1	H	SURB			
1183	2	1	1.6104	1	V				
1183	3	1	1.3901	2	H				
1183	4	1	1.3730	2	V				
1183	5	1	1.4460	2	H				
1183	6	1	1.3619	1	V	SURB			
1183	7	1	1.2347	2	H	SURB			
1183	8	1	1.4013	2	V	MAST			
1183	9	1	1.3283	2	H				
1183	10	1	1.3664	1	V				
1183	11	1	1.3406	2	H	MAST			
1183	12	1	1.3827	1	V				
1183	13	1	1.3897	1	H				
1183	14	2	.	.	.				
1183	15	1	1.4608	1	V	ROSK			
1196	1	1	1.3420	2	V				
1196	2	1	1.4660	1	H				
1196	3	1	1.3170	2	V				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

400 ppm Methyl Ethyl Ketone

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1196	4	1	1.285	2	H				
1196	5	1	1.289	2	V	MAST			
1196	6	1	1.348	2	H				
1196	7	1	1.354	2	V				
1196	8	1	1.257	2	H				
1196	9	1	1.293	2	V				
1196	10	1	1.436	1	H				
1196	11	1	1.333	1	V				
1196	12	1	1.230	2	H	MAST	CLPA		
1196	13	1	1.354	1	V	MAST			
1196	14	1	1.344	1	H				
1282	1	1	1.516	2	H				
1282	2	2	.	.	.				
1282	3	1	1.449	2	V				
1282	4	1	1.439	2	H	SURB			
1282	5	1	1.417	2	V				
1282	6	1	1.289	2	H	OSST	SURB		
1282	7	2	.	.	.				
1282	8	1	1.318	1	V	ROSK			
1282	9	2	.	.	.				
1282	10	1	1.416	2	H				
1282	11	1	1.476	1	V	ROSK			
1339	1	1	1.313	2	H				
1339	2	1	1.222	2	V				
1339	3	1	1.179	2	H				
1339	4	1	1.297	1	V				
1339	5	1	1.454	1	H				
1339	6	1	1.312	1	V				
1339	7	1	1.226	2	H				
1339	8	1	1.317	1	V				
1339	9	1	1.219	2	H	MAST			
1339	10	1	1.168	1	V				
1339	11	1	1.276	2	H				
1339	12	1	1.204	1	V				
1339	13	1	1.228	2	H	MAST	FUST		
1339	14	1	1.295	1	V				
1339	15	1	1.236	2	H				
1344	1	1	1.322	2	V				
1344	2	1	1.294	1	H	SURB			
1344	3	1	1.368	1	V	SURB			
1344	4	1	1.316	2	H	SURB			
1344	5	1	1.379	1	V				
1344	6	1	1.328	1	H				
1344	7	1	1.177	2	V				
1344	8	1	1.360	1	H	SURB			
1344	9	1	1.231	2	V	SURB			
1344	10	1	1.280	2	H				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 400 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1344	11	4	.	.					
1344	12	1	1.383	2	V	SURB			
1344	13	1	1.348	2	H	SURB			
1352	1	1	1.678	2	H				
1352	2	1	1.858	2	V				
1352	3	1	1.471	1	H				
1352	4	1	1.317	2	V				
1352	6	1	1.448	1	H				
1352	8	1	1.457	1	V				
1352	7	2	.	.					
1352	8	4	.	.					
1352	9	1	1.258	2	H	MAST			
1352	10	1	1.243	2	V	ROST			
1352	11	1	1.458	1	H				
1352	12	1	1.337	2	V				
1352	13	1	1.377	2	H				
1357	1	1	1.381	2	H				
1357	2	1	1.357	1	V				
1357	3	1	1.172	2	H				
1357	4	1	1.334	1	V				
1357	6	1	1.212	2	H				
1357	8	1	1.335	1	V				
1357	7	4	.	.					
1357	8	2	.	.					
1357	9	1	1.334	1	H				
1357	10	1	1.402	1	V				
1357	11	1	1.142	1	H				
1357	12	1	1.237	1	V				
1357	13	1	1.227	2	H				
1357	14	1	1.372	1	V				
1357	15	1	1.451	1	H				
1359	1	1	1.388	1	V				
1359	2	1	1.258	2	H				
1359	3	1	1.277	1	V				
1359	4	1	1.268	2	H	SURB			
1359	6	1	1.227	1	V	SURB			
1359	8	1	1.233	2	H				
1359	7	4	.	.					
1359	8	4	.	.					
1359	9	1	1.255	2	V				
1359	10	1	1.181	2	H				
1359	11	1	1.172	2	V	SURB			
1359	12	1	1.158	1	H				
1381	1	1	1.534	1	V				
1381	2	1	1.387	1	H				
1381	3	1	1.522	1	V				
1381	4	1	1.451	2	H				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 400 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1361	6	1	1.437	2	V				
1361	6	1	1.372	1	H				
1368	1	1	1.400	2	H				
1368	2	1	1.428	1	V				
1368	3	1	1.489	1	H	CLPA	SURB		
1368	4	1	1.268	2	V	MAST			
1368	5	1	1.413	1	H	SURB			
1368	6	1	1.442	1	V	MAST			
1368	7	1	1.311	2	H				
1368	8	1	1.405	1	V				
1368	9	1	1.401	2	H				
1368	10	1	1.302	2	V				
1368	11	1	1.399	2	H	MAST			
1368	12	1	1.470	1	V	MAST			
1369	1	1	1.459	1	V				
1369	2	1	1.369	1	H				
1369	3	1	1.368	1	V				
1369	4	1	1.460	1	H				
1369	5	1	1.280	2	V				
1369	6	1	1.277	2	H				
1369	7	1	1.428	1	V				
1369	8	1	1.377	1	H				
1369	9	1	1.212	2	V				
1369	10	1	1.422	1	H				
1369	11	1	1.265	2	V	SURB			
1369	12	1	1.288	1	H				
1369	13	1	1.359	2	V				
1370	1	1	1.370	1	H				
1370	2	1	1.429	1	V				
1370	3	1	1.341	1	H				
1370	4	1	1.363	2	V				
1370	5	1	1.325	2	H				
1370	6	1	1.331	2	V				
1370	7	1	1.452	1	H				
1370	8	1	1.431	2	V				
1370	9	1	1.185	2	H				
1370	10	1	1.374	2	V				
1370	11	1	1.324	2	H				
1370	12	1	1.419	1	V				
1370	13	1	1.372	1	H				
1375	1	1	1.399	2	H	SURB			
1375	2	1	1.412	1	V				
1375	3	1	1.409	2	H				
1375	4	1	1.363	2	V				
1375	5	1	1.392	1	H				
1375	6	1	1.383	2	V				
1375	7	1	1.488	2	H				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 400 ppm Methyl Ethyl Ketone -----									
Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1375	0	1	1.5030	1	V				
1380	1	1	1.3890	2	V	SURB			
1380	2	1	1.4470	1	H				
1380	3	1	1.4780	2	V				
1380	4	1	1.5020	2	H				
1380	5	1	1.4010	1	V				
1380	6	5	.	.	.				
1380	7	1	1.3550	1	H	ROST	SURB		
1380	8	1	1.3470	1	V				
1380	9	1	1.3780	2	H	SURB			
1380	10	4	.	.	.				
1380	11	1	1.2820	1	V	SURB			
1380	12	1	1.4520	1	H	SURB	MAST	ROST	
1380	13	1	1.2940	2	V	OSST	SURB		
1390	1	1	1.2920	2	H				
1390	2	1	1.1940	2	V	SURB			
1390	3	1	1.2540	1	H	SURB			
1390	4	1	1.2220	2	V				
1390	5	1	1.1780	2	H	SURB			
1390	6	4	.	.	.				
1390	7	1	1.2800	1	V	SURB			
1390	8	1	1.3780	1	H	SURB			
1390	9	4	.	.	.				
1390	10	1	1.3890	2	V	SURB			
1412	1	1	1.3930	1	V				
1412	2	1	1.3140	1	H	ROST			
1412	3	1	1.3100	2	V				
1412	4	1	1.3140	2	H				
1412	5	1	1.2090	2	V				
1412	6	1	1.1390	2	H				
1412	7	1	1.3500	2	V	MAST			
1412	8	1	1.4510	1	HV	LMFL			
1412	9	1	1.4000	2	V				
1412	10	1	1.3400	1	H	ROST			
1412	11	1	1.3430	1	V				
1430	1	1	1.4410	2	V				
1430	2	1	1.4110	2	H				
1430	3	1	1.4774	2	V	OSST			
1430	4	1	1.4101	1	H	OSST			
1430	5	2	.	.	.				
1430	6	1	1.5555	1	V	OSST			
1430	7	1	1.5000	2	H				
1430	8	1	1.4291	2	V				
1430	9	1	1.5175	2	H	MAST			
1430	10	1	1.5233	2	V	MAST	OSST		
1430	11	1	1.5223	1	H				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption
 Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 400 ppm Methyl Ethyl Ketone -----									
Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1375	8	1	1.5030	1	V				
1380	1	1	1.8890	2	V	SURB			
1380	2	1	1.4470	1	H				
1380	3	1	1.4780	2	V				
1380	4	1	1.6020	2	H				
1380	5	1	1.4010	1	V				
1380	6	5	.	.	.				
1380	7	1	1.3550	1	H	ROST	SURB		
1380	8	1	1.3470	1	V				
1380	9	1	1.3780	2	H	SURB			
1380	10	4	.	.	.				
1380	11	1	1.2020	1	V	SURB			
1380	12	1	1.4520	1	H	SURB	MAST	ROST	
1380	13	1	1.2940	2	V	OSST	SURB		
1390	1	1	1.2920	2	H				
1390	2	1	1.1940	2	V	SURB			
1390	3	1	1.2540	1	H	SURB			
1390	4	1	1.2220	2	V				
1390	5	1	1.1780	2	H	SURB			
1390	6	4	.	.	.				
1390	7	1	1.2800	1	V	SURB			
1390	8	1	1.3730	1	H	SURB			
1390	9	4	.	.	.				
1390	10	1	1.3090	2	V	SURB			
1412	1	1	1.3930	1	V				
1412	2	1	1.3140	1	H	ROST			
1412	3	1	1.8100	2	V				
1412	4	1	1.3140	2	H				
1412	5	1	1.2090	2	V				
1412	6	1	1.1390	2	H				
1412	7	1	1.3500	2	V	MAST			
1412	8	1	1.4510	1	HV	LMFL			
1412	9	1	1.4000	2	V				
1412	10	1	1.9400	1	H	ROST			
1412	11	1	1.3430	1	V				
1430	1	1	1.4410	2	V				
1430	2	1	1.4110	2	H				
1430	3	1	1.4774	2	V	OSST			
1430	4	1	1.4101	1	H	OSST			
1430	5	2	.	.	.				
1430	6	1	1.5555	1	V	OSST			
1430	7	1	1.5060	2	H				
1430	8	1	1.4291	2	V				
1430	9	1	1.5175	2	H	MAST			
1430	10	1	1.5233	2	V	MAST	OSST		
1430	11	1	1.5223	1	H				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 1000 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1106	1	1	1.1670	1	H	ROST	MAST	FURB	SURB
1106	2	1	1.1320	2	V	SURB			
1106	3	1	0.9840	2	H	SURB			
1106	4	1	1.1290	1	V				
1106	5	1	1.1780	1	H	MAST			
1106	6	1	1.0210	2	V	MAST	ROST	SURB	
1106	7	1	1.2310	2	H				
1106	8	1	1.1780	2	V				
1106	9	1	1.1650	2	H				
1106	10	1	1.2420	2	V				
1106	11	1	1.3070	1	H				
1110	1	2	.	.					
1110	2	1	1.3222	2	H	SURB			
1110	3	1	1.3683	1	V	SURB			
1110	4	4	.	.					
1110	5	1	1.2571	2	H	SURB			
1110	6	1	1.3220	2	V	SURB			
1110	7	1	1.3013	1	H	MAST			
1110	8	1	1.3132	1	V	MAST	SURB		
1110	9	1	1.1700	1	H	ROST	SURB		
1110	10	1	1.2890	2	V	SURB			
1110	11	2	.	.					
1110	12	1	1.2432	2	H	SURB			
1110	13	1	1.3980	1	V	SURB			
1110	14	1	1.3093	2	H				
1137	1	1	1.5490	2	V				
1137	2	1	1.4900	2	H				
1137	3	1	1.3040	1	V				
1137	4	1	1.4630	1	H				
1137	5	2	.	.					
1137	6	1	1.3540	2	V				
1137	7	1	1.2840	1	H				
1137	8	1	1.4950	2	V	MAST	ROST		
1137	9	1	1.4190	2	H				
1137	10	1	1.4790	1	V				
1137	11	2	.	.					
1143	1	1	1.4270	2	V				
1143	2	1	1.3580	2	H				
1143	3	1	1.4720	1	V				
1143	4	1	1.4070	2	H				
1143	5	1	1.4280	1	V				
1143	6	1	1.6170	1	H				
1143	7	1	1.0940	2	V				
1143	8	1	1.4250	2	H				
1143	9	1	1.2900	2	V				
1143	10	1	1.3840	2	H				
1143	11	1	1.3380	2	V				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 1000 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1143	12	2	.	.	.				
1143	13	1	1.370	1	H				
1163	1	1	1.361	1	V				
1163	2	1	1.364	1	H				
1163	3	1	1.410	2	V				
1163	4	1	1.286	2	H				
1163	5	1	1.358	1	V				
1163	6	1	1.346	2	H				
1163	7	1	1.490	1	V				
1163	8	1	1.366	2	H	MAST			
1163	9	1	1.438	1	V				
1163	10	1	1.432	2	H				
1163	11	1	1.353	2	V				
1163	12	1	1.343	2	H				
1164	1	1	1.363	2	H				
1164	2	1	1.392	2	V	MAST			
1164	3	1	1.379	1	H				
1164	4	1	1.194	2	V				
1164	5	1	1.076	2	H	MAST	SURB		
1164	6	2	.	.	.				
1164	7	1	1.307	2	V	MAST	ROST		
1164	8	1	0.898	1	H	MAST	ROST	SURB	
1164	9	2	.	.	.				
1165	1	1	1.371	1	H				
1165	2	1	1.153	2	V	MAST			
1165	3	1	1.206	2	H	SURB			
1165	4	1	1.320	1	V	SURB			
1165	5	1	1.216	2	H	SURB			
1165	6	1	1.222	2	V	ROST			
1165	7	1	1.177	2	H				
1165	8	4	.	.	.				
1165	9	1	1.347	2	V	MAST	SURB		
1165	10	1	1.290	2	H				
1165	11	1	1.305	2	V				
1165	12	1	1.203	2	H	MAST	ROST		
1165	13	1	1.314	2	V	MAST			
1165	14	1	1.464	2	H	MAST	ROST		
1180	1	1	1.088	1	V				
1180	2	1	1.351	1	H				
1180	3	1	1.179	1	V	MAST	ROST		
1180	4	1	1.356	1	H				
1180	5	1	1.173	2	V				
1180	6	1	1.302	2	H				
1180	7	1	1.253	1	V				
1180	8	1	1.324	2	H	MAST	ROST		
1180	9	4	.	.	.				
1180	10	1	1.397	1	V				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 1000 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1180	11	1	1.251	2	H				
1180	12	1	1.393	1	V				
1180	13	1	1.394	2	H				
1180	14	1	1.396	2	V				
1188	1	1	1.374	2	V				
1188	2	1	1.422	2	H				
1188	3	1	1.349	2	V				
1188	4	1	1.199	2	H	SURB			
1188	5	1	1.123	1	V	ROSK	SURB		
1188	6	1	1.189	1	H	SURB			
1188	7	1	1.171	2	V				
1188	8	1	1.306	2	H	SURB			
1188	9	1	1.289	2	V				
1188	10	1	1.176	2	H				
1197	1	1	1.484	1	V				
1197	2	2	.	.	.				
1197	3	1	1.522	1	H	SURB			
1197	4	1	1.394	2	V				
1197	5	2	.	.	.				
1197	6	1	1.466	1	H				
1197	7	1	1.392	2	V				
1197	8	1	1.431	1	H	SURB			
1197	9	2	.	.	.				
1197	10	1	1.168	2	V				
1197	11	1	1.399	2	H	WIVE			
1197	12	1	1.338	2	V				
1197	13	1	1.382	2	H	MAST			
1197	14	1	1.493	2	V				
1255	1	1	1.407	2	H				
1255	2	1	1.307	2	V				
1255	3	1	1.131	1	H				
1255	4	1	1.338	2	V				
1255	5	1	1.276	2	H				
1255	6	1	1.287	2	V				
1255	7	1	1.386	2	H				
1255	8	1	1.247	2	V	ROST			
1255	9	1	1.268	2	H				
1261	1	1	1.258	2	V				
1261	2	1	1.313	2	H	SURB			
1261	3	1	1.269	1	V				
1261	4	1	1.173	2	H				
1261	5	1	1.267	1	V	SURB			
1261	6	1	1.188	2	H				
1261	7	1	1.345	1	V				
1261	8	1	1.375	1	H	SURB			
1261	9	1	1.332	2	V	SURB			
1261	10	2	.	.	.				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 1000 ppm Methyl Ethyl Ketone -----									
Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1261	11	1	1.2950	1	H	SURB			
1276	1	1	1.2602	2	H	SURB			
1276	2	1	1.3476	1	V				
1276	3	1	1.3151	2	H	SURB			
1276	4	1	1.2738	1	V	SURB			
1276	5	2	.	.					
1276	6	1	1.2655	2	H	SURB			
1276	7	1	1.2858	2	V				
1276	8	1	1.3097	2	H	SURB			
1276	9	1	1.4044	1	V	ROST	SURB	MAST	
1276	10	1	1.3158	1	H	SURB			
1276	11	1	1.3430	1	V	SURB			
1276	12	2	.	.					
1276	13	1	1.2870	1	H	SURB			
1281	1	1	1.3111	2	H				
1281	2	1	1.3162	2	V				
1281	3	1	1.3674	1	H	MAST			
1281	4	1	1.3183	1	V				
1281	5	1	1.4372	1	H				
1281	6	1	1.2721	1	V				
1281	7	1	1.3424	1	H				
1281	8	1	1.2520	2	V				
1281	9	1	1.4239	2	H				
1281	10	1	1.4340	2	V				
1281	11	1	1.3931	2	H				
1281	12	1	1.0125	1	V				
1293	1	1	1.3690	1	V				
1293	2	1	1.2420	2	H				
1293	3	1	1.3230	1	V	SURB			
1293	4	1	1.2510	2	H	OSST	SURB		
1293	5	1	1.2070	2	V				
1293	6	1	1.3190	2	H				
1293	7	1	1.3390	1	V				
1293	8	1	1.3520	1	H				
1293	9	1	1.2510	2	V	SURB			
1293	10	1	1.3190	1	H				
1293	11	1	1.2170	2	V				
1293	12	1	1.3080	1	H				
1307	1	1	1.4090	2	H				
1307	2	1	1.3690	2	V				
1307	3	1	1.3720	2	H				
1307	4	1	1.3460	2	V	MAST			
1307	5	1	1.2980	1	H				
1307	6	1	1.2190	1	V	MAST			
1307	7	1	1.2540	2	H	MAST			
1307	8	4	.	.					
1307	9	1	1.2700	2	V				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 1000 ppm Methyl Ethyl Ketone -----									
Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1307	10	1	1.3220	1	H				
1307	11	1	1.3120	1	V				
1307	12	1	1.2450	2	H				
1320	1	1	1.3330	2	V	SURB			
1320	2	1	1.2050	2	H	SURB			
1320	3	1	1.3470	2	V				
1320	4	1	1.2500	2	H				
1320	5	1	1.3700	2	V				
1320	6	1	1.3720	1	H				
1320	7	1	1.4090	2	V				
1320	8	1	1.4440	1	H				
1320	9	1	1.4340	2	V				
1320	10	1	1.4350	1	H				
1320	11	1	1.4000	1	V				
1332	1	4	.	.					
1332	2	1	1.4090	1	V	SURB			
1332	3	1	1.3020	1	H	SURB			
1332	4	1	1.4840	1	V				
1332	5	1	1.4170	2	H	MAST	SURB		
1332	6	1	1.3520	2	V	MAST	SURB		
1332	7	1	1.2060	1	H	SURB			
1332	8	1	1.3120	2	V				
1332	9	1	1.2820	2	H	SURB			
1332	10	1	1.3020	2	V	MAST	SURB		
1332	11	4	.	.					
1332	12	1	1.3430	1	H	SURB			
1332	13	1	1.3560	2	V	MAST	SURB		
1332	14	1	1.4260	1	H	CLPA	SURB		
1343	1	1	1.6245	1	H	OSST			
1343	2	1	1.6660	1	V				
1343	3	2	.	.					
1343	4	1	1.4030	2	H	MAST			
1343	5	1	1.4694	1	V	MAST			
1343	6	2	.	.					
1343	7	1	1.4079	1	H				
1343	8	1	1.4776	1	V	OSST			
1343	9	1	1.1713	2	H	MAST			
1343	10	1	1.4194	1	V	FUST	MAST		
1343	11	1	1.4124	1	H				
1343	12	1	1.4504	2	V	OSST			
1362	1	1	1.4340	2	H	MAST			
1362	2	1	1.3050	1	V				
1362	3	1	1.2850	2	H				
1362	4	1	1.2820	2	V				
1362	5	1	1.3240	1	H				
1362	6	1	1.3660	1	V				
1362	7	1	1.2920	2	H	OSST	SURB		

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 1000 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1362	8	1	1.402	1	V				
1362	9	1	1.405	1	H	MAST			
1362	10	1	1.389	1	V				
1362	11	1	1.367	2	H	MAST			
1362	12	1	1.430	1	V				
1371	1	1	1.451	2	V				
1371	2	1	1.322	2	H				
1371	3	1	1.248	2	V				
1371	4	1	1.277	2	H				
1371	5	1	1.301	1	V				
1371	6	1	1.307	1	H				
1371	7	1	1.232	2	V	SURB			
1371	8	1	1.315	2	H				
1371	9	1	1.091	2	V	ROST			
1371	10	1	1.247	2	H				
1371	11	1	1.337	2	V				
1371	12	1	1.479	1	H				
1371	13	1	1.357	1	V				
1371	14	1	1.273	2	H				
1373	1	1	1.512	1	V				
1373	2	1	1.397	1	H				
1373	3	2	.	.	.				
1373	4	1	1.540	1	V	MAST			
1373	5	1	1.335	1	H	MAST			
1373	6	1	1.297	2	V				
1373	7	1	1.370	1	H				
1373	8	1	1.436	1	V				
1373	9	1	1.261	1	H	MAST			
1373	10	1	1.350	2	V	MAST	ROST		
1373	11	1	1.276	2	H	MAST			
1373	12	1	1.393	2	V				
1415	1	1	1.341	2	H				
1415	2	1	1.249	1	V				
1415	3	1	1.177	2	H				
1415	4	1	1.234	1	V				
1415	5	1	1.174	2	H	MAST			
1415	6	4	.	.	.				
1415	7	1	1.036	1	V				
1415	8	1	1.203	2	H	MAST			
1415	9	4	.	.	.				
1415	10	1	1.235	2	V				
1415	11	1	1.303	1	H	MAST			
1415	12	4	.	.	.				
1415	13	1	1.277	1	V	MAST			
1415	14	1	1.248	1	H	SURB			
1415	15	1	1.183	1	V				
1415	16	1	1.250	1	H				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 1000 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1415	17	1	1.284	1	V				
1418	1	1	1.879	2	H	MAST			
1418	2	1	1.418	2	V	ROSK	ROST		
1418	3	1	1.261	1	H				
1418	4	1	1.351	1	V	MAST			
1418	5	2	.	.	.				
1418	6	1	1.233	2	H				
1418	7	1	1.413	1	V				
1418	8	1	1.377	2	H				
1418	9	1	1.438	1	V	MAST			
1418	10	1	1.358	2	H				
1418	11	2	.	.	.				
1421	1	1	1.488	1	V				
1421	2	1	1.251	2	H				
1421	3	1	1.388	1	V				
1421	4	1	1.211	2	H	SURB			
1421	5	1	1.288	2	V				
1421	6	1	1.388	1	H	MAST			
1421	7	1	1.848	2	V				
1421	8	1	1.417	1	H	MAST			
1421	9	1	1.281	1	V				
1421	10	1	1.278	1	H				
1421	11	1	1.328	2	V				
1421	12	1	1.378	1	H				
1431	1	1	1.421	2	V				
1431	2	1	1.443	2	H				
1431	3	1	1.388	1	V				
1431	4	1	1.341	2	H				
1431	5	1	1.335	2	V				
1431	6	1	1.311	2	H				
1431	7	1	1.317	1	V				
1431	8	1	1.258	2	H				
1431	9	1	1.382	2	V				
1431	10	1	1.488	2	H				
1431	11	1	1.397	1	V				
1431	12	1	1.341	2	H				
1431	13	4	.	.	.				

C.29

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption
Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 3000 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1102	1	1	0.9898	2	V				
1102	2	1	1.1425	1	H	SURB			
1102	3	1	1.0083	1	V	SURB			
1102	4	1	1.0806	2	H				
1102	5	1	1.0749	2	V	SURB			
1102	6	1	1.0602	2	H				
1102	7	1	1.0258	2	V				
1102	8	1	1.0111	2	H	SURB			
1102	9	5	.	.					
1102	10	1	1.0313	1	V	SURB			
1102	11	1	1.0141	2	H	SURB			
1102	12	1	1.0547	2	V				
1102	13	2	.	.					
1102	14	1	1.1585	1	H	MAST			
1107	1	1	1.4240	1	H	MAST			
1107	2	1	1.3460	1	V				
1107	3	1	1.3690	2	H				
1107	4	1	1.3210	1	V				
1107	5	1	1.3580	1	H				
1107	6	1	1.3470	2	V				
1107	7	1	1.3390	2	H				
1107	8	1	1.3390	1	V				
1107	9	1	1.3080	1	H				
1107	10	1	1.3080	1	V				
1107	11	1	1.3790	2	H	MAST			
1107	12	1	1.4150	1	V				
1110	1	1	1.3750	1	H	SURB			
1110	2	1	1.3420	1	V				
1110	3	2	.	.					
1110	4	1	1.3480	1	H				
1110	5	1	1.3330	1	V	MAST	SURB		
1110	6	1	1.2540	2	H				
1110	7	1	1.2450	2	V				
1110	8	1	1.1540	2	H	SURB			
1110	9	1	1.3890	2	V				
1110	10	1	1.2230	1	H	MAST			
1110	11	1	1.3920	2	V				
1110	12	1	1.3570	2	H	SURB			
1110	13	1	1.3650	2	V				
1122	1	1	1.3610	2	V				
1122	2	1	1.3710	1	H	MAST			
1122	3	1	1.3380	2	V	SURB			
1122	4	1	1.2950	2	H				
1122	5	1	1.3710	1	V				
1122	6	1	1.3210	1	H				
1122	7	1	1.2210	2	V				
1122	8	1	1.1870	2	H	MAST	ROST		

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 3000 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1122	9	1	1.212	2	V	MAST	ROST		
1122	10	1	1.362	1	H				
1122	11	1	1.309	1	V	MAST	ROST		
1122	12	1	1.265	2	H				
1130	1	1	1.271	1	H	SURB			
1130	2	1	1.267	1	V	ROSK	SURB		
1130	3	1	1.092	2	H	SURB			
1130	4	1	1.131	2	V	ROSK	SURB		
1130	5	1	1.168	1	H				
1130	6	1	1.196	1	V	SURB			
1130	7	1	1.222	2	H	SURB			
1130	8	1	1.093	2	V				
1130	9	1	1.094	2	H				
1130	10	1	1.177	1	V	SURB			
1130	11	1	1.066	2	H	SURB			
1130	12	4	.	.	.				
1130	13	1	1.154	1	V				
1130	14	1	1.107	2	H				
1136	1	1	1.319	2	H				
1136	2	1	1.386	1	V	SURB			
1136	3	1	1.337	1	H				
1136	4	1	1.288	1	V				
1136	5	1	1.208	1	H				
1136	6	1	1.283	2	V				
1136	7	1	1.284	2	H				
1136	8	1	1.211	2	V				
1136	9	1	1.237	2	H				
1136	10	1	1.260	1	V				
1136	11	1	1.247	2	H				
1136	12	1	1.313	1	V				
1136	13	1	1.252	2	H				
1179	1	1	1.324	1	V				
1179	2	1	1.205	2	H				
1179	3	1	1.216	2	V	LMFL			
1179	4	1	1.315	1	H				
1179	5	1	1.132	2	V				
1179	6	1	1.264	2	H				
1179	7	1	1.246	1	V				
1179	8	1	1.119	2	H				
1179	9	1	1.316	1	V				
1179	10	1	1.242	1	H				
1179	11	1	1.233	2	V	MAST			
1179	12	1	1.335	1	H	MAST			
1179	13	1	1.200	2	V				
1179	14	1	1.212	2	H	MAST			
1179	15	1	1.282	2	V	MAST			
1184	1	1	1.307	2	V				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 3000 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1184	2	1	1.291	1	H	MAST			
1184	3	1	1.333	2	V				
1184	4	1	1.321	1	H				
1184	5	1	1.378	1	V				
1184	6	1	1.149	2	H	SURB			
1184	7	1	1.261	1	V				
1184	8	1	1.297	1	H				
1184	9	1	1.324	2	V				
1184	10	1	1.144	2	H				
1186	1	1	1.396	2	V				
1186	2	1	1.217	2	H				
1186	3	1	1.288	2	V				
1186	4	1	1.288	1	H	MAST			
1186	5	1	1.289	2	V				
1186	6	1	1.272	2	H				
1186	7	1	1.343	2	V	MAST			
1186	8	1	1.319	1	H				
1186	9	1	1.384	1	V				
1186	10	1	1.289	1	H				
1186	11	1	1.272	1	V	MAST	SURB		
1186	12	1	1.244	1	H				
1186	13	1	1.161	2	V				
1186	14	1	1.286	1	H				
1186	15	1	1.296	1	V				
1187	1	1	1.341	2	V	SYND			
1187	2	1	1.289	2	HV	SYND			
1187	3	1	1.218	2	V	SYND	MAST		
1187	4	1	1.268	1	H	SURB			
1187	5	1	1.315	2	V				
1187	6	1	1.298	2	H				
1187	7	1	1.178	2	V				
1187	8	1	1.228	2	H	MAST	ROST		
1187	9	1	1.286	1	V	SYND	MAST		
1187	10	1	1.252	2	H	MAST			
1187	11	1	1.262	2	V	SYND			
1193	1	1	1.318	2	H	SURB			
1193	2	1	1.257	1	V	ROSK			
1193	3	1	1.257	2	H	SURB			
1193	4	1	1.248	2	V	SURB			
1193	5	1	1.311	2	H	SURB			
1193	6	1	1.313	1	V	ROSK	SURB		
1193	7	1	1.336	1	H	MAST			
1193	8	1	1.329	1	V	ROSK			
1193	9	1	1.278	2	H				
1193	10	1	1.488	1	V	MAST	SURB		
1203	1	1	1.417	2	V				
1203	2	1	1.386	1	H				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 3000 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1203	3	1	1.353	1	V				
1203	4	1	1.333	1	H				
1203	5	2	.	.	.				
1203	6	1	1.343	2	V				
1203	7	1	1.348	1	H				
1203	8	1	1.463	1	V				
1203	9	1	1.274	2	H				
1203	10	1	1.286	2	V				
1203	11	1	1.306	2	H				
1203	12	1	1.860	2	V				
1206	1	1	1.379	2	V				
1206	2	1	1.803	2	H				
1206	3	1	1.122	2	V				
1206	4	1	1.433	1	H	SURB			
1206	5	1	1.473	1	V				
1206	6	1	1.241	2	H				
1206	7	1	1.342	1	V				
1206	8	1	1.304	1	H				
1206	9	1	1.489	1	V	SURB			
1206	10	1	1.399	1	H				
1206	11	1	1.399	1	V				
1206	12	1	1.177	1	H				
1206	13	1	1.250	1	V				
1206	14	1	1.401	2	H				
1209	1	1	1.363	1	H	ROST	MAST		
1209	2	1	1.276	1	V	SURB			
1209	3	1	1.384	2	H	MAST			
1209	4	1	1.359	2	V				
1209	5	1	1.291	1	H	MAST	SURB		
1209	6	1	1.376	1	V	SURB			
1209	7	1	1.340	2	H				
1209	8	1	1.312	2	V				
1209	9	1	1.309	2	H	MAST			
1209	10	2	.	.	.				
1209	11	1	1.152	2	V	FUST	MAST	OSST	SURB
1209	12	1	1.352	1	H	MAST	SURB		
1209	13	1	1.167	2	V	SURB			
1209	14	1	1.370	2	H	MAST	SURB		
1209	15	1	1.383	1	V	MAST	SURB		
1266	1	1	1.291	2	V				
1266	2	1	1.306	1	H	SURB			
1266	3	1	1.301	2	V				
1266	4	1	1.436	1	H				
1266	5	4	.	.	.				
1266	6	1	1.309	1	V				
1266	7	1	1.364	1	H				
1266	8	1	1.319	1	V				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 3000 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1266	9	1	1.4140	2	H				
1266	10	1	1.3710	1	V				
1266	11	1	1.3270	1	H				
1290	1	5	.	.					
1290	2	1	1.4300	1	H	MAST			
1290	3	4	.	.					
1290	4	1	1.2630	2	V				
1290	5	1	1.3440	2	H				
1290	6	1	1.3530	1	V				
1290	7	1	1.3930	1	H				
1290	8	1	1.4340	2	V				
1290	9	1	1.3930	1	H				
1290	1	1	1.2790	1	H	OSST			
1290	2	1	1.3210	1	V	OSST	SURB		
1290	3	1	1.2850	2	H				
1290	4	1	1.2550	1	V	SURB			
1290	5	4	.	.					
1290	6	1	1.2670	1	H				
1290	7	1	1.3530	1	V				
1290	8	1	1.3800	1	H	SURB			
1290	9	1	1.4170	1	V				
1290	10	1	1.3750	1	H	SURB			
1300	1	2	.	.					
1300	2	1	1.3305	2	H	SURB			
1300	3	1	1.3087	1	V				
1300	4	1	1.1910	1	H				
1300	5	1	1.2780	1	V				
1300	6	1	1.2297	1	H	MAST			
1300	7	4	.	.					
1300	8	1	1.2430	2	V				
1300	9	1	1.2404	1	H				
1300	10	1	1.2890	1	V	SURB			
1300	11	1	1.2583	1	H				
1300	12	1	1.1731	1	V	MAST	SURB		
1300	13	1	1.2405	2	H				
1310	1	1	1.0194	2	H				
1310	2	1	1.3024	2	V				
1310	3	1	1.4087	1	H				
1310	4	1	1.8088	2	V				
1310	5	1	1.3283	2	H	MAST			
1310	6	1	1.2541	2	V	MAST			
1310	7	1	1.3549	1	H				
1310	8	1	1.3381	2	V				
1310	9	1	1.3455	2	H	MAST			
1317	1	1	1.1510	1	V	ROST			
1317	2	1	1.1050	2	H				
1317	3	1	1.0770	1	V				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 3000 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1317	4	1	1.198	2	H	ROST			
1317	5	4	.	.					
1317	6	1	1.158	1	V	ROST			
1317	7	1	1.048	1	H	ROST			
1317	8	1	1.028	1	V				
1317	9	1	1.257	1	H	ROST			
1317	10	1	1.189	1	V				
1325	1	1	1.417	1	H				
1325	2	1	1.285	2	V				
1325	3	1	1.401	2	H	SURB			
1325	4	2	.	.					
1325	5	1	1.284	1	V	SURB			
1325	6	1	1.372	2	H	SURB			
1325	7	1	1.308	2	V	MAST			
1325	8	1	1.279	2	H				
1325	9	1	1.427	1	V				
1325	10	1	1.327	2	H				
1325	11	1	1.384	1	V	SURB			
1325	12	1	1.245	2	H				
1325	13	1	1.281	2	V				
1334	1	1	1.322	1	V				
1334	2	1	1.241	1	H				
1334	3	1	1.217	1	V	SURB			
1334	4	1	1.220	2	H				
1334	5	1	1.278	2	V				
1334	6	1	1.302	2	H				
1334	7	1	1.252	2	V				
1334	8	1	1.297	2	H	MAST			
1334	9	1	1.244	2	V				
1334	10	2	.	.					
1334	11	1	1.199	1	H				
1334	12	1	1.261	2	V				
1334	13	1	1.237	1	H				
1348	1	4	.	.					
1348	2	1	1.427	1	V	ROST	SURB		
1348	3	1	1.372	1	H	OSST			
1348	4	1	1.240	2	V	MAST			
1348	5	1	1.393	1	H	OSST			
1348	6	4	.	.					
1348	7	1	1.310	1	V				
1348	8	1	1.198	2	HV	LMFL			
1348	9	1	0.975	1	V				
1348	10	1	1.279	2	H				
1348	11	1	1.262	1	V	MAST			
1348	12	4	.	.					
1348	13	1	1.318	2	H				
1348	14	1	1.366	2	V				

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

----- 3000 ppm Methyl Ethyl Ketone -----

Matno	Site	Status	Fetal Wt(g)	Sex	Head or Visceral	ABN1	ABN2	ABN3	ABN4
1366	1	1	1.446	2	H				
1366	2	1	1.477	1	V	SURB			
1366	3	1	1.457	1	H				
1366	4	1	1.350	2	V	MAST			
1366	5	1	1.396	1	H				
1366	6	1	1.507	1	V	SURB			
1366	7	1	1.471	1	H	MAST			
1366	8	4	.	.					
1366	9	1	1.428	1	V				
1366	10	1	1.294	2	H	MAST			
1366	11	1	1.461	1	V				
1366	12	1	1.415	1	H				
1384	1	1	1.387	1	V	FURB			
1384	2	4	.	.					
1384	3	1	1.411	2	H	MAST			
1384	4	2	.	.					
1384	5	1	1.405	1	V	SURB			
1384	6	1	1.344	2	H				
1384	7	1	1.359	2	V	MAST	SURB		
1384	8	1	1.370	2	H				
1384	9	1	1.196	2	V	SURB			
1384	10	1	1.271	2	H	SURB			
1384	11	1	1.216	2	V	MAST			
1384	12	1	1.317	1	H	SURB			
1406	1	1	1.346	1	H	MAST			
1406	2	1	1.382	1	V	MAST			
1406	3	1	1.349	1	H				
1406	4	1	1.251	1	V				
1406	5	1	1.411	1	H				
1406	6	1	1.391	1	V				
1406	7	1	1.242	2	H	MAST	ROST	SURB	
1406	8	1	1.248	2	V				
1406	9	1	1.342	1	H				
1406	10	1	1.208	1	V				
1406	11	1	1.427	1	H				
1429	1	1	1.282	2	V				
1429	2	1	1.252	1	H				
1429	3	1	1.303	1	V	MAST			
1429	4	1	1.259	1	H				
1429	5	1	1.201	1	V				
1429	6	1	1.124	2	H	MAST			
1429	7	1	1.219	2	V				
1429	8	1	1.273	1	H	MAST			
1429	9	1	1.274	1	V	MAST	ROST		
1429	10	1	1.113	2	H	MAST	ROST		
1429	11	1	1.223	2	V				
1429	12	1	1.236	1	H	MAST			

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption

Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

```

----- 3000 ppm Methyl Ethyl Ketone -----
Matno   Site   Status   Fetal   Sex   Head   ABN1   ABN2   ABN3   ABN4
         Wt(g)   or Visceral
1429     13     1       1.073   1     V     SURB
1429     14     1       1.259   2     H
1440     1     1       1.548   1     V     LMFL   SURB
1440     2     1       1.388   2     H     MAST
1440     3     1       1.479   2     V     SURB
1440     4     1       1.319   1     H     MAST
1440     5     1       1.888   2     V
1440     6     1       1.520   1     H     OSST
1440     7     1       1.424   2     V
1440     8     1       1.308   2     H
1440     9     1       1.393   2     V
1440    10     2
1440    11     1       1.452   1     H
1440    12     1       1.360   2     V     SURB
1440    13     1       1.360   2     H
1440    14     1       1.497   1     V

```

Status: 1 = Live; 2 = Early Resorption; 4 = Late Resorption
Sex: Male = 1; Female = 2; See Code Sheet 29 for Identification of abnormalities [ABNn]

Methyl Ethyl Ketone Mouse Teratology Study: Raw Fetal Data

Code Sheet for Fetal Abnormalities

LMFL	Limb Flexure
MAST	Malaligned Sternebrae
OSST	Ossification Site Between Sternebrae
SURB	Supernumerary Rib
ROST	Reduced Ossification Sternebra
ROSK	Reduced Ossification Skull
KITA	Kinked Tail
CLPA	Cleft Palate
FUST	Fused Sternebra
FURB	Fused Ribs
MIVE	Missing Vertebrae
SYND	Syndactyly

Contemporary Control Data for Swiss (CD-1) Mice
(N = 111 Litters; Mean $\pm$ SD).

	Number	Percent
Maternal Weight; 18 dg	54.3 $\pm$ 4.9	—
Gravid Uterine Weight	19.9 $\pm$ 3.9	—
Extra-gestational Weight Gain	6.6 $\pm$ 2.0	—
Implants	12.5 $\pm$ 2.4	—
Live Fetuses	11.7 $\pm$ 2.4	93.7 $\pm$ 7.2
Early Resorptions	0.6 $\pm$ 0.8	4.4 $\pm$ 6.2
Late Resorptions	0.2 $\pm$ 0.5	1.9 $\pm$ 3.8
Dead Fetuses	0.0 $\pm$ 0.0	0.0 $\pm$ 0.0
Total Intrauterine Death	0.8 $\pm$ 0.9	6.3 $\pm$ 7.2
Litters with Resorptions	72	64.9
Fetal Weight	1.35 $\pm$ 0.13	—
Male	1.38 $\pm$ 0.12	—
Female	1.33 $\pm$ 0.12	—

Contemporary Control Data on Swiss (CD-1) Mouse Teratology Studies:
Malformations and Variations.

		Fetuses (a) Number (Percent)	Litters Number (Percent)	Mean Percent per Litter ($\pm$ SD)
Total examined (b)		1144	111	—
Heads examined (c)		—	—	—
Skulls examined (d)		—	—	—
Malformations				
Exencephaly	No. (%)	1 (0.1)	1 (0.9)	0.1 ± 1.1
Folded Retina	No. (%)	2 (0.2)	2 (1.8)	0.2 ± 1.3
Limb Flexure	No. (%)	12 (1.0)	8 (7.2)	0.8 ± 3.3
Total Fetuses (Litters) with Malformations		No. (%)	14 (12.0)	1.0 ± 3.5
Variations				
Misaligned Sternebrae	No. (%)	26 (2.3)	17 (15.3)	2.0 ± 5.8
Supernumerary Rib	No. (%)	207 (18.1)	65 (58.6)	18.0 ± 24.4
Reduced Ossifications				
Sternebrae	No. (%)	35 (3.1)	24 (21.6)	2.7 ± 5.8
Skull	No. (%)	9 (0.8)	5 (4.5)	0.8 ± 4.0
Total Fetuses (Litters) with Variations or Reduced Ossifications		No. (%)	269 (23.6)	23.2 ± 24.5

- (a) A single fetus may be represented more than once in this table.
 (b) All fetuses examined for external, visceral and skeletal defects. All fetuses stained with alcian blue and alizarin red S, one-half had heads removed prior to staining.
 (c) Heads removed from fetuses and fixed in Bouin's solution then examined for soft-tissue cranio-facial malformations.
 (d) Heads remained on the fetuses that were stained for skeletal examination; see (a) above.

Methyl Ethyl Ketone Mouse Teratology: Calendar of Events

Exposure levels; treatments 1-4	0, 400, 1000, 3000 ppm MEK
Ordered mice	5-16-88
Received mice ARS #880059	6-20-88
Eartagged and weighed	7-7-88
Virgins selected	7-7-88
Health screen	7-11-88
Virgins individually caged	7-11-88
Virgins weighed and randomized	7-17-88
Mated 0dg (# positive)	(A) 7-14-88 (41)
weighed, randomized, individually caged	(B) 7-15-88 (36)
	(C) 7-16-88 (77; 55 on study)
Released from quarantine	7-17-88
Moved to exposure room	7-18-88
Exposure (7 hours/day; 6-15 dg)	(A) 7-20 to 7-29-88
	(B) 7-21 to 7-30-88
	(C) 7-22 to 7-31-88
Placed into holding chamber 16dg	(A) 7-30-88
	(B) 7-31-88
	(C) 8-1-88
Weighed (6dg) started exposure	(A-C) 7-20 to 7-22-88
Weighed (9dg)	(A-C) 7-23 to 7-25-88
Weighed (12dg)	(A-C) 7-26 to 7-28-88
Weighed (15dg)	(A-C) 7-29 to 7-31-88
Sacrificed (18dg)	(A) 8-1-88
	(B) 8-2-88
	(C) 8-3-88
Virgins - exposed 10 days	7-21 to 7-30-88
Placed into holding chamber day 11	7-31-88
Weighed exposure day 1	7-21-88
Weighed exposure day 5	7-25-88
Weighed exposure day 10	7-30-88
Sacrificed	8-2-88
Completed fetal specimen exams	9-7-88

METHYL ETHYL KETONE MOUSE TERATOLOGY STUDY DISPOSITION

Exposure Group	Treatment	Virgins	Plug-Positive Teratology Mice			
			On Study	Removed From Study	Sacrifice	Litters Examined
Control (0 ppm)	1	10	33	1 (a)	33	26
400 ppm	2	10	33	3 (b)	33	23
1000 ppm	3	10	33	0	33	26
3000 ppm	4	10	33	1 (a)	33	28

(a) One removed from study because <2 implants.

(b) Two removed from study because <2 implants.

One removed from study because of premature delivery.

APPENDIX D

ANIMAL HEALTH SCREEN

ARC RODENT HEALTH SCREEN REPORT

Investigator: Mast	Lab no: R-114
Study: Methylerythylketone	Animal/Shipment no: 880059
Building: LSL II	Date rec'd: 6/20/88
Room: 433	Source: CR 603
Date initiated: 7/11/88	Species/Strain: Mice/JD-1
	Sex: M/F Age: ED 4/20/88

Status: Received 6 male (#1-6) and 4 female (#7-10) mice for pre-exposure health screen to include gross necropsy, nasopharyngeal wash for culture and serology.

Gross Necropsy

1/10*   Skeletal   Left hind foot amputated at distal tibia; no gross evidence of infection, however tibia protrudes through skin

*Number affected/number examined

Nasopharyngeal culture

0/10 *   Beta hemolytic streptococci
0/10   Borderetella bronchiseptica
0/10   Citrobacter freundii
0/10   Coagulase positive staphylococci
0/10   Klebsiella oxytoca
0/10   Klebsiella pneumoniae
0/10   Pasturella sp.
0/10   Pseudomonas aeruginosa
0/10   Streptococcus pneumoniae

*Number of positive cultures/number cultured

Serology: Mouse

0/10 *   Mycoplasma pulmonis
0/10   Sendai virus
0/10   Pneumonia virus of mice
0/10   Mouse hepatitis virus
0/10   GD VII virus

*Number of positive tests/number tested

Histopathology

3/10 *   Liver   Rare to occasional tiny focus of inflammation in hepatic parenchyma

*Number affected/number examined

Correlation/Summary

The animal with the amputated foot was a cull and the only such animal identified from the group. The liver lesions seen are not considered indicative of significant infection or other disease. All findings are acceptable.

rec'd 7/22/88

Released for Study on 7/17/88.

Released from Quarantine on 7/17/88.

AE Gannell 7/22/88
Technologist

Hy E/kw 7/22/88
Veterinarian

Mast
Evanoff

ARC RODENT HEALTH SCREEN REPORT

Investigator: Mast	Lab no: R-129
Study: MEK - IRT	Animal/Shipment no: 880059
Building: LSL II	Date rec'd: 6/20/88
Room: 436	Source: CR R03
Date initiated: 8/1/88	Species/Strain: Mice/CD-1
	Sex: F Age: ED 4/25/88

Status: Ten mouse blood specimens received from the terminal sacrifice of the study (Animal #'s: 1185, 1113, 1290, 1194, 1259, 1206, 1211, 1316, 1406, 1102) for serologic testing.

Serology: Mouse

0/10 *	<u>Mycoplasma pulmonis</u>
0/10	Sendai virus
0/10	Pneumonia virus of mice
0/10	Mouse hepatitis virus
0/10	GD VII virus

*Number of positive tests/number tested

Correlation/Summary

All serology test results are negative for the common mouse pathogens listed above.

AE Farver 8/8/88
Technologist

John E. Kane 8/8/88
Veterinarian

Mast
✓Evanoff
Brown

APPENDIX E

QUALITY ASSURANCE STATEMENT

INHALATION TERATOLOGY STUDY OF METHYL ETHYL KETONE IN MICE

Quality Assurance Statement

Listed below are the phases and/or procedures included in the study described in this report which were reviewed by the Quality Assurance Unit during the period, 6/15/88 - 9/15/88, or specifically for this study and the dates the reviews were performed and findings reported to management. (All findings were reported to the study director or his designee at the time of the review.)

Phase/Procedure Reviewed	Review Date	Date Findings Submitted in Writing to Study Director/Management
Animal Receipt	6/20/88*	6/20/88
Data	7/4/88*	7/4/88
Animal Identification	7/7/88*	7/8/88
Body Weights	7/7/88*	7/8/88
Health Screen	7/11/88*	7/20/88
Dosing	7/14/88	8/8/88
Necropsy	8/3/88*	8/9/88
Data	8/31/88 & 9/1&7/88*	10/10/88
Data	9/13, 20 & 29/88*	9/30/88
Data	10/7/88*	10/7/88
Data	10/28/88*	11/2/88
Final Report	2/14-17, & 23/89	2/23/89

* Reviewed specifically for this study.

 Quality Assurance Specialist

2/23/89
 Date

APPENDIX F

PROTOCOL AND CAGE MAPS

STUDY PROTOCOL

**Inhalation Teratology Study of
Methyl Ethyl Ketone
in Mice**

Submitted to:

**Dr. Bernard Schwetz
Dr. Richard Morrissey
National Toxicology Program
National Institute Environmental Health Sciences
Research Triangle Park, NC**

Submitted by:

**Dr. Terryl J. Mast
Battelle - Pacific Northwest Laboratory
Richland, WA 99352**

June 21, 1988

F.1

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ATTACHMENT 2   INHALATION EXPOSURE SYSTEM

INHALATION REPRODUCTIVE TOXICOLOGY STUDY PROTOCOL

METHYL ETHYL KETONE

I. TITLE: Teratology Study of Methyl Ethyl Ketone in Mice

II. INTRODUCTION

METHYL ETHYL KETONE

INTRODUCTION

Literature pertaining to the toxicology of methyl ethyl ketone (MEK) has been reviewed through mid-1985 by R.S.H. Yang (Yang 1986); consequently, this review will deal specifically with aspects pertinent to reproductive and developmental toxicity studies. For a broader perspective the reader is referred to Dr. Yang's excellent review.

PHYSICAL AND CHEMICAL PROPERTIES

Table 1. Summary of Physical and Chemical Properties

Methyl ethyl ketone ^a	
Synonym: 2-butanone (CAS #78-93-3)	MW: 72.11
Colorless liquid with mint-like odor	Volatile
Melting Point: -86.35°C (-123.4°F)	Boiling Point: 79.6°C (175.3°C)
Flash Point: -9°C (16°F)	Specific Gravity: 0.81 @ RT
Vapor Density (air = 1): 2.42	
Flammability Limits (by volume):	
Lower: 1.8%	Upper: 11.5%
Solubility:	
Miscible in: Ether, benzene and oils	
Soluble in: Water or alcohol ≥ 100 mg/ml @ 19°C	
TLV: 8-hr, 200 ppm	

^a Condensed from Little (1987) and references therein.

METABOLISM AND PHARMACOKINETICS

The metabolism and pharmacokinetics of MEK have been studied in several laboratory species as well as in the man. DiVencenzo, Kaplan, and Dedinas (1976) reported the serum $t_{1/2}$ in male guinea pigs following a single ip injection of MEK to be 270 min (4.5 h) and the clearance time to be 12 h. These were the longest values of any of several ketones, alcohols, or diones examined. Although no pharmacokinetic parameters were reported for guinea pigs receiving repeated injections over a period of several days, the half-lives and clearance values may decrease significantly over time since MEK is known to induce hepatic metabolizing enzymes in several species. Metabolites found in the serum and urine of animals exposed to MEK have been well-characterized, are formed by both oxidative and reductive pathways, and are similar for all species examined; guinea pigs (DiVencenzo, Kaplan, and Dedinas 1976), rats (Dietz and Traiger 1979), rabbits (Sanoyeshi 1911), and humans (Perbellini et al. 1984), Figure 1. The alcohols formed may subsequently enter into intermediary metabolism or be conjugated with sulfuric

or glucuronic acid and excreted in the urine. Although, at least in the human, urinary excretion is not a major elimination route. Perbellini et al. (1984) reported that only 0.1% of the original MEK dose can be accounted for by urinary excretion products in the human, MEK and 3-hydroxy-2-butanone, thus the major elimination routes, at least in the human, remain undefined. Since MEK (as the parent compound) rapidly appears in expired air following dermal application of liquid MEK to the human skin, expiration may be a significant route of elimination (Wurster and Munies 1965).

Figure 1. Proposed metabolic pathway of MEK in mammals.

Indirect evidence for hepatic mixed-function oxidase induction by MEK (P₄₅₀-induction) was demonstrated by quantitating parent compound or major metabolites in male Wistar rats which had been exposed to mixtures of MEK and methyl butyl ketone (MBK) or to MBK alone (Abdel-Rahman 1976). Male rats were exposed by inhalation to an MEK/MBK mixture (750:225 ppm; 975 ppm total), or to MBK alone (400 ppm). That MEK and/or its metabolites apparently induce the hepatic MFO system was shown when MEK plasma values immediately post-exposure to the MEK/MBK mixture were lower following continuous exposure for 23 days than they were following a single 8-hr exposure. The opposite was shown to be the case for MBK in the presence of MEK when neither MBK nor its metabolites

were detectable in blood after a single 8-hr exposure, but increased to 24.0 mg% after the 23rd day of exposure. Plasma MBK levels for animals exposed to MBK alone were below detection limits following either a single 8-hr exposure or a 23-day continuous exposure to 400 ppm MBK, indicating that the presence of MEK affected the metabolism of the MBK. [The difference in total solvent concentration between the two exposure regimens should be kept in mind when considering these results. It is possible that the changes observed in MBK metabolism following a 23-day exposure period was not a specific alteration in the pharmacodynamics of MBK by MEK, but instead was due to general toxicity.]

Further evidence for hepatic changes following exposure of Sprague-Dawley rats to 800 ppm of MEK, six h/day, five day/wk for a duration of four weeks, was reported by Toftgard, Nilsen and Gustafsson (1981) who found increased liver weights and liver to body weight ratios in exposed animals. Microsomes prepared from the livers of exposed animals had a greater level of cytochrome P₄₅₀ per milligram of protein than did control liver microsomes, and also demonstrated an increased ability to hydroxylate benzo[a]pyrene to the corresponding phenols and quinones. However, SDS-polyacrylamide gel electrophoresis of treated microsomes revealed no significant changes in the composition of the various cytochrome P₄₅₀'s.

Distribution of MEK throughout the body is rapid due to its high solubility in blood ([blood]/[alveolar air] $\approx$ 104). Nearly equal amounts are present in all tissues, e.g. brain, kidney, lung, fat, heart, muscle, and liver. Furthermore, a statistically significant correlation was found between environmental concentrations of MEK in an Italian shoe factory, and tissue and urine levels of MEK in exposed workers (Perbellini et al. 1984).

TOXICOLOGY

In vitro

MEK has not been found to be mutagenic in either mammalian or bacterial cell test systems, but has been shown to induce aneuploidy in a yeast strain. See Yang (1986) for detail.

Animal Studies

The acute toxicity of MEK is relatively low in rodent species. See Yang (1986) for detail.

Subchronic:

Cavender, et al. (1983) performed a 90-day inhalation study of MEK on male and female Fisher 344 rats. The animals were exposed to 0, 1250, 2500, or 5000 ppm MEK, 6 h/day, 5 day/wk, for 90 days. No adverse effect on the clinical health or growth of either sex was reported for this chemical. No significant neurological lesions were observed following examination of the medulla and the right and left sciatic and tibial nerves. Evidence of hepatic mixed-function oxidase induction was indicated by significantly increased liver to body weight ratios in both sexes.

No reports on similar studies in mice were found.

Chronic:

MEK is known to potentiate n-hexane neurotoxicity as well as that caused by other hydrocarbons. It also potentiates the hepatotoxicity of chloroform. See Yang (1986) for detail.

Reproductive and Developmental:

Schwetz, Leong, and Gehring (1974) reported MEK to be embryotoxic, fetotoxic, and potentially teratogenic on the basis of results obtained from an inhalation teratology study on Sprague-Dawley rats. Timed-pregnant rats were exposed to 0, 1000, or 3000 ppm MEK on 6-15 dg. MEK exposure was found to have no effect on the number of resorptions, no treatment-related effect on the fetal crown-rump length, no effect on the sex ratio, nor any effect on maternal body weight or weight gain during gestation. Fetal body weight was slightly decreased for both exposure groups, but the decrease was significant for only the 1000 ppm group. Major fetal malformations were observed only in the 3000 ppm exposure group; one fetus in each of four litters. Two of these fetuses were acaudate and two were brachygnathic. There was also a significant increase in the percent of litters containing fetuses with skeletal anomalies (reduced ossifications and extra ribs) for both exposure groups when compared to controls. Ninety-five percent of the litters in the 1000 ppm group were affected in this manner and 81% in the 3000 ppm group. The incidence of soft-tissue anomalies (subcutaneous edema and dilated ureters) was also found to be greater in the MEK exposed groups than in the controls. This increase was statistically significant for the 3000 ppm group.

As a result of the tenuous conclusions from the study of Schwetz, Leong, and Gehring (1974), Deacon et al. (1981) further investigated the embryo- and fetotoxicity of inhaled MEK in Sprague-Dawley rats. In this study sperm-positive rats were exposed to 400, 1000, or 3000 ppm MEK, 7 hr/day, 6 - 15 dg. Dams did not exhibit any clinical signs of toxicity; however, an unspecified reduction in weight gain in the 3000 ppm exposure group was reported, an effect not observed in the earlier study [actual maternal weight data was not included in the report of Deacon et al. (1981)]. As in the earlier study there was no effect of exposure on the mean number of live fetuses or resorptions per dam. However, in agreement with the previous study, the percent of litters with fetuses exhibiting delayed ossification of vertebral centra was increased in the highest exposure group. Also previously reported, the percent of litters with fetuses having reduced ossification of the skull bones was lower in the 3000 ppm exposure group than in any of the other treatment groups or in the controls. [No fetal weight data were given in this report, nor was reference made to such data.]

In summary, the findings of these two teratology studies on MEK in the Sprague-Dawley rat are in basic agreement. Although there was no evidence of frank teratogenicity or embryotoxicity in either study, the equivocal results do not establish that MEK is free from fetotoxic or teratogenic potential in this rodent species. The decrease in the incidence of reduced ossification of the skull bones with increasing exposure concentrations, coupled with the parallel increase in the incidence of reduced vertebral ossification may be indicative of a toxic effect on development. Since no data are available for other test species, further examination of the potential of MEK to cause developmental toxicity is warranted.

Since 2-butanol is a known metabolite of MEK (Figure 1) a recent report on the developmental toxicity of that compound is of interest here. The developmental toxicity of 2-butanol was investigated by Brightwell et al. (1987) in Sprague-Dawley rats. Pregnant females were exposed in inhalation chambers to 3500, 5000, or 7000 ppm 2-butanol, 7 h/day, throughout gestation until sacrificed on 20 dg. There was evidence of maternal toxicity in the highest exposure group, manifested by a reduction in weight and food intake; however, there was no increase in the incidence of fetal malformations for any

exposure group. A reduction in mean fetal weight was observed for the 7000 ppm exposure group although this was not stated by the authors to be indicative of developmental toxicity. [No comments were made regarding the number of live offspring or resorptions.]

No reports on the effects of MEK exposure on male or female fertility were found.

Human

Due to the high volatility of MEK occupational exposures are likely to occur via inhalation whenever MEK is employed in poorly ventilated or unconfined situation. Since MEK is rapidly absorbed through the skin (described below) unprotected dermal contact may also represent a significant exposure route.

Munies and Wurster (1965) reported that MEK undergoes dermal absorption through human skin with subsequent release in expired air. The rate of dermal absorption is apparently quite rapid as evidenced by the release of MEK into expired air within 2-3 min following application of the solvent to the skin. The rates of elimination via expired air following oral or dermal exposures are similar indicating that the route of administration has little effect on the route of elimination.

Epidemiological Studies

Alderson and Rattan (1980) performed an historical perspective study on 446 men who had worked in two MEK dewaxing plants to determine the effect, if any, of occupational exposure to MEK on mortality or the incidence of malignant disease. MEK exposure was not found to have an effect on the number of observed deaths in this group; furthermore, the number of deaths due to neoplasms in this group was less than predicted. Although not considered to be clear evidence of a cancer hazard, significantly more deaths due to buccal cavity and pharynx cancers were detected in this group than had been predicted.

Considerable concern exists regarding the exposure of women of child-bearing age to industrial solvents and the subsequent potential for adverse effects on reproductive and developmental processes. 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 unexposed mothers. MEK was among the organic solvents to which the affected cohort was exposed. These authors further report that no significant difference in the incidence of children with CNS defects was found when occupational exposures to metals, pesticides, dyes, noise, temperature extremes, fumes, or radiation were used as the analysis variable.

Summary

MEK has a low acute and subchronic toxicity in experimental animals and apparently in humans. However, as evidenced by both rodent studies and human epidemiological findings, there is a cause for concern over the potential of this compound to cause developmental toxicity.

RECOMMENDATIONS

A standard teratology study in Swiss (CD-1) mice is recommended to further define the potential for MEK to cause developmental toxicity. In order that the results of this study be comparable to earlier studies conducted in the rat, it is suggested that exposure conditions be duplicated in the mouse study, e.g. 0, 400, 1000, or 3000 ppm MEK, 7 hr/day, 6 - 15 dg. Maternal liver and kidney weights should also be obtained to observe indications of MFO-induction.

III. SPONSOR AND SPONSOR'S REPRESENTATIVE

A. Sponsor:

National Institute of Environmental Health Sciences
National Toxicology Program (NTP)
P.O. Box 12233;
Research Triangle Park, N.C. 27709

B. Sponsor's Representatives:

Dr. Bernard Schwetz
Dr. Richard Morrissey

IV. TESTING LABORATORY

A. Facility

Battelle - Pacific Northwest Laboratory (PNL)
P.O.Box 999; Richland, Washington 99352

B. Study Director:

Dr. Terryl J. Mast

V. PROPOSED SCHEDULE OF EVENTS (This proposed schedule may be altered. All changes will be appended to the protocol.)

Mice

A. Animals arrive week of:	6/20/88
B. Identification of females:	7/6/88
C. Health screen :	7/11/88
D. Prestart audit for GLP compliance:	7/11/88
E. Initiate breeding procedures:	7/13/88
F. Initiate exposure :	7/20/88
G. Initiate necropsy:	8/1/88
H. Complete Exposure:	8/2/88
I. Evaluate fetal specimens:	8/8/88-9/2/88
J. Submit draft report:	10/1/88
K. Submit final report:	12/1/88

VI. TEST SYSTEM

- A. Species: mouse
- B. Strain: Mice: CrI:CD-1(ICR)BR.
- C. Number of Animals and Supplier: Charles River Breeding Laboratories,
Raleigh, NC. Mice: 90 males
330 females
- D. Age of Animals Upon Arrival: Mice: 7-8 weeks
- E. Experimental Animals (Females): 40 virgin female mice will be randomly selected and assigned to four dose groups (10/group) from the total female pool (ØB-DT-3BØB). The remaining females will be mated by placing at least two females with one male overnight in a breeding cage (ØB-DT-3BØD). Nine AM of the day that copulation is established will be designated as 0 dg (ØB-DT-3BØD).
- F. Number of Animals in Study: A minimum of 33 plug-positive female mice (to obtain 20 pregnant females) will comprise each of the four treatment groups; the minimum number of mated females to be exposed will be 132 mice. There will also be 10 virgins (females) per exposure level.

VII. EXPERIMENTAL DESIGN AND DOSE LEVELS

- A. Experimental Design: Four groups of mated female mice will be exposed to the test chemical on 10 consecutive days (6 dg - 15 dg). The animals will be removed from the exposure chambers and placed in ~~[an empty chamber, with the doors left open,~~ a holding chamber]^{6A} in the exposure room for dg 16 and 17. Each level of cages will contain a different exposure group. The animals will be necropsied on 18 dg for maternal and fetal evaluations.

In addition, 10 virgin females will be added to each exposure group for the purpose of obtaining ovaries to be used for quantitative ovarian follicle counts. These animals will be exposed for 10 days, concurrently with the mated females, and sacrificed ~~[immediately~~ 3 days]^{6A} after the last exposure period.

- B. Exposure Regimen: Chamber atmospheric concentrations of methyl ethyl ketone will be 0 (filtered air), 400, 1000, and 3000 ppm. Plug-positive and virgin mice will be exposed for 7 hrs/day for 10 consecutive days. The exposure chamber doors will be closed throughout the exposure and non-exposure periods, except during animal care procedures. Exposure chamber temperatures will be maintained at $75 \pm 3^{\circ}\text{F}$ and relative humidities at $55 \pm 15\%$. Air flow

will be maintained at 15 ± 3 CFM and the chamber pressure at approximately 1" water negative with respect to room pressure.

- C. Selection of Atmospheric Concentrations: Exposure chamber concentrations are based both on information obtained from previously published reports on inhalation toxicology studies of methyl ethyl ketone and on safety considerations.

VIII. TEST SYSTEM HOUSING, HANDLING AND ENVIRONMENTAL CONDITIONS

A. Quarantine and Acclimatization (ØB-AR-3FØ3)

1. Animal shipping crates will be examined upon arrival for evidence of conditions likely to permit exposure to pathogens (soiled, wet or otherwise damaged).
2. The uncrating will be conducted at the door of the quarantine room. While being removed from the crates the animals will be examined for evidence of shipping stress.
3. The animals will be quarantined and acclimatized in room 433 of the LSL-II Building for 3-4 weeks prior to the start of the study.
4. During part of the quarantine/acclimatization period the animals will be housed by sex, approximately 10 mice per cage in wire cages on flush racks. The cage space will meet the requirements stated in the NIH "Guide for Care and Use of Laboratory Animals".
5. During the breeding period the animals will be housed in the quarantine room.
6. Plug-positive mice will be acclimated from 0 dg in individual compartments of wire-mesh cages within exposure chambers (with chamber doors open). Virgin females will be acclimated for approximately 1 week prior to exposure under the same conditions.
7. Room temperature during the acclimatization and exposure periods will be maintained at $75\pm 3^{\circ}$ F and relative humidity at $50\pm 15\%$. These measurements will be recorded at least twice daily.
8. Twelve hours light and twelve hours dark will be maintained with light starting at 0600.
9. Five male and five female animals will be randomly selected for pre-exposure health screening (ØB-AR-3FØ2). They will be examined by gross necropsy, histopathology and nasopharyngeal culture for evidence of disease and the presence of potentially pathogenic organisms.
10. The clinical veterinarian will make a visual inspection of the animals to be used in the study just prior to their release for the study (documented on the last quarantine/ acclimatization record).
11. As an added screen for viral infection, 5 animals from the control group and 5 animals from the highest dose group will be

tested promptly after sacrifice at BNW for viral pathogens (ØB-AR-3B1R).

12. Females not selected for the study or health screen will be discarded during the first exposure week. The disposition of these females will be recorded on the Animal Disposition Record and retained in the study files (ØB-AR-3FØ3). Males (they are not individually identified) will also be discarded.

B. Feed (ØB-AR-3FØ5)

1. NTP pre-approved NIH-Ø7 Open Formula Diet (pellets) from Ziegler Bros., Inc., Gardner, PA will be used during the quarantine/acclimatization periods and throughout the duration of the experiment.
2. Feed will be provided ad libitum in slot feeders during the experiment, except during exposure hours.

C. Water

1. Fresh softened water (ion exchange softener, Illinois Water Treatment Company, Model 2R-2240, Rockford, IL) will be supplied ad libitum at all times. The hardness of the water will be checked approximately once every week. Records will be retained in the LSL-II Building Engineer's office.
2. The automatic watering system (Edstrom Industries, Waterford, WI) will be used for the quarantine/acclimatization period and throughout the duration of the study.
3. A representative sample of animal drinking water from one of the NTP study rooms will be analyzed for contaminants at least once each calendar year.

- D. Randomization: Virgin females will be randomly chosen from the pool of female animals based on the first body weight (taken at the time of ear tagging). During the week prior to the start of exposure virgins will be weighed and randomly assigned to a treatment group by means of a computer-assisted randomization program which is based on a single blocking factor, body weight (ØB-DT-3BØB).

On the day of plug detection (0 dg), the mated animals will be weighed and assigned to dose groups as described above.

E. Identification:

1. All female animals will be individually identified by metal ear tags during the first weighing session (ØB-AR-3FØC)
2. Cage maps (ØB-DT-3BØ3) showing placement of individual animals in each cage unit of the exposure chamber will be prepared and updated as needed. Each exposure chamber will be identified by chamber number and exposure level. The proposed arrangement of the exposure chambers in the exposure room is included in Figure 2.

IX. TEST ARTICLE

A. Chemical name: methyl ethyl ketone

B. Formula: $\text{CH}_3\text{COCH}_2\text{CH}_3$ or $\text{C}_4\text{H}_8\text{O}$

C. CAS No.: 78-93-3

D. Manufacturer: J.T. Baker Chemical Company
222 Red School Lane
Phillipsburg, N.J. 08865
1-800-582-2537

E. BNW LOT No.: 52713-28 (received May 19, 1988); RTI No.: 5598-136-01. Manufacturers Lot No.: not assigned. BNW Lot No. 52713-12 (received May 13, 1988) will be used for test generation purposes only.

F. The vehicle control will be filtered air.

G. Storage conditions: The reservoir is maintained in a flammable storage cabinet at room temperature in the LSL-II Building. The remaining inventory is stored at or below 75°F in a chemical storage facility adjacent to the LSL-II.

H. Analytical Chemistry

1. Upon receipt, identity and gross purity analyses of the bulk chemical will be performed by infrared spectroscopy. Bulk purity is periodically determined using gas chromatography.

2. Methyl ethyl ketone concentrations within the exposure chambers will be monitored using an HP-5840 gas chromatographic system. Details of the calibration method are given in Attachment 2.

Detector: Flame Ionization

Column: 20" x 1/8" OD nickel

Packing: Porapak PS

Column Temperature: 130°C (isothermal)

Carrier: Nitrogen

Carrier Flow: 20-30 ml/min

Sample valve: Hastalloy C mounted in GC oven (Valco)

Sample Loop: 0.25 ml nickel

Stream Select Valve: 8-port, Hastalloy C mounted in GC oven (Valco)

On-Line standard: 1000 ppm Methyl Ethyl Ketone in N_2

Calibration Frequency: Daily check against on-line standard, additional checks against grab samples as indicated by the on-line standard and as indicated by I.6 in section IX.

Control Range: Target concentration $\pm 10\%$

Critical Limits: Target concentration $+20\%$, alarmed (shut off vapor flow to the chamber). Target concentration -20% , alarmed (operator makes necessary adjustments and documents the excursion).

3. The calibration of the on-line chamber monitor is based on analysis of bubbler grab samples. The calibration of the on-line monitor is directly tied to gravimetrically prepared standard solutions in dimethylformamide (DMF) through a GC which is off-line. The gravimetrically calibrated off-line GC is used to measure the quantity of methyl ethyl ketone collected from exposure chambers in DMF filled bubblers. The relationship between the peak area observed with the on-line GC and the concentration of concentrations determined by the gravimetrically calibrated GC. The analysis of bubbler grab samples is performed using a HP5840 GC with a glass column packed with 10% Carbowax 20 m (TPA) on 80/100 mesh Chromosorb WAW with an oven temperature of 50°C (with follow-up temperature programing to elute the DMF solvent peak).
4. Building exhaust effluent is analyzed for residual test material by sample collection on charcoal and analysis by gas chromatography.
5. Chamber samples will be analyzed for degradation products by gas chromatography.

I. Analysis Schedule

1. Purity analysis will be performed on the bulk chemical upon receipt, at four month intervals thereafter, and will be performed within 30 days of the start of animal exposures.
2. The highest concentration exposure chamber will be monitored for residual methyl ethyl ketone once before the start and once during the study.
3. The building exhaust will be monitored for residual chemical once during the study.
4. The composition of residual test material taken from the generator at the end of an exposure day will be characterized prior to the start of the study.
5. The stability of the test material in the highest and lowest concentration exposure chambers will be characterized prior to the start of the study. This characterization will be repeated with occupied chambers following the initiation of animal exposures.
6. During exposures the on-line monitor calibration will be confirmed by quantitative analysis of grab samples during the first week of exposure and every other week thereafter.
7. Drift of the on-line monitor calibration will be checked daily against an on-line compressed gas standard.

X. DESCRIPTION OF INHALATION EXPOSURE SYSTEM

The inhalation chambers will be located in room 436 of the LSL-II building. A detailed description of the inhalation exposure system to be used in this study is included in Attachment 2 of this protocol. The location of the exposure room and chamber layout are shown in Figure 2.

A. Environmental Monitoring

1. Air filtration: HEPA and charcoal filters will be used for intake air, and a HEPA filter will be used for exhaust air.
2. Temperatures will be monitored by RTDs multiplexed to a digital thermometer with computer data acquisition at approximately 4-hour cycles for 24 hours per day. The control range is $75 \pm 3^\circ \text{F}$ with critical limits, <70 or $>80^\circ \text{F}$. Any chamber temperature excursion beyond the critical limits will be recorded and alarmed automatically.
3. Relative humidity will be monitored by a single dew point hygrometer in conjunction with a multiplexed sampling system with computer data acquisition at approximately 4-hour cycles, 24 hours per day. The control range is $55 \pm 15\%$ with critical limits of $<35\%$ or $>75\%$. Any relative humidity excursion beyond the critical limits will be recorded and alarmed automatically.
4. Chamber air flow will be monitored at an exhaust orifice using a multiplexed Validyne pressure transducer system with computer data acquisition at approximately 4-hour cycles, 24 hours per day. The control range is 15 ± 3 air changes/hour ($=15 \pm 3 \text{ CFM}$) with critical limits of $<10 \text{ CFM}$ or $>20 \text{ CFM}$. Any chamber flow excursion beyond critical limits will be recorded and alarmed automatically. A critically low flow will result in automatic termination of the exposure. Methyl ethyl ketone concentrations in the chambers will be controlled primarily by the adjustment of chamber air flow.
5. Chamber vacuum will be monitored using a multiplexed Validyne pressure transducer system with computer data acquisition at approximately 4-hour cycles, 24 hours per day. The control range is -0.2 to -2.0 inches of water pressure with critical limits set at the same values. Any chamber vacuum excursion beyond the critical limits will be recorded and alarmed automatically. If chamber vacuum exceeds the limits of -0.2 inch of water, the exposure will be automatically terminated.
6. Uniformity of the concentration of the test chemical in each of the chambers will be determined during the development of exposure generation without animals. Chamber uniformity will be verified within the first week of the mouse teratology study. A between port and within port variability of $\leq 5\%$ RSD will be considered acceptable.
7. The exposure chambers test chemical buildup and decay time will be determined prior to start of the study to determine the T_{90} value.

These curves will be verified within the first week of the mouse exposures.

8. Prior to the start of the study and once in the high level chamber during the mouse exposures, samples will be taken from all chambers using a Gardner condensation nuclei counter to assure that the vapor generation does not produce an aerosol of methyl ethyl ketone.
9. A study of test material stability in the exposure chambers and in the generator reservoir will be conducted during the developmental work without animals in the chambers and once during the first week of the mouse exposures. The chamber samples will be taken from the high and low dose chambers during the last hour of exposure. A generator reservoir sample will be taken at the end of an exposure day.

Figure 2. Detailed layout of the exposure rooms of the Exposure Suite in which the Methyl Ethyl Ketone Study will be conducted.

B. Effluent Treatment

Chamber exhaust will be diluted to comply with applicable State and Federal Regulations prior to release from the building exhaust stack.

XI. EXPERIMENTAL OBSERVATIONS

A. Clinical Observations: The animals will be observed daily for mortality, morbidity, and signs of toxicity (ØB-DT-3BØ3). The date and time of death or euthanasia of moribund animals will be recorded and the animals will be necropsied by trained prosectors according to (ØB-DT-3BØF).

B. Body Weights: All females will be weighed when eartagged. Plug-positive mice will be weighed on 0, 6, 9, 12, 15, and 18 dg (ØB-AR-3GØH). Virgin females will be weighed on the 1st, 5th, 10th day of exposure and at sacrifice.

C. Scheduled Necropsy: The mice are scheduled to be euthanized with CO₂ on 18 dg. At necropsy (ØB-DT-3BØG) maternal animals will be weighed and examined for gross tissue abnormalities. Maternal liver, [~~adrenals~~]^{-A} and kidney weights will be obtained at the time of sacrifice. In order to document the presence of lesions which may be due to chemical exposure, any organs or tissues with lesions will be preserved in neutral buffered formalin (NBF); in this case, comparable organs or tissues from approximately 20% of the control animals will be preserved in NBF; all other tissues will be discarded.

The uterus will be removed and weighed, and the number, position and status of implants will be recorded. The placentas will be examined. Any apparently non-gravid uteri will be stained with 10% ammonium sulfide to detect implantation sites. The identity of live fetuses (by study, dam number and uterine position) will be retained throughout all examinations and archiving. Live fetuses will be examined for gross defects and weighed. Following euthanasia, a complete visceral examination will be performed on 50% of all fetuses and on any fetuses with gross abnormalities. (ØB-DT-3BØG) Sex will be determined on all fetuses by internal examination. All skeletons will be double-stained and examined for cartilage formation and centers of ossification (ØB-DT-3BØG); however, ~50% of these will have had their heads removed. These fetal heads will be examined by razor-blade sectioning after fixation in Bouin's fluid (Wilson, 1965; [ØB-DT-3BØI]). Records of morphologic lesions observed in gross and visceral examinations will include photographs of representative lesions.

Both ovaries from the virgin females and [~~one ovary from each of~~]^{-A} the pregnant females will be collected at the time of sacrifice. (ØB-DT-3BØG). Collected ovaries will be fixed for 24 hr in Bouin's fluid then transferred to 70% ethanol and sent to the NIEHS archives for future sectioning and quantitative follicle counts.

D. Indices of Effects: The following parameters, expressed as mean $\pm$ SD, when appropriate, will be computed from data for inseminated

animals and their litters and will be presented in the Final Report for each treatment group:

- Number of dead maternal animals, animals removed from the study and reason for removal
- Summary of maternal toxicity, including incidence of changes detected during clinical observations
- Number and percent pregnant
- Maternal body weights:
  - Mice on 0, 6, 9, 12, 15 and 18 dg
- Weight of gravid uterus
- Maternal liver, adrenal, and kidney weights
- Extragestational weight and weight gain
- Number of implantation sites/litter
- Number of litters with live fetuses
- Number and percent of live fetuses/litter
- Body weight of live fetuses/litter
- Body weight of male and female fetuses/litter
- Sex ratio of fetuses/litter
- Number and percent of early and late resorptions/litter
- Number and percent of non-live/litter (early and late resorptions and dead fetuses)
- Listing of malformations and variations observed in fetuses/litters
- Number and percent of malformed fetuses
- Number and percent of litters with malformed fetuses

XII. PROPOSED STATISTICAL METHODS

The methods proposed for the statistical analyses of representative maternal, reproductive and fetal indices of effects are: summary statistics, N, mean, standard deviation, with accompanying ANOVA based on multiple comparisons where appropriate. Arc sin transformations will be performed on data presented as percent incidence. Further statistical analyses may be performed at the discretion of the sponsor.

XIII. RECORDS RETENTION

Records that accumulate during the study will be retained at BNW until requested and shipped to NTP archives. Some of these records may be presented as part of the protocol or reports. These will include but not be limited to the following records:

A. Personnel Records

1. List of BNW personnel participating in the study.
2. Name, address, and function of any outside consultant(s)
3. Record of removal of any individual from direct contact of the test system due to illness.

B. Health and Safety Records (original records and five copies of microfiche will be submitted to NTP within approximately two months after the end of each fiscal year). Chemical specific records will be submitted with the study. Facility specific records will be submitted annually.

1. Medical records of all personnel participating in the study. These records will be retained by Hanford Environmental Health Foundation (HEHF), P.O. Box 100, Richland, WA 99352 for a minimum of 40 years. A letter verifying this arrangement will be retained for each test material file.
2. Records and results of any biological monitoring on laboratory personnel (if applicable).
3. NTP Health and Safety package for methyl ethyl ketone.
4. BNW biohazard protocols and BNW Health and Safety Plan.
5. Chemical specific health and safety training records.
6. Waste disposal records.
7. Respiratory protection program with documentation of user training (specific fit testing if needed) for each type of respirator.
8. Building ventilation system, hoods and exhausting system monitoring records (pertinent to NTP studies).
9. Health and Safety Section of the Monthly Progress Reports.
10. Accident/injury reports for personnel involved in this study.
11. NTP site visit reports, attention items and related correspondence on health and safety.

C. Protocols

1. Approved and dated BNW study protocol.

2. Protocol amendments including NTP technical contract modifications which affect the study.
3. Documentation of any deviation from the protocol.
4. Documenting any unforeseen circumstances that may affect the integrity of the study and corrective actions taken.

D. Test Material Records

1. Test material identity records including manufacturer, quantity, lot number(s), purity grade and date(s), etc.
2. NTP analytical contractor characterization reports.
3. NTP analytical contractor bulk stability reports.
4. NTP analytical contractor shipment records (if available).
5. BNW test chemical receipt records.
6. BNW storage records including storage conditions.
7. BNW bulk analysis and degradation records.
8. BNW method development records.
9. Chemical exposure generation system description and procedures.
10. Chamber concentration monitoring records, including GC tracings.
11. Uniformity (chamber balance) records.
12. Gas chromatograph calibration records.
13. Generation and chamber degradation study records.
14. BNW test material inventory and usage records.
15. Records of shipment to NTP repository of any unused test material.
16. Gas chromatograph maintenance records.
17. Aerosol determination records.
18. Chamber concentration buildup, decay, and overnight monitoring records.
19. Exposure generation operating parameter records.

E. Animal Records - Pretest

1. Animal receiving records including supplier, species, strain, birth week, sex, number of animals for each sex, receiving date and receiving conditions (photocopy of a representative animal shipping crate label).
2. Quarantine and acclimatization records.

3. Pretest health screening records and animal health notebook.
4. Randomization records.
5. Animal identification records.
6. Written release records from clinical veterinarian.
7. Disposal of excess animals.

F. Animal Records - On Test

1. Exposure room location and chamber layout records.
2. Chamber cage map.
3. Cage type, rack type and the rotation scheme during study.
4. Cageboard type.
5. Type of watering system.
6. Body weight records.
7. Daily observation records.
8. Clinical signs of toxicity records.
9. Serology data and reports.
10. Pathological specimen inventory records.

G. Feed

1. Feed tags with manufacturer, lot numbers and milling dates.
2. Feed analysis records as provided by NTP analytical contract laboratory.

H. Water

1. Annual water analysis.
2. Weekly water hardness check (records will be maintained in building engineer and/or building manager's office).

I. Quarantine Room, Exposure Room, and Inhalation Exposure Chamber Records

1. Exposure chamber description.
2. Exposure suite control center description.
3. Temperature raw data and daily and monthly summation reports.
4. Relative humidity raw data and daily and monthly summation reports.
5. Air flow raw data and daily and monthly summation reports.

6. Chamber vacuum raw data and daily and monthly summation reports.
7. Exposure system monitors calibration and maintenance records.
8. Description of the lighting system and light/dark regimen.
9. Sanitation procedures and pest control program.

J. All Relevant Correspondence

K. Reports

1. Monthly Progress Report.
2. Special study reports if any:
3. Incident reports (if applicable).
4. Final Teratology Report.

L. Internal Computer Generated Forms and Tables

1. Teratology results and statistical analyses.
2. Analytical chemistry results.
3. Exposure suite control center computer printouts.
4. XYBION printouts (if any).

XIV. OTHER SPECIFICATIONS

- A. This study will be performed in compliance with the FDA Good Laboratory Practice Regulations for Non-Clinical Laboratory Studies (21 CFR 58) except where deviations are required by the NTP April, 1987 General Statement of Work and subsequent modifications.
- B. This Protocol will be the controlling document in case of discrepancies between the Protocol and SOPs. If this occurs the Study Director is to be notified immediately for clarification.
- C. A list of all relevant Standard Operating Procedures (SOPs) for this study is present in Attachment 1.

XV. HEALTH AND SAFETY

BNW's Health and Safety Plan (ØB-HS-3S1C) has been approved by NTP. In addition, a respiratory program is instituted. This is supplemented by using supplied-air respirators (ØB-HS-3S19) which will be worn by personnel during periods of animal care while the chambers are open and by having available self-contained breathing apparatus for use when entering a room under emergency conditions following a leak.

METHYL ETHYL KETONE
MOUSE TERATOLOGY

ØB-DT-1F1K-ØØ-Ø213

Page: 22 of 24

XVI. APPROVAL BY PNL

D. West
Study Director

Date: 6/24/88

R. A. Gelman
Quality Assurance Auditor

Date: 6/24/88

XVII. APPROVAL BY NTP

Bernard A. Schwetz
Co-Study Officer

Date: 30 June 88

Richard E. Morrissey
Co-Study Officer

Date: 29 June 88

XVIII. AMMENDMENTS AND REVISIONS

XVI. APPROVAL BY PNL

_____
Study Director

Date: _____

_____
Quality Assurance Auditor

Date: _____

XVII. APPROVAL BY NTP

_____
Co-Study Officer

Date: _____

_____
Co-Study Officer

Date: _____

XVIII. AMMENDMENTS AND REVISIONS

Revision A. 9/28/88

Page 8 VII.A:

Change: [~~an empty chamber, with the doors left open, a~~
holding chamber]

Reason: To correct error in original protocol.

Change: [~~immedately~~ 3 days]

Reason: To correct error in original protocol.

Page 16 XI.C:

Deleted: [~~adrenal~~]

Reason: This item deleted following conversations with
Project Officer.

Deleted: [~~one ovary from each of~~]

Reason: Correct error in original protocol.

XVIX.   REFERENCES

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ATTACHMENT 1

STANDARD OPERATING PROCEDURES FOR INHALATION REPRODUCTIVE
TOXICOLOGY STUDIES

REPRODUCTIVE AND DEVELOPMENTAL TOXICOLOGY

ØB-DT-3BØ3	Cage Location Maps and Daily Observations
ØB-DT-3BØB	Randomization of Animals
ØB-DT-3BØD	Rodent Mating Procedures
ØB-DT-3BØF	Necropsies of Dead or Moribund Animals
ØB-DT-3BØG	Developmental Evaluations for Teratology Studies
ØB-DT-3BØI	Examination of Fetal Heads Fixed in Bouin's Solution
ØB-DT-3BØY	Examination of Double-Stained Fetal Rat and Mouse Skeletons
ØB-DT-3B1J	Preparation of the Reproductive System for Histologic Evaluation
ØS-SI-3EØ1	Macintosh Data Collection System Using Arbor Balance for Teratology and Dominant Lethal Sacrifice
ØS-SI-3EØ3	Data Transfer from Macintosh to VAX Using MacTerminal
ØB-HI-3GØ9	Operation of Sealer
ØB-HI-3FØ2	Shipping Histology Materials
ØB-BE-3B2M	Inhalation Room Procedures During Exposure Periods
ØB-AR-3GØH	Rodent Weighing using Toledo 8142 Automatic System
ØB-AR-3FØC	Rodent Identification with Ear Tags
ØB-AR-3DØ1	Handling and Care of Calibrated Standard Weights
ØB-AR-3FØT	Guidelines for Euthanasia
ØB-AR-3BØN	Moving Animals from the LSLII Animal Resources Section

ANIMAL FACILITIES

ØB-AR-3BØG	Barrier Procedures for LSL-II Animal Facility
ØB-AR-3GØ1	Pre-Cleaning Equipment and Operation of Cage - Bottle and Rack Washers
ØB-AR-3BØ3	Handling and Changing Out Exposure Chambers and Cage Units
ØB-AR-3BØ8	Handling Escaped Small Animals

ØB-AR-3FØ2	Pre-Exposure Health Screening of Rodents
ØB-AR-3FØ3	Quarantine of Animals
ØB-AR-3FØ5	Management of Animal Feed
ØB-AR-3FØB	Selection and Notification Procedures: Moribund Removal and Animals Found Dead
ØB-AR-3B1R	Pathogen Monitoring
ØB-AR-3FØA	Daily Care of Bioassay Animals and Cleaning of Exposure Rooms
ØB-AR-3B23	Inhalation Room Procedures for Animal Care Personnel

INHALATION EXPOSURE AND BIOENGINEERING

ØB-BE-3B3H	Buildup and Decay and Overnight Concentration Monitoring
ØB-BE-3B24	Inhalation Exposure Chamber Balance
ØB-BE-3CØL	RTD Thermometer Calibration
ØB-BE-3DØE	Exposure Suite QC, Maintenance, and Calibration
ØB-BE-3EØ9	Study Protocol Entry Into Exposure Suite Computers
ØB-BE-3GØ4	Exposure Suite Routine Computer Operation
ØB-BE-3EØB	Exposure Suite Data Analysis Program Operation
ØJ-BE-3CØJ	EG&G Hygrometer: Operation, Maintenance, and Calibration
ØB-BE-3CØV	Calibration and Check of Chamber Airflow Using Digital Anemometer
ØB-BE-3B1X	Relative Humidity Determination Via Use of Dewpoint Hygrometer
ØB-BE-3GØ3	Operating Procedures for the Gardner Type CN Small-Particle Detector
ØB-BE-3C13	General FGD Calibration-Exposure Chamber and Generator Cabinets
ØB-BE-3B3J	Methyl Ethyl Ketone Exposure System Daily Operating Procedure (Teratology Studies)
ØB-BE-3DØS	Methyl Ethyl Ketone Exposure System QC Maintenance and Calibration (Teratology Studies)
ØB-BE-3DØ6	Chamber Leak Test
ØB-BE-3EØE	Exposure Suite Data Editing Program Operation

DOCUMENTS

ANALYTICAL CHEMISTRY

ØB-AC-3A1J	Bulk Analysis of Methyl Ethyl Ketone
ØB-AC-3A1K	Analysis of Building Exhaust for Methyl Ethyl Ketone
ØB-AC-3DØ2	Maintenance of Hewlett Packard Model 5840 Gas Chromatograph
ØB-AC-3C13	Methyl Ethyl Ketone: Calibration of the Chamber Monitor
ØB-AC-3B27	Operation of HP5840 GC for Monitoring Methyl Ethyl Ketone

SAFETY

ØB-HS-3S19	The 3M Brand W-2860 Hardcap, Continuous-Flow Air Line Respirator
ØB-HS-3S1C	Bioassay Studies: Health and Safety Plan
ØB-HS-3S1A	Scott Presur-Pak II Self-contained Breathing Apparatus
ØB-HS-3S1B	Bioassay Studies: Respiratory Protection Program
ØB-HS-3S2E	Biohazard Protocol - Methyl Ethyl Ketone

NTP PROJECT OFFICE

ØB-9A-3EØ6	Data Handling and Storage of NTP Study Documents and Materials
ØB-QA-3EØA	Filling Out Data Sheets
ØB-QA-3BØ7	Job Orientation and Training

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INHALATION EXPOSURE SYSTEM DESCRIPTION

I. Animal Exposure Chamber

The animals will be exposed and maintained in inhalation exposure chambers developed at BNW (U.S. Patent No. 4,261,741, August 12, 1980; Moss, 1980; Brown and Moss, 1981; Moss et al. 1982) and now commercially produced by the Harford Division of Lab Products, Inc., Aberdeen, MD. The chamber (Figure 1) facilitates multiple-tier exposures of various laboratory rodent species to aerosol- and vapor-laden atmospheres. The total volume of the chamber is 2.3 m³ with an active mixing volume of 1.7 m³, the remainder being the inlet and exhaust volumes where animals are not placed. There are three levels of caging, each level split into two tiers which are offset from each other and from the chamber walls. Drawer-like stainless steel cage units composed of individual animal cages are suspended in the space above each tier. Stainless steel catch pans for the collection of urine and feces are suspended below each cage unit. Catch pans are left in position during each exposure period. Cageboards are added to these catch pans during non-exposure periods to reduce ammonia concentrations.

The chamber was designed so that uniform aerosol or vapor concentrations can be maintained throughout the chamber when the catch pans are left in position. Incoming air containing a uniform mixture of test material is diverted so that it flows vertically along the inner surfaces of the chamber. Eddies are formed (Figure 1) at each tier as the aerosol or vapor flows past the catch pans. Stagnant zones that would normally exist above each pair of catch pans are cleared by exhaust flow through the space between the tiers. Aerosol or vapor reaching the lowest level is deflected across the bottom tiers by metal strips in the space between the catch pan and the wall. Tests have shown that aerosol or vapor concentration homogeneous to within 8% throughout the chamber can be obtained repeatedly provided the aerosol or vapor is uniformly mixed before passing through the chamber inlet (Griffis et al. 1981).

The dimensions of the individual cages are as follows:

Animal Species	Cages/ Unit	Floor Dimensions (cm)	Floor Area (cm ²)	Height (cm)
Mouse	60	14.0 x 7.6	106	15.0

Figure 1. Inhalation Exposure Chamber Designed at BNW
A. Oblique Cutaway View of the Chamber;
B. Airflow Patterns.

II. Exposure Suite System Description

The exposures will be conducted using an automated data acquisition and control system in an exposure Suite (Figure 2) consisting of three exposure rooms and a Suite Control Center room (only one of the exposure rooms will be used for this study). A central computer monitors the basic chamber functions (i.e., test chemical concentration, air flow, vacuum, temperature, and relative humidity) in each of the three exposure rooms. The executive computer is a Hewlett-Packard (HP) Model 9816. All data acquisition and system control originates from this computer.

All experimental protocols related to the data acquisition and control system (such as data channel assignments, monitoring frequencies and alarm settings) reside in the executive computer and are entered into tables accessed by menus.

Data input to the executive computer is accomplished through several interface instruments. All on-line chemical monitor data are collected and preconditioned by HP-85B computers, one for each of the exposure rooms. Conditioned data are transferred to the executive computer for analysis, concentration control, data storage, and printing. Data from all monitoring equipment other than chemical monitors are inputted through a Colorado Data Systems (CDS) Model 53A-IBX Intelligent Interface System (IIS).

System control is provided from the computer by means of control relays in the CDS IIS. These relays control such devices as valves, drive motors, audible alarms, indicator lamps, etc.

Data and comments from each exposure room are stored on separate magnetic diskettes by HP Model 9121 micro-floppy disk drives. Data and comments from each exposure room are printed on separate thermal dot matrix printers (HP Model 2671G). Data are printed and stored immediately upon completion of the measurement to the "Daily Log". At the end of the day (24-hour period), the daily data are analyzed and a summary is printed. This summary includes the mean, standard deviation, % relative standard deviation, maximum, minimum, and number of measurements for each set of data for the 24-hour period. A second printout provides a table of outliers (i.e., all data points which are beyond the critical limits defined in the protocol). This outlier table allows rapid determination of problem areas in the data. A third printout provides a list of all comments generated by the computer and operators. This allows rapid inspection of generation start and stop times and any problem areas.

A complete description of the software for this system is contained in BNW document ØB-BE-5EØ1. Maintenance of this system is detailed in SOP # ØB-BE-3DØE. Routine operation of the system software and hardware are detailed in SOP # ØB-BE-3GØ4.

Figure 2. Detailed layout of the exposure rooms of the Exposure Suite in which the Methyl Ethyl Ketone Study will be conducted.

III. Test Article Generation and Monitoring

A. Test Article Generation System

A schematic diagram of the methyl ethyl ketone vapor generation and delivery system is shown in Figure 3. The methyl ethyl ketone generator is housed in a vented cabinet located in the Suite Control Center.

The vapor generator will employ a rotary evaporation system (Bucchi Rotavapor, Model EL-131S) to produce methyl ethyl ketone vapor. The bulk methyl ethyl ketone will be transferred to a 5-gallon pressurized delivery container where low pressure nitrogen (4 - 6 psi) will be introduced into the inlet of the vessel, forcing liquid methyl ethyl ketone out at a steady rate. Chemical flow rate will be adjusted with a metering valve and monitored with a flowmeter. The liquid will be delivered to a rotating flask immersed in a hot water bath. The resulting vapor will be forced out of the mouth of the flask into a chilled water condenser where much of the vapor will be recondensed, returning to the evaporator flask. Nitrogen will be metered into the bottom of the condenser and will flow out its top. As nitrogen moves through the condenser, it will become saturated with methyl ethyl ketone vapor. The temperature of the saturated nitrogen will be monitored using a sensor at the top of the condenser. The saturation vapor pressure can be calculated and is used to determine the output (ppm of methyl ethyl ketone and flow rate of saturated nitrogen) of the generator. For example, at an exit temperature of 16°C, the methyl ethyl ketone concentration will be approximately 80,000 ppm at a typical flow rate of 28 lpm. The vapor will enter a short distribution manifold from which individual delivery lines will carry a metered amount of vapor to the exposure chambers. Vacuum transducer pumps at the chamber end of each line will generate the negative pressure needed to move the methyl ethyl ketone vapor. Within the chemical storage cabinet, each line will be connected to the distribution manifold through a fine metering valve and flowmeter. Adjustment of chamber concentration will be done with the metering valves and/or adjustment of compressed air pressure to the pumps. Injection of the nitrogen/vapor mix into the conditioned airstream entering the chamber will occur at a point sufficiently removed from the chamber to allow for proper mixing. This will assure uniformity of chemical-laden atmosphere within the chamber.

To prevent degradation of the vapor before delivery to the chamber inlet, the vapor must be generated and delivered in nitrogen. In the high dose chamber, this results in a reduction in the oxygen content of the chamber to 20.1% from the normal level of 20.9%.

Normal operation will call for approximately 20% excess vapor to be exhausted from the manifold through a flowmeter. This will cause a slight positive pressure in the manifold and allows independent adjustment of the chamber flow rates. However, there will be the possibility of creating a negative pressure in the manifold and generator which could draw air into the nitrogen/methyl ethyl ketone atmosphere since the vacuum transducer pumps will be withdrawing vapor from the manifold. This would occur if nitrogen delivery is interrupted or the pump delivery rates are grossly misadjusted. To monitor for this situation, a pressure transducer (Photohelic) will measure the pressure drop across the excess vapor flowmeter. A drop in pressure to below 2 cm of water will result in a shutdown of the generation system.

Generation will proceed in stages: warmup, generation and shutdown. During warmup, filling of the evaporating flask and heating of the water

bath will proceed together. During this time, some evaporation will occur but all vapor will be exhausted from the distribution manifold through the excess flow exhaust. When the bath temperature and fluid level reach the correct values, computer-controlled startup of the delivery pumps will be initiated. Until concentration is equilibrated in the delivery lines, nitrogen/methyl ethyl ketone vapor will be vented to exhaust at each chamber through pneumatic 3-way valves. These valves will allow for the more rapid diversion of chemical flow from chambers in the event rapid shutdown is necessary. After stabilization of the vapor temperature and possible fine adjustments of the vapor delivery and nitrogen flow rates, the generator will be in its normal operating stage. During this stage, the generator will operate under computer and exposure operator supervision. The exposure operator will monitor the fluid level in the flask as well as other operating parameters. The operator can adjust the overall generator output by changing the flow rate of cooling water to the condenser. This will affect the temperature of the vapor leaving the condenser and hence, the concentration of chemical in the vapor. Overall generator output could also be controlled by adjusting the flow rate of dilution nitrogen. The computer will be able to initiate a shutdown of the generator output under certain conditions by stopping flask rotation and turning off the bath heater. Further reduction in the generator output could then be initiated by the operator by reducing the nitrogen flow and tripping a solenoid-controlled valve which will introduce chilled water into the water bath.

Shutdown at the end of the generation stage will be similar to a computer-initiated shutdown. Following closure of the valves at the chambers and discontinuation of flask rotation, the operator will trip the solenoid, dumping additional cooling water into the bath. The remaining methyl ethyl ketone in the evaporating flask will be removed to a waste bottle. Nitrogen will continuously purge the generation system until preparation for the next day's generation.

Routine operation of the generation system is detailed in SOP# ØB-BE-3B3J. Maintenance and calibration of the system is contained in SOP# ØB-BE-3DØS.

Figure 3. Schematic Diagram of the Methyl Ethyl Ketone Generation and Delivery System

B. Test Article Concentration Monitoring

An on-line Hewlett-Packard Model 5840 gas chromatograph (GC) equipped with a flame ionization detector will be used to monitor the exposure chambers, the control chamber, the holding chamber, the room, a certified standard vapor of methyl ethyl ketone in nitrogen, and a nitrogen blank. Sampling from multiple positions will be accomplished by means of an oven-mounted, 8-port stream select valve. The sampling system (Figure 4) is incorporated into the relative humidity (RH) sampling system. Samples of the atmosphere from each sample location are continuously drawn by a vacuum pump through polytetrafluoroethylene-lined stainless steel tubes to a location near the input of the stream select valve. This assures fresh samples at the monitor. The sample lines, which continue from the point where they tee-off to the 8-port valve to the dewpoint monitor, are polytetrafluoroethylene.

Sample values are accumulated and printed by an HP Model 85B computer until samples from all twelve ports of the stream select valve have been measured. These values are then sent to the executive computer for printing and storage. Each value accumulated by the HP85B is compared with limit values for that particular location. If the value is beyond the control limits, the HP85B will immediately send the information to the executive computer which will take the appropriate action as follows:

- Concentration $\geq$ non-critical low limit and $\leq$ non-critical high limit: No action.
- Concentration $<$ non-critical low limit but $\geq$ critical low limit: Indicate on daily printout
- Concentration $<$ critical low limit: Indicate on daily printout and activate audible alarm
- Concentration $>$ non-critical high limit but $\leq$ critical high limit: Indicate on daily printout
- Concentration $>$ critical high limit: Indicate on daily printout, activate audible alarm, terminate generation of test material.

The on-line gas chromatograph will be calibrated against quantitatively analyzed bubbler grab samples collected from the exposure chambers. Standards will be prepared gravimetrically.

Additionally, the operation of the on-line GC will be checked daily against a commercial standard of methyl ethyl ketone vapor in nitrogen. This check will provide a measure of day-to-day instrument drift. The concentration of methyl ethyl ketone in the on-line standard will be determined via analysis of the standard using the calibrated on-line monitor. The on-line standard will be analyzed before the start of the exposure day and every eighth sample thereafter. If following the first analysis, the standard exceeds $\pm 10\%$ of the assigned target value, the exposure will be delayed for consultation between the exposure control task leader and the chemist. During the course of the exposure, on-line standard measurements within $\pm 5\%$ of target will require no change in calibration. On-line standard readings beyond $\pm 5\%$ will require that the exposure specialist notify the chemist immediately. For on-line standard values between 10 and 15% of target, the response factor may be updated by the exposure specialist after consultation with the chemist. Cumulative drift beyond 15% will require additional grab

Figure 4. Schematic of the Dewpoint and Chemical Monitoring System

sampling.

Daily operation procedures for the concentration monitoring system are contained in SOP# ØB-AC-3B27. Maintenance and calibration of the monitoring system is contained in SOP# ØB-AC-3C13.

The uniformity of the distribution of the test chemical in the chamber will be checked following SOP# ØB-BE-3B24.

The buildup and decay curves of the concentration in the chambers, the determination of T₉₀, and the determination of the persistence of the test article in the chambers following termination of test article generation (i.e., overnight monitoring) will be done following SOP# ØB-BE-3B3H.

IV. Chamber Environmental Control and Monitoring

A. Temperature

Nearly all of the heat load contributed to the exposure chamber by the animals is dissipated from the chamber by radiation through the chamber wall (Bernstein and Drew, 1980). Temperature of the air supplied to the chamber has little effect on the temperature of the chamber. On the other hand, temperature of the room housing the the chamber has a great deal of effect. Consequently, chamber temperature is maintained in the proper range primarily by controlling the room temperature.

Temperatures of the exposure chambers, exposure room and, if necessary, test chemical generators are measured by Resistance Temperature Devices (RTDs). The RTDs are placed in a representative location in each chamber (a top sample port on the back side). Each RTD is connected to an Omega Model 412B Digital Thermometer by either a manual select switch or by computer controlled scanner relays. This allows the temperature to be read manually or to be recorded automatically by the exposure system executive computer. Temperatures are automatically recorded at regular intervals during each 24 hour day. All temperature measurement equipment except the RTDs is located in the Exposure Suite Control Center. RTDs are calibrated to within 0.5°F of a certified mercury thermometer (SOP# ØB-BE-3CØL) before the start of each study and at least every two months thereafter.

B. Relative Humidity

Relative humidity (RH) in the exposure chambers is controlled by the system depicted in Figure 5. Equipment located in the RH Control Equipment Room (Room 335 of the LSL-II basement) provides separate ducts of dry and moist air to each exposure chamber. Filtered air with a maximum dewpoint of about 53°F is supplied to the RH Control Equipment by the building HVAC system. This air is evenly delivered to two ducts. Air from the first duct passes into a plenum where steam, generated from city tap water with no additional additives, is injected to bring the air to a dewpoint of about 60°F. This provides the moist air source for the chambers. The air from the second duct passed through a refrigeration coil which reduces the moisture content of the air to a dewpoint of about 40°F. This provides the source of "dry" air for the chambers. A manually controlled mixing valve for each chamber mixes the proper proportions of the moist and dry air to maintain the proper RH in each chamber.

Figure 5. Schematic Diagram of the Chamber Relative Humidity Control System

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Relative humidity is measured using an EG&G Model 910 dewpoint hygrometer located in the Exposure Suite Control Center. Air from the exposure chambers is sampled from a representative location (a top port on the back side). A Teflon® filter is placed at the chamber end of the sample line if the test article is an aerosol. Samples of the air from each measurement location are continuously pulled through polytetrafluoroethylene (PTFE) tubing to a central location in the Exposure Suite Control Center. This assures a fresh sample at the dewpoint hygrometer. Sample air from a particular location is routed by a multiplexed valve system to either the exposure system exhaust or the dewpoint hygrometer for RH determination. The valves are controlled by either a manual switch or by a computer controlled relay, allowing RH to be measured manually or automatically by the exposure system executive computer. RH is automatically recorded at regular intervals during the 24-hour day.

Once the dewpoint has been determined by the hygrometer, the RH is automatically calculated by the exposure system executive computer using the dewpoint value and the temperature (measured simultaneously at the same location by the RTD system). The following equation is used for this calculation:

$$\%RH = \frac{10^{\left[9.91 - \frac{2714.55}{(5/9)(T_1 - 32) + 293.13}\right]}}{10^{\left[9.91 - \frac{2714.55}{(5/9)(T_2 - 32) + 293.13}\right]}} \times 100$$

Where: T_1 = dewpoint temperature (°F)
 T_2 = drybulb temperature (°F)

Calibration of the dewpoint hygrometer is established prior to the start of the study and checked at least once every two months following SOP# ØB-BE-3CØJ. Initial calibration requires comparison at three RH levels (= 30%, 50% and 70%) of the RH calculated by the monitor to measurements made by a calibrated portable hygrometer and RTD located near the chamber.

C. Chamber Airflow

Air flow in the chambers is maintained by the vacuum in the central chamber exhaust duct. This vacuum is created by the chamber exhaust flow fans located in the South Equipment Room of the LSL-II Building. There are two parallel exhaust fans, one operating with the other providing backup. Both fans operate from emergency power.

Chamber air flow rate is controlled by a gate valve in each individual chamber exhaust duct. A drive motor attached to the stem of this valve allows the control of chamber flow either by computer or manually from the Exposure Control Center.

Fine control of exposure concentration can be accomplished by automatically or manually adjusting the valve position to control chamber dilution air flow within the allowable limits. Gross adjustment of concentration must be done manually by adjusting the generation system.

Chamber air flow is measured by a multiplexed orifice-meter system consisting of a calibrated orifice located in each chamber exhaust, a Validyne Model DP-45 pressure transducer, a Validyne Model CD-18 carrier demodulator, and a Validyne Model PM-12 digital voltmeter. The pressure transducer is multiplexed to each chamber's flow orifice by valves remotely controlled either manually or by means of the executive computer. This allows flow to be measured either manually or automatically. Flow is automatically recorded at regular intervals during the 24-hour day.

Calibrated flow orifice meters are located at both the inlet and exhaust to each chamber. By comparing the measured flow at the inlet and exhaust, leaks in the chamber can be detected. A leak check is automatically performed by the executive computer when each chamber is closed. If a leak is detected, the executive computer will notify the operator and will not allow exposures to proceed until the leak is repaired. This system is sensitive to very small leaks which may cause an imbalance of test article concentration within the chamber.

Calibration of the flow orifices will be done before the start of each study and will be checked once every two months following SOP # ØB-BE-3CØV. Each flow orifice is calibrated to within ± 0.5 CFM by comparison to a calibrated digital vane anemometer temporarily inserted in the chamber duct during non-exposure periods.

D. Vacuum

The chambers are maintained at a slight negative pressure compared to the room in order to reduce the possibility of escape of test article. This negative pressure is created by the pressure drop across the HEPA and charcoal filters at the inlet to each chamber.

The same Validyne pressure transducer system used to measure chamber flows is used to measure chamber vacuum. Vacuum in the chamber is measured relative to atmospheric pressure in the Suite Control Room. Vacuum is automatically recorded at regular intervals during the 24-hour day.

Vacuum is also continuously monitored by a mechanical pressure switch attached to each chamber. In the event of leak in the chamber, the pressure switch will immediately shut off the flow of test article to the chamber and activate an audible alarm.

V. Animal Facility Air Handling System

Supply air enters the building through two identical parallel air handling systems (Figure 6). Each system consists of a pre-heat coil, a filter system, a heating coil, a chilling coil, and a supply fan. The pre-heat coil heats the air to a minimum of 45°F. The filter system, comprising a roll filter, pre-filter, and a bag filter, rids the air of most particles. The heating and chilling coils maintain the temperature of the air exiting the air conditioning system at about 53°F. The chilling coils also dry the air to a dewpoint not greater than 53°F.

Figure 6. Air Handling System for Animal Rooms of the Life Science II Building

Although simultaneous operation of both of the parallel air supply systems is necessary to provide the 20 air changes per hour typically supplied to each animal room, only one of these systems, which can be operated from the emergency power system, is required to maintain the rooms within the temperature and flow specifications required by the protocol. Exposure of the animals to the test article can continue in the event of the failure of one of the air supply systems. However, exposures generally do not continue unless all building systems are functioning normally.

The air from the two parallel building air supply systems is mixed together by an air mixing unit and is divided into two ducts which feed the rooms on the East and West sides of the animal quarters. If necessary, steam is injected into the air in these ducts to maintain the relative humidity of all rooms in the basement at a minimum of 35%. In rooms where further room RH control is necessary, it is provided by individual steam generators located in the room. Prior to entering the animal room, the air is filtered through a HEPA filter. Air for exposure chambers is supplied to a chamber relative humidity conditioning system from the building air supply systems. A single supply system is sufficient to supply air to the RH conditioning systems for all exposure chambers in the facility.

Exhaust from the animal room is filtered by a room HEPA filter and again through a bank of building exhaust HEPA filters assuring no escape of aerosol particles from the facility. Three parallel exhaust fans provide exhaust from the rooms. Two of these fans are in operation with the third as a backup unit. One fan can be operated from the emergency power system in case of power failure.

A separate exhaust duct system for the chambers allows for the addition of scrubbers to remove particles or vapors before exhausting from the building. Because the chamber exhaust system has a separate fan, failure of one of the building exhaust fans will not prevent the continuation of exposures. However, exposures generally do not continue unless all building systems are functioning normally.

VI. Exposure Suite Alarm System

An extensive system of alarms has been incorporated into the exposure suite automated data acquisition and control system to provide safety for the system operators, protect the health of the animals and ensure the integrity of the study. There are actually two separate alarm systems; one provided by the computer and a separate "physical" alarm system which provides redundancy for some of the computer alarm functions.

Following each function measured by the computer, the value is compared to the alarm limit values (stored in the computer memory) for that function. There are four limit values for each function and location monitored by the computer; high and low non-critical and high and low critical. For example, chamber flows may have the following limits:

Critical low	10 air changes per hour
Non-critical Low	12
Non-critical High	18
Critical High	20

The result of an alarm condition depends on the function measured and the measurement location. Each function and location has an alarm response assignment in the computer. Again using chamber flow as an example, flows

exceeding the non-critical limits but remaining within the critical limits will cause the computer to print a "beyond-non-critical-limits" symbol, "(" if low and ")" if high, next to the data on the daily log printed by the computer. A chamber flow which exceeds the critical limits will cause the computer to print a "beyond-critical-limits" symbol, ">" if high and "<" if low, on the daily log and to turn on the critical alarm audio alert. A critical low flow alarm will also shut off the flow of test article to the chamber. Although it is possible for the computer to make automatic corrections to air flow in the chamber, this is not done because to do so would affect concentration of the test article in the chamber. A critical low negative pressure in a chamber (which may be the result of a leak in the chamber) will also cause the computer to shut off the flow of test article to the chamber. Similar responses result from alarms arising from temperature and relative humidity measurements in the chambers, however these alarms have no affect on the operation of the test article generator.

All critical alarms arising from measurements of generator function (such as vaporizer temperature) will result in all functions of the generator being turned off.

The physical alarm system includes the following continuously monitoring devices:

- Chamber pressure (also detects critically low flow if it is the result of pump failure and not a clogged chamber inlet duct)
- Generator cabinet exhaust flow
- Chamber exhaust system flow
- Building exhaust system flow
- Explosive level detectors monitoring the chambers and generator cabinet (present only if test article is flammable)

In all cases an alarm condition from any one of these monitors is considered critical and results in the test article generator being shut off.

VII. Chamber Exhaust Waste Treatment

The exhaust from the central chamber exhaust duct is mixed with the exhaust from the entire animal facility (= 75,000 CFM) prior to being exhausted from the building stack. Dilution of the chamber exhaust with the building exhaust should result in an acceptable stack concentration of 1.2 ppm. The Threshold Limit Value for the test article is 200 ppm.

VIII. Data Handling

Data from each exposure room are stored in the Exposure Suite Control Center on separate magnetic disks by Hewlett-Packard (HP) Model 9121 micro-floppy disc drives. Data and comments from each exposure room are printed by separate thermal dot matrix printers (HP Model 2171G) or by ink jet printers (HP Model 2225A). Data are printed and stored immediately upon completion of the measurement to a Daily Log (example, Figure 7). Both the Daily Log and the disks will be maintained in the study files. The Daily Log will be considered the raw data. The Daily Log includes the time of measurement, the measurement location (such as chamber), the measurement function (such as temperature), the value of the measurement, the percent of target, an alarm code, and a status code. See Figure 7 for an explanation of the alarm and status codes.

F.47

At the end of the day (24-hour period), the daily data are analyzed and three summaries are printed. The first (example, Figure 8) includes the mean, % of target, standard deviation, % relative standard deviation, maximum, minimum, and number of measurements for each function (such as temperature) and location (such as chamber) monitored over the 24-hour period. The second (example, Figure 9) provides a list of outliers; that is, all data points which were beyond the defined critical operating limits. This printout allows for quick review of data which are outside the operating limits. The final summary (example, Figure 10) is a printout of all comments made by the computer, Exposure Specialist, and Exposure Operator during the 24-hour period. This includes comments on startup time, exposure termination, new calibration factors entered, and other information. This summary allows a quick review of events that occurred during the day.

Data handling and analysis procedures are described in SOPs ØB-BE-3EØB and ØB-BE-3EØE.

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Time	Data Origin	Function	Data	
	HCC- 200 pcc-H	-T90 Time Expired-Including Conc Data		
	HCC- 50 pcc-H	-T90 Time Expired-Including Conc Data		
	HCC- 50 pcc-H	-T90 Time Expired-Including Conc Data		
	HCC- 10 pcc-H	-T90 Time Expired-Including Conc Data		
09:54	Hewlett Packard 5816 (Access Level: Programmer)			
	HCC- 10 pcc-H	-T90 Time Expired-Including Conc Data		
09:53	Hewlett Packard 856 (Access Level: Specialist)			
	HCC- 10 pcc-H	-Data Excluded-Data Time<T90 Time & Data<Target		
	Low Limit Exceeded. (Data not stored to disk)			
09:59	HCC- 50 pcc-H	GC#16-805566	OKI 4.44E+1 pcc	89%
	High Limit Exceeded. (Data not stored to disk)			
10:02	HCC- 50 pcc-H	GC#16-805566	OKI 5.64E+1 pcc	113%
	High Limit Exceeded. (Data not stored to disk)			
10:09	HCC- 200 pcc-H	GC#16-805566	OKI 2.22E+2 pcc	111%
09:40	HCC- Room	GC#16-805566	OKI 0.00E+0 pcc	0%
09:43	HCC- 0 pcc-H	GC#16-805566	OKI 0.00E+0 pcc	0%
09:46	HCC- 0 pcc-H	GC#16-805566	OKI 0.00E+0 pcc	0%
09:50	HCC- 0 pcc-H	GC#16-805566	OKI 0.00E+0 pcc	0%
09:53	Hewlett Packard 856 (Access Level: Specialist)			
	HCC- 10 pcc-H	-Data Excluded-Data Time<T90 Time & Data<Target		
09:53	HCC- 10 pcc-H	GC#16-805566	OKI 8.89E+0 pcc	89%
09:55	HCC- 10 pcc-H	GC#16-805566	OKI 9.11E+0 pcc	92%
09:59	HCC- 50 pcc-H	GC#16-805566	OKI 4.44E+1 pcc	89%
10:02	HCC- 50 pcc-H	GC#16-805566	OKI 5.64E+1 pcc	113%
10:05	HCC- 200 pcc-H	GC#16-805566	OKI 2.04E+2 pcc	103%
10:09	HCC- 200 pcc-H	GC#16-805566	OKI 2.22E+2 pcc	111%
10:16	HCC- Standard Gas	GC#16-805566	OKI 9.80E+1 pcc	99%
10:21	HCC- Room	GC#16-805566	OKI 0.00E+0 pcc	0%
10:24	HCC- 0 pcc-H	GC#16-805566	OKI 0.00E+0 pcc	0%
10:28	HCC- 0 pcc-H	GC#16-805566	OKI 0.00E+0 pcc	0%
10:31	HCC- 0 pcc-H	GC#16-805566	OKI 0.00E+0 pcc	0%
10:34	HCC- 10 pcc-H	GC#16-805566	OKI 1.05E+1 pcc	107%
10:37	HCC- 10 pcc-H	GC#16-805566	OKI 9.37E+0 pcc	94%
10:40	HCC- 50 pcc-H	GC#16-805566	OKI 4.26E+1 pcc	99%
10:44	HCC- 50 pcc-H	GC#16-805566	OKI 5.43E+1 pcc	109%
10:47	HCC- 200 pcc-H	GC#16-805566	OKI 1.93E+2 pcc	97%
10:50	HCC- 200 pcc-H	GC#16-805566	OKI 2.05E+2 pcc	103%
10:56	HCC- Standard Gas	GC#16-805566	OKI 9.81E+1 pcc	99%
11:12	HCC- Vaporizer	Temperature	OKI 180.1 F	100%
11:14	HCC- Room	Temperature	OKI 63.0 F	99%
11:32	HCC- 200 pcc-H	Relative Humidity	OKI 54.0 %	99%
11:35	HCC- 200 pcc-H	Relative Humidity	OKI 50.0 %	91%

Figure 7. Example of 24-Hour "Daily Log" Printout from Data Acquisition and Control Computer. See Following Page for Explanation of Columns.

Figure 7. (continued)

DESCRIPTION OF COMPUTER "DAILY LOG" OUTPUT

The date, exposure name, program version and page number will be printed at the top of each page of the daily log.

Column 1: Time -- time that measurement was taken

Column 2: Location -- location of measurement (for example, chamber)

Column 3: Function -- measurement function (for example, temperature)

Column 4: Data --

Alarm Code -- "(" Indicates data < non-critical low but ≥ critical low alarm value
")" Indicates data > non-critical high but ≤ critical high alarm value
"<" Indicates data < critical low alarm value
">" Indicates data > critical high alarm value

Status Code -- "OK" Indicates monitoring instrument is functioning properly and is calibrated
"BS" Indicates service time of monitoring instrument has expired. (Usually indicates that instrument calibration should be checked. Does not necessarily mean that data are not valid)
"I" Indicates data will be included in summary
"E" Indicates data will be excluded from summary

Data Value -- Data may be expressed in scientific notation (x.xxxEyy)

Units Label -- Units of measurement (e.g., ppm, °F, mg/m³)

Summation for the File: Jun_11_67 Exposure: hexachlorocyclooctadiene

Exhaust Air Flow	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	Num X's
200	14.7	99%	.14	1%	14.8	14.4	8.
200	14.9	99%	.07	0%	15.0	14.8	8.
50	14.8	99%	.05	0%	14.9	14.7	8.
50	14.8	99%	.12	1%	15.0	14.7	8.
10	14.9	100%	.05	0%	15.0	14.9	8.
10	15.0	100%	.07	0%	15.1	14.9	8.
0	14.8	99%	.19	1%	15.0	14.3	8.
0	14.2	99%	.63	5%	15.1	12.5	8.
0	15.0	100%	.04	0%	15.0	14.9	8.
Humidity	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	Num X's
200	.8	76%	.02	2%	.8	.8	8.
200	1.0	99%	.01	1%	1.0	.9	8.
50	.9	93%	.02	2%	1.0	.9	8.
50	.8	64%	.01	1%	.9	.8	8.
10	1.2	125%	.01	1%	1.2	1.2	8.
10	1.0	99%	.01	1%	1.0	.9	8.
0	1.0	104%	.02	2%	1.1	1.0	8.
0	1.1	108%	.10	9%	1.2	1.0	8.
0	1.1	106%	.01	1%	1.1	1.0	8.
Relative Humidity	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	Num X's
200	56.1	102%	4.45	8%	64.0	49.0	8.
200	54.2	99%	5.57	10%	61.0	47.0	8.
50	54.6	99%	4.47	8%	61.0	47.0	8.
50	54.9	100%	9.09	17%	61.0	43.0	8.
10	55.5	101%	5.10	9%	61.0	46.0	8.
10	58.6	107%	7.33	12%	67.0	48.0	8.
0	59.6	101%	4.24	6%	62.0	49.0	8.
0	59.6	107%	6.83	12%	61.0	49.0	8.
0	59.1	107%	5.51	9%	67.0	50.0	8.
Temperature	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	Num X's
200	180.2	100%	.13	0%	180.4	180.0	8.
200	69.9	57%	.55	1%	70.5	69.0	8.
200	74.7	100%	.75	1%	75.2	73.9	8.
200	74.5	99%	.48	1%	75.1	73.6	8.
50	72.5	97%	.65	1%	73.3	71.6	8.
50	73.5	101%	.74	1%	75.3	72.2	8.
10	74.3	99%	.63	1%	75.1	73.1	8.
10	75.2	100%	.41	1%	75.8	74.5	8.
0	74.9	100%	.73	1%	75.5	74.1	8.
0	74.2	99%	.61	0%	74.8	73.5	8.
0	73.2	99%	.84	1%	75.0	72.1	8.
CO2	Mean	% Target	Std Dev	% RSD	Maximum	Minimum	Num X's
200	2.05E+2	104%	3.50E+0	3%	2.22E+2	1.89E+2	8.
200	2.06E+2	103%	3.20E+0	3%	2.12E+2	1.94E+2	8.

Figure 8. Example of 24-Hour "Data Summation" Printout From Data Acquisition and Control Computer.

Outlier Table for the File: Jun_11_87 Exposure: HexachloroCyclopentaDiene

Origin	Instrument	Time	Data	Lower	Target	Higher
No Outlier (Critical Limits exceeded) data points found.						

Figure 9. Example of 24-Hour "Data Outlier Table" Printout from Data Acquisition and Control Computer. Table Shows Data Which Were Beyond the Defined Critical Limits.

Daily Comments	Hexachlorocyclopentadiene	File: Jun_11_87
Time	Operator	Comment
09:14	David J. Bailey	Chamber Leak Check for HCCP- 10 ppm-H
09:14	David J. Bailey	Exhaust Flow=14.9 Inlet Flow=14.5 (2.7% leak) [Acceptable]
09:15	David J. Bailey	Chamber Leak Check for HCCP- 10 ppm-R
09:15	David J. Bailey	Exhaust Flow=15 Inlet Flow=14.9 (.7% leak) [Acceptable]
09:16	David J. Bailey	Chamber Leak Check for HCCP- 0 ppm-H
09:16	David J. Bailey	Exhaust Flow=14.5 Inlet Flow=14.5 (0% leak) [Acceptable]
09:16	David J. Bailey	Chamber Leak Check for HCCP- 0 ppm-R
09:16	David J. Bailey	Exhaust Flow=14.9 Inlet Flow=14.9 (0% leak) [Acceptable]
09:17	David J. Bailey	Chamber Leak Check for HCCP- 0 ppm-H-SC
09:17	David J. Bailey	Exhaust Flow=15 Inlet Flow=15.3 (-2% leak) [Acceptable]
09:17	David J. Bailey	All Chambers have been found ACCEPTABLE.
09:28	Hewlett Packard 858	HCCP- Standard Gas-GC Data Excluded-No Exposure at Data Time
09:32	Hewlett Packard 858	HP858 found Parameters Okay & Ready for Exposure Start.
09:33	Hewlett Packard 8816	Exposure Timing started. [Time=1(0)]
09:33	Hewlett Packard 8816	Generator ON
09:34	Hewlett Packard 8816	HCCP- 200 ppm-H -ON Exposure-Enable Environ Data Collection
09:34	Hewlett Packard 8816	HCCP- 200 ppm-R -ON Exposure-Enable Environ Data Collection
09:34	Hewlett Packard 8816	HCCP- 50 ppm-H -ON Exposure-Enable Environ Data Collection
09:34	Hewlett Packard 8816	HCCP- 50 ppm-R -ON Exposure-Enable Environ Data Collection
09:34	Hewlett Packard 8816	HCCP- 10 ppm-H -ON Exposure-Enable Environ Data Collection
09:34	Hewlett Packard 8816	HCCP- 10 ppm-R -ON Exposure-Enable Environ Data Collection
09:54	Hewlett Packard 8816	HCCP- 200 ppm-H -T90 Time Expired-Including Conc Data
09:54	Hewlett Packard 8816	HCCP- 200 ppm-R -T90 Time Expired-Including Conc Data
09:54	Hewlett Packard 8816	HCCP- 50 ppm-H -T90 Time Expired-Including Conc Data
09:54	Hewlett Packard 8816	HCCP- 50 ppm-R -T90 Time Expired-Including Conc Data
09:54	Hewlett Packard 8816	HCCP- 10 ppm-H -T90 Time Expired-Including Conc Data
09:54	Hewlett Packard 8816	HCCP- 10 ppm-R -T90 Time Expired-Including Conc Data
09:53	Hewlett Packard 858	HCCP- 10 ppm-H-GC Data Excluded-Data Time<T90 Time & Data<Target
09:53	Hewlett Packard 858	HCCP- 10 ppm-R-GC Data Excluded-Data Time<T90 Time & Data<Target
15:54	Hewlett Packard 8816	Exposure Terminated. Exposure timers stopped.
15:54	Hewlett Packard 8816	Generator OFF
15:54	Hewlett Packard 8816	HCCP- 200 ppm-H -OFF Exposure-Disable Environ Data Collection
15:54	Hewlett Packard 8816	HCCP- 200 ppm-R -OFF Exposure-Disable Environ Data Collection
15:54	Hewlett Packard 8816	HCCP- 200 ppm-R -OFF Exposure-Disable Environ Data Collection
15:54	Hewlett Packard 8816	HCCP- 200 ppm-R -OFF Exposure-Disable Environ Data Collection
15:54	Hewlett Packard 8816	HCCP- 50 ppm-H -OFF Exposure-Disable Environ Data Collection
15:54	Hewlett Packard 8816	HCCP- 50 ppm-R -OFF Exposure-Disable Environ Data Collection
15:54	Hewlett Packard 8816	HCCP- 50 ppm-R -OFF Exposure-Disable Environ Data Collection
15:54	Hewlett Packard 8816	HCCP- 50 ppm-R -OFF Exposure-Disable Environ Data Collection
15:54	Hewlett Packard 8816	HCCP- 10 ppm-H -OFF Exposure-Disable Environ Data Collection
15:54	Hewlett Packard 8816	HCCP- 10 ppm-R -OFF Exposure-Disable Environ Data Collection
15:54	Hewlett Packard 8816	HCCP- 10 ppm-R -OFF Exposure-Disable Environ Data Collection
15:54	Hewlett Packard 8816	HCCP- 10 ppm-R -OFF Exposure-Disable Environ Data Collection
15:13	Hewlett Packard 8816	Environmental Data from Chambers 'Off-line' not monitored.
15:13	Hewlett Packard 8816	HCCP- 200 ppm-H -OFF Exposure-Disable Environ Data Collection
15:13	Hewlett Packard 8816	HCCP- 200 ppm-R -OFF Exposure-Disable Environ Data Collection
15:13	Hewlett Packard 8816	HCCP- 50 ppm-H -OFF Exposure-Disable Environ Data Collection
15:13	Hewlett Packard 8816	HCCP- 50 ppm-R -OFF Exposure-Disable Environ Data Collection
15:13	Hewlett Packard 8816	HCCP- 10 ppm-H -OFF Exposure-Disable Environ Data Collection
15:13	Hewlett Packard 8816	HCCP- 10 ppm-R -OFF Exposure-Disable Environ Data Collection

Figure 10. Example of 24-Hour "Comment Summary" Printout from Data Acquisition and Control Computer. Table shows a Summary of all comments recorded on "Daily Log" printout.

IX. Equipment and Power Failure Protection Systems

Power is provided to the Battelle complex from two separate city substations through an automatic switching device. This significantly reduces the possibility of losing city power. Power from the city is routed to equipment in the LSL-II building through two types of motor control centers. One type can switch power from the LSL-II diesel generator. The other has access only to city power. The emergency-power-type motor control center has a low voltage detector on each leg of the three-phase input power. If the city supplied power should fail or "brown out", these detectors automatically start the emergency power diesel generator and route the emergency power to the equipment connected to the emergency-power-type motor control center.

All equipment critical to the well-being of the animals is connected to the emergency-power-type motor control center including:

- Emergency lighting and electrical outlets
- Building air conditioning chillers #1 and #2
- Building heating boilers and feedwater pump systems #1 and #2
- Air compressors #1 and #2
- Air supply fans #1 and #2
- Air exhaust fans #1 and #2

Note that there are two identical units of all equipment that is vital to the well-being of the animals (heating, cooling, supply air, exhaust air, and compressed air). Either of the two units has sufficient capacity to maintain the animal environment within a safe range. In all cases, the emergency power system will operate one of the two identical systems.

All building or chamber systems which are essential to the survival of the animals are alarmed. If a system malfunctions, an alarm is tripped in the Power Operator's office. A Power Operator is on duty 24 hours/day, 7 days/week. If the Power Operator is not authorized to correct the problem that caused the alarm, he immediately calls the appropriate personnel of the programs affected.

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PROJECT: NTP-IRT
STUDY: MOUSE TERATOLOGY
ROOM: 436

CHEMICAL: METHYL ETHYL KETONE
CHAMBER: 1 ØPPM
DATE: 7-22-88 to 7-29-88

7JB

LEVEL 2

1409			
1382			
1358			
1313			
1304			
1279			
1259			
1211			
1194			
1185			
1113			

GRP A

LEVEL 3

		1439	
1404		1413	
1297		1388	
1291		1372	
1239		1331	
1212		1327	
1208		1292	
1189		1268	
1135		1241	
1127		1131	

GRP B

VIRGINS

LEVEL 4

1392			
1364			
1360			
1354			
1336			
1256			
1250			
1247			
1226			
1182			
1139			
1104			
1103			

GRP C

LEVEL 5

COMMENTS _____

PROJECT: NTP-IRT

UDY: MOUSE TERATOLOGY

ROOM: 436

CHEMICAL: METHYL ETHYL KETONE

CHAMBER: 2 400 PPM

DATE: 7-22-88 to 7-29-88

LEVEL 2

1376			
1369			
1361			
1359			
1357			
1352			
1335			
1227			
1196			
1121			

GRP A

LEVEL 3

		1424	
1412		1408	
1375		1341	
1299		1330	
1282		1274	
1272		1264	
1254		1221	
1237		1173	
1207		1169	
1112		1125	

GRP B

VIRGINS

LEVEL 4

1430			
1396			
1380			
1370			
1368			
1344			
1339			
1183			
1176			
1174			
1168			
1151			
1149			
1119			

GRP C

LEVEL 5

COMMENTS _____

PROJECT: NTP-IRT
STUDY: MOUSE TERATOLOGY
ROOM: 436

CHEMICAL: METHYL ETHYL KETONE
CHAMBER: 3 1000 PPM
DATE: 7-22-88 to 7-29-88

LEVEL 2

1371			
1281			
1276			
1261			
1188			
1164			
1144			
1143			
1142			
1118			

GRP A

LEVEL 3

		1441	
1431		1437	
1418		1386	
1373		1298	
1307		1294	
1275		1257	
1270		1220	
1197		1210	
1165		1150	
1163		1124	

GRP B

VIRGINS

LEVEL 4

1421			
1415			
1362			
1353			
1343			
1332			
1328			
1293			
1255			
1213			
1180			
1137			
1110			
1106			

GRP C

LEVEL 5

COMMENTS

PROJECT: NTP-IRT
STUDY: MOUSE TERATOLOGY
ROOM: 436

CHEMICAL: METHYL ETHYL KETONE
CHAMBER: 4 3000 PPM
DATE: 7-22-88 to 7-29-88
PJB

LEVEL 2

1476			
1406			
1405			
1316			
1300			
1290			
1280			
1206			
1136			
1102			

GRP A

LEVEL 3

		1407	
1429		1263	
1384		1251	
1334		1249	
1317		1246	
1296		1217	
1209		1198	
1193		1181	
1187		1172	
1107		1132	

GRP B

VIRGINS

LEVEL 4

1440			
1366			
1348			
1325			
1266			
1214			
1205			
1203			
1186			
1184			
1179			
1130			
1122			
1116			

GRP C

LEVEL 5

COMMENTS _____

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