Appendix B

Robust Summaries for Selected Studies

MEK TOXICITY HAZARD KEY ROBUST SUMMARIES

[RS - 1]

Acute Oral Toxicity

Test Substance:	Methyl ethyl ketone (MEK; 2-Butanone)
CAS #:	78-93-3
Method:	Experimental (Non-regulatory)
Type:	LD50
GLP:	Pre-GLP
Year:	1971
Species/Strain:	Rat / Sprague-Dawley
Sex:	Male or Female (newborns and 14-day olds groups); Males (young and older adult groups)
#/dose:	6-12 (either sex for newborns and 14-day olds); 6 (young and older adult groups)
Vehicle:	None
Route of Admin:	Oral Gavage
Doses:	Single dose
Dose Volume Administered:	≥ 1ml/kg
Post Dose Observation Period :	7 Days
Results (LD50):	**<** 1.0 ml/kg (newborns) 3.1 ml/kg (2.5-3.9) 14-day olds 3.6 ml/kg (2.9-4.4) Young Adults 3.4 ml/kg (2.6-4.4) Older Adults
Remarks:	The acute toxicity studies were carried out in newborn rats (24-48 hours old and 5-8 grams), in immature rats (14-day old and 16-50 grams), young adults (80-160 grams), and older adults (80-160 grams). The LD50 and associated confidence limits were calculated by the method of Litchfield and Wilcoxon as well as by a probit analysis statistical program via an IBM-1800 calculator. LD50 for the newborns could not be determined due to volume limitations and were given a value of < 1.0 ml/kg.
Conclusion:	The LD50 ranged from 3.1-3.6 ml/kg with the young adults slightly less sensitive than the younger 14-day or the older adults.
Data Quality:	2 - Reliable study with Restrictions. Study is pre-GLP but sufficiently documented, meets generally accepted scientific principles, acceptable for assessment
Reference:	Kimura, E.T., D.M. Ebert and P.W. Dodge. "Acute Toxicity and Limits of Solvent Residue for Sixteen Organic Solvents." Toxicology and Applied Pharmacology 19: 699-704, 1971

[RS - 2]

Acute Oral Toxicity

Test Substance:	Methyl ethyl ketone (MEK; 2-Butanone)
CAS #:	78-93-3
Method:	Experimental (Non-regulatory)
Type:	LD50
GLP:	Pre-GLP
Year:	1962
Species/Strain:	Rat / Carworth-Wistar
Sex:	Female
#/dose:	5
Vehicle:	Unknown (water, corn oil, or a solution of 25% sodium 3,9-diethyl-6-tridecanol sulfate "Tergitol Penetrant 7")
Route of Admin:	Oral Gavage
Doses:	Logarithmic series differing by a factor of two.
Dose Volume Administered:	Single dose
Post Dose Observation Period :	14 Days
Results (LD50):	6.86 mL/kg (5.59 - 8.45)
Remarks:	The animals were 4 - 5 weeks of age and weighed 90 - 120 grams and were not fasted prior to dosing. The most probable LD_{50} value and the fiducial range were estimated by the method of Thompson using the tables of Weil.
Conclusion:	The acute oral LD50 for MEK in female Carworth-Wistar rats is 6.86 ml/kg (5.59 - 8.45)
Data Quality:	2 - Reliable study with Restrictions. Study is pre-GLP but sufficiently documented, meets generally accepted scientific principles, acceptable for assessment
Reference:	Smyth Jr., H.F., C.P. Carpenter, C.S. Weil, U.C. Pozzani, and J.A. Striegel, “Range Finding Toxicity Data: List VI," Am. *Ind. Hyg. Assoc. J.,* 23, 95-107. 1962.

[RS - 3]

Genetic Tox *In Vitro*

Test Substance:	Methyl Ethyl Ketone (MEK)
CAS #:	78-93-3
Purity:	> 99 %
Method:	EU Annex V, B.14; OECD 471"Genetic Toxicology: Salmonella

	thyphimurium Reverse Mutation Assay"
Type:	Microbial Mutagenesis in Salmonella Mammalian Microsome Plate Incorporation Assay (Ames Cytogenetic Assay)
System of Testing:	Bacterial
GLP:	Yes
Year:	1992
Species/Strain:	S. typhimurium / TA97, TA98, TA100, TA1535, TA1537
Metabolic Activation:	With and Without
Species/cell type:	Male Sprague-Dawley rat and Syrian hamster / Livers; Aroclor 1254-induced (S-9 fraction)
Concentrations: **Tested** **Vehicle**	 100-333-1000-3333-10000 ug/plate Distilled Water
Remarks for Test Conditions:	Control plates were set up with solvent alone and with an appropriate known positive control compound. The S9 fractions were prepared from Aroclor -induced rats and hamsters. MEK was tested initially in TA100 with a range of test concentrations to establish the appropriate dose range for the mutagenicity assay. MEK was tested at half-log dose intervals up to 10000 ug/plate. The mutagenicity assay was then performed based on the results taking into account the effect on cell viability and any possible positive increases in mitotic gene conversion. Control plates were set up with solvent alone and with the positive control compounds in the absence of S-9 metabolic activation (sodium azide for TA1535 and TA100; 4-nitro-o-phenylenediamine for TA98 and TA1538 and cyclophosphamide) and with S-9 metabolic activation (2-aminoanthracene for all strains). MEK was designated nonmutagenic only after it had been tested in strains TA98, TA100, TA1535, TA97 and TA1537 without activation, and with 10% and 30% rat and hamster S-9 activation.
Results:	Negative
Remarks:	MEK did not induce reverse gene mutation in bacteria.
Conclusion:	Not Mutagenic
Data Quality:	1 - Reliable without Restrictions. No circumstances occurred that would have affected the quality or integrity of the data.
Reference:	Zeiger, E., B. Anderson, S. Haworth, T. Lawlor, and K. Mortelmans. (1992). Salmonella Mutagenicity Tests: V. Results from the Testing of 311 Chemicals. *Environmental and Molecular Mutagenesis*, Volume 19 (Supplement 21):2-141.

[RS - 4]

Genetic Tox *In Vitro*

Test Substance:	Methyl Ethyl Ketone (MEK)
CAS #:	78-93-3
Purity:	> 99 %

Method:	EU Annex V, B.14; OECD 471"Genetic Toxicology: Salmonella thyphimurium Reverse Mutation Assay"
Type:	Microbial Mutagenesis in Salmonella Mammalian Microsome Plate Incorporation Assay (Ames Cytogenetic Assay)
System of Testing:	Bacterial
GLP:	Yes
Year:	1988
Species/Strain:	S. typhimurium / TA98, TA100, TA1535, TA1537, TA1538
Metabolic Activation:	With and Without
Species/cell type:	Rat Liver (S9 fraction)
Concentrations: **Tested** **Vehicle**	 100-500-1000-5000-10000 ug/plate DMSO
Remarks for Test Conditions:	Control plates were set up with solvent alone and with an appropriate known positive control compound. All tests were carried out in triplicate. Two replicate assays were carried out on different days in order to confirm the reproducibility of the results. The S9 fractions were prepared from Aroclor -induced rats. Initially, a range of test concentrations of test material was tested and a second experiment was then performed based on the results taking into account the effect on cell viability and any possible positive increases in mitotic gene conversion. Control plates were set up with solvent alone and with the positive control compounds 4-nitroquinoline-*N*-oxide and cyclophosphamide.
Results:	Negative
Remarks:	MEK did not induce reverse gene mutation in bacteria.
Conclusion:	Not Mutagenic
Data Quality:	1 - Reliable without Restrictions. No circumstances occurred that would have affected the quality or integrity of the data.
Reference:	Brooks, T. M., Meyer, A., and Hutson, D. H. (1988). The genetic toxicology of some hydrocarbon and oxygenated solvents. *Mutagenesis*, 3(3):227-232.

[RS - 5]

Genetic Tox *In Vitro*

Test Substance:	Methyl Ethyl Ketone (MEK)
CAS #:	78-93-3
Method:	Specified Not
Type:	Yeast Mitotic Gene Conversion
System of Testing:	Saccharomyces cerevisiae
GLP:	Yes

Year:	1988
Species/Strain:	Saccharomyces cerevisiae
Metabolic Activation:	With and Without
Species/cell type:	Rat Liver (S9 fraction)
Concentrations:	
Tested	Maximum conc. 5 mg/ml
Vehicle	DMSO
Remarks for Test Conditions:	Yeast cells were grown in log phase, washed and re-suspended in 2/5 strength YEPD broth at a concentration of 10 X 10^6cells/ml. The suspension was then divided into 1.9 ml amounts in 30-ml universal containers and 0.1 ml of the test compound solution was added (-S9). For the experiments with metabolic activation (+S9), 0.1 ml of the compound was added to 1.6 ml of yeast suspension, together with 0.3 ml of S9 mix. The cultures were incubated with shaking, with shaking, at 30˚C for 18 hours. Aliquots were then plated onto the appropriate culture media for the selection of mitotic gene convertants and cells surviving the treatment.
Results:	Negative
Remarks:	MEK did not induce mitotic gene conversion in yeast.
Conclusion:	Not mutagenic
Data Quality:	1- Reliable without Restrictions. No circumstances occurred that would have affected the quality or integrity of the data.
Reference:	Brooks, T. M., Meyer, A., and Hutson, D. H. (1988). The genetic toxicology of some hydrocarbon and oxygenated solvents. *Mutagenesis*, 3(3):227-232.

[RS - 6]

Genetic Tox *In Vitro*

Test Substance:	Methyl Ethyl Ketone (MEK)
CAS #:	78-93-3
Method:	Not Specified
Type:	Chromosome Aberration Assay
System of Testing:	Rat Liver (RL_4)
GLP:	Yes
Year:	1988
Species/Cell Type:	Rat / Liver
Metabolic Activation:	Without - RL_4 cells are metabolically competent
Concentrations Tested:	0.5, 0.25, and 0.125 of the GI_{50} (50% Growth Inhibition).
Vehicle:	DMSO or water

Remarks for Test Conditions:	Cultured rat liver cells were grown and treated on glass microscope slides contained in 10o-ml volume glass Leighton tubes. After 22 hours exposure to test solvent, colcemid was added to each culture. After a further 2 hours, the slides were removed, subjected to hypotonic treatment followed by fixation (methanol:acetic acid, 3:1) and stained with Giemsa. The preparations were randomly coded and 100 cells from each culture were analyzed microscopically.
Results:	Negative - No increase in chromosomal aberrations
Remarks:	MEK did not induce chromosome damage in RL_4 mammalian cells.
Conclusion:	Not Mutagenic
Data Quality:	1 - Reliable without Restrictions. No circumstances occurred that would have affected the quality or integrity of the data.
Reference:	Brooks, T. M., Meyer, A., and Hutson, D. H. (1988). The genetic toxicology of some hydrocarbon and oxygenated solvents. *Mutagenesis*, 3(3):227-232.

[RS - 7]

Repeated Dose Inhalation Toxicity

Test Substance:	Methyl Ethyl Ketone (MEK)
CAS #:	78-93-3
Purity:	> 99.5%
Method:	90-Day Subchronic Toxicity
Type:	EPA Guideline Repeated Dose Inhalation Study
GLP:	Yes
Year:	1981
Species/Strain:	Fischer 344
Sex:	Male and Female
#/sex/dose:	15 (10/sex routine pathology and 5/sex special neuropathology)
Vehicle:	None
Route of Administration:	Inhalation
Duration of Test:	90 days; 6 Hours/Day; 5 Days/Week.
Doses:	0, 1250, 2500, or 5000 ppm - Vapor
Results:	The 90-day exposures had no adverse effect on the clinical health or growth of male or female rats except for a depression of mean body weight in the 5000-ppm exposure group. No animals died during the study. No signs of nasal irritation were observed during the study. There were no treatment-related effects in food consumption or ophthalmologic studies in any of the rats exposed to MEK vapors. The 5000-ppm animals had a slight but significant increase in liver weight, liver weight/body weight ratio and liver weight/brain weight ratio at the time of necropsy. Serum glutamic-pyruvic transaminase (SGPT) activity in the 2500-ppm female rats was

	elevated while the 5000-ppm female rats exhibited significantly decreased SGPT activity. In addition, alkaline phosphatase, potassium, and glucose values for the 5000-ppm female rats were increased. Special neuropathological and routine pathological studies did not reveal any lesions that could be attributed to MEK exposure.
Remarks:	An extensive pathologic investigation was conducted and no lesions were found that could be attributed to MEK exposure. There was no indication that repeated exposure to relatively high levels of MEK had any effect on reproductive tissues. The examined tissues included testes, epididymides, seminal vesicles, vagina, cervix, uterus, oviducts, and ovaries.
Conclusion:	MEK has a low order of toxicity. The NOAEL is 5000 ppm.
Data Quality:	1 - Reliable study with restrictions. Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Reference:	Cavender, F.L., Casey, H.W., Salem, H., Swenberg, J.A., and Gralla, E.J. (1983). A 90-day vapor inhalation toxicity study of methyl ethyl ketone. Fund. Appl. Toxicol. 3:264-270. Toxigenics. (1981). Study # 420-0305. Toxigenics, Inc., Decatur, IL 62526.

[RS - 8]

Reproductive Toxicity

Test Substance:	sec-Butanol (sBA) [Direct Parent Compound to Methyl Ethyl Ketone (MEK)]
CAS #:	78-92-2
Purity:	≥ 99 %
Method:	Comparable to an OECD 416 guideline study.
Type:	2-Generation Reproduction Study with Teratology Screen
GLP:	Pre-GLP
Year:	1975 Report and 1977 Abstract publication
Species:	Rat
Strain:	FDRL-Wistar Stock
Sex:	Males and Females
#/sex/dose:	30/sex/group
Duration of Test:	2 Generations
Exposure Period:	8 Weeks Premating Males; 8 Weeks Premating Females
Route of Administration:	Drinking Water
Frequency of Treatment:	Daily - ad libitum
Doses/Concentration:	**F_0 Generation:** 0, 0.3, 1.0, or 3.0% solutions (0, 538, 1644, and 5089 mg/kg-day for males and 0, 594, 1771, and 4571 mg/kg-day for females) **F_1 Generation:** 0, 0.3, 1.0, or 2.0% (2.0% calculated to be equivalent to 3384 mg/kg-day for males and 3122 mg/kg-day for females)

Control Group:	Yes - Water
Vehicle:	Drinking Water
Results:	Maternal NOEL: 1% (~1500 mg/kg/day) Maternal NOAEL: 1771 mg/kg/day Pup NOEL: 1% (~1500 mg/kg/day) Pup NOAEL: 1771 mg/kg/day
Remarks:	sec-Butanol was initially administered to the F_0 generation at concentrations of 0, 0.3, 1.0, and 3.0% in the drinking water. Due to toxicity, the high level was reduced to 2.0% during the second-generation study (F_1). The F_1 generation animals (30/sex/group) were reared to maturity (up to week 12), mated to produce a F_2 generation, then sacrificed for organ weights, and gross and microscopic pathological evaluations (10/sex/group). Hematological, biochemical, and urinary examinations were conducted terminally on the F_1 rats. A series of mild changes in the kidney (non-reactive tubular degeneration, tubular casts, foci of tubular regeneration, microcysts) were observed animals treated at 2.0% sBA. The authors concluded that these findings were not a result of direct toxicity and did not have clear pathologic significance. Rather they were non-specific effects due to increased renal work load, possibly from increased urine volume and pressure at the high dose of sBA (Cox *et al*, 1975). No other findings of note were seen. The no-effect level for the study was 1.0% (estimated to be 1500 mg/kg/day by the authors and 1771 mg/kg/day by EPA/IRIS).
Conclusion:	sBA is not a reproductive hazard.
Data Quality:	2 - Reliable study with restrictions. No circumstances occurred that would have affected the quality or integrity of the data. Comparable to a guideline study; test procedures were in accordance with generally accepted scientific standards and described in sufficient detail.
References:	Report: Cox, G.E., D.E. Bailey and K. Morgareidge. (1975). Toxicity studies in rats with 2-butanol including growth, reproduction and teratologic observations. LaB No. 2093. Food and Drug Research Laboratories, Inc., Waverly, NY. Abstract: Gallo, M.A., Oser, B.L., Cox, G.E., and Bailey, D.E. (1997). Studies on the long-term toxicity of 2-butanol. Toxicology and Applied Pharmacology, 41:135.

[RS - 9]

Developmental Toxicity

Test Substance:	Methyl Ethyl Ketone (MEK)
CAS #:	78-93-3
Purity:	Reagent Grade (99.6%)
Method:	Comparable to an OECD 414 guideline study.
Type:	Developmental Toxicity

GLP:	Unknown
Year:	1981
Species:	Rat
Strain:	Sprague-Dawley
Route of Administration:	Inhalation
Doses/Concentration:	0, 400, 1000 or 3000 ppm
Sex:	Female
Exposure Period:	7 hr/day
Frequency of Treatment:	Gestation Days 6-15
Control Group:	Yes
Duration of Test:	21 Days
Statistical Methods:	A modified Wilcoxon test to evaluate incidence of fetal alterations. Other specific tests are not mentioned.
#/dose:	25
Vehicle:	None
Results:	Maternal NOEL: 1000 ppm Maternal NOAEL: 3000 ppm Pup NOEL: 1000 ppm Pup NOAEL: 3000 ppm
Remarks:	Groups of 25 rats were exposed by inhalation to 400, 1000 or 3000 ppm MEK, 7 hours/day on days 6-15 of gestation; the dams were sacrificed on day 21. There were 35 rats in the control group. The day on which sperm was seen in a vaginal smear was considered day 0 of pregnancy. Animals were housed in wire-bottom cages and maintained on commercial laboratory chow (Purina Rat Chow), and water ad libitum in a room controlled for temperature, humidity, and light cycle. Food and water consumption was measured at intervals of 3 days during the experimental period. Neither food nor water was provided during the exposure. Body weights were recorded pretest, and on days 6, 8, 10 and 16. Exposures were conducted in a 0.16 m^3 stainless steel, cubic dynamic exposure chambers. MEK vapors were generated by metering the liquid with a precision syringe pump into a vaporization flask and diluted with filtered air at a rate calculated to give the desired concentration. The analytical concentrations were determined by sampling the chamber concentrations 15 min/hr with a Miran I variable filter infrared analyzer at a wavelength of 8.5 µm. Exposures to MEK had no effect on the dams' appearance or demeanor. Maternal toxicity was evidenced by decreased weight gain and increased water consumption at the 3000 ppm exposure level. Inhalation of 400, 1000, or 3000 ppm MEK had no significant effect on the incidence of pregnancy, average number of implantations or live fetuses per dam. The incidence of resorptions for each dose level was comparable to controls. There were no adverse effects on fetal body weights or crown-rump lengths. There

	were no soft-tissue alterations at any dose level that were statistically significantly different from controls. No significant increase in the incidence of major malformations in fetuses exposed to MEK was observed. The exposure to 3000 ppm of MEK, a slightly maternal toxic level, resulted in some minor variations in the development of the fetal skeleton in rats and was considered a slight fetotoxic effect. Neither significant embryotoxicity nor a teratogenic effect was discerned in rats inhaling up to 3000 ppm MEK for 7 hr/day during the period of major organogenesis.
Conclusion:	MEK is not a teratogen.
Data Quality:	2- Reliable study with restrictions. Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Reference:	Deacon, M.M., M.D. Pilney, J.A. John, B.A. Schwetz, F.J. Murray, H.O. Yakel, and R.A. Kuna, "Embryo- and Fetotoxicity of Inhaled Methyl Ethyl Ketone in Rats," *Toxicol. Appl. Pharmacol*., 59, 620-622. 1981.

[RS - 10]

Developmental Toxicity

Test Substance:	Methyl Ethyl Ketone (MEK)
CAS #:	78-93-3
Purity:	Reagent Grade (99.7%)
Method:	Comparable to an OECD 414 guideline study.
Type:	Developmental Toxicity
GLP:	Pre-GLP
Year:	1974
Species:	Rat
Strain:	Sprague-Dawley
Route of Administration:	Inhalation
Doses/Concentration:	0, 1000 or 3000 ppm
Sex:	Female
Exposure Period:	7 hr/day
Frequency of Treatment:	Gestation Days 6-15
Control Group:	Yes
Duration of Test:	21 Days
Statistical Methods:	Fisher Exact Probability, ANOVA, Dunnett's test, and Tukey's test as appropriate.
#/dose:	43, 23 and 21 (Control, Low and High Dose Groups, respectively)
Vehicle:	None
Results:	Maternal NOEL: <3000 ppm

	Maternal NOAEL: 3000 ppm Pup NOEL: <1000 ppm Pup NOAEL: 1000 ppm
Remarks:	Groups of 43 (total control animals), 23 and 21rats were exposed by inhalation to 0, 1000 or 3000 ppm MEK, 7 hours/day on days 6-15 of gestation; the dams were sacrificed on day 21. The day on which sperm was seen in a vaginal smear was considered day 0 of pregnancy. Animals were housed in wire-bottom cages and maintained on commercial laboratory chow (Purina Rat Chow), and water ad libitum in a room controlled for temperature, humidity, and light cycle. Neither food nor water was provided during the exposure. Food consumption was measured at 2-day intervals and body weights were measured at pretest, day 6, 13 and 21. Exposures were conducted in a 3.7m^3 stainless steel, cubic dynamic exposure chambers. MEK vapors were generated by metering the liquid at known rates into a temperature controlled evaporating flask and diluted with filtered air at a rate calculated to give the desired concentration. The analytical concentrations were determined by sampling the chamber concentrations 3 times daily with a Beckman IR10 infrared spectrophotometer. MEK was reported by the authors to be embryotoxic, fetotoxic, and potentially teratogenic to rats at 3000 ppm but not at 1000 ppm based on findings of delayed ossification of sternebrae, a low incidence of gross anomalies (i.e., a total of 4 fetuses), and a statistically significant incidence of "total" soft tissue anomalies. There was no single soft tissue anomaly that occurred at an increased incidence in the 3000-ppm group. There were neither gross, soft tissue nor specific skeletal anomalies that occurred at a significantly increased incidence among litters of dams exposed to 1000 ppm MEK. However, the total number of litters containing fetuses with anomalous skeletons was significantly increased compared to controls. There was an almost six-fold difference in the occurrence of delayed ossification of sternebrae in the two concurrent control groups for the 1000 ppm and 3000 ppm exposure groups. The fetal body weights and crown-rump lengths were significantly different from controls in the 1000 ppm group but not in the 3000 ppm group. There was no maternal toxicity. The incidence of major malformations was not sufficiently high to support a positive teratogenic conclusion.
Conclusion:	MEK is not a teratogen.
Data Quality:	2- Reliable study with restrictions. Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Reference:	Schwetz, B.A., B.K. Leong, and P.J. Gehring. (1974). "Embryo and Feto Toxicity of Inhaled Carbon Tetrachloride, 1,1-Dichloroethane and Methyl Ethyl Ketone in Rats," *Toxicol. Appl. Pharmacol.*, 28, 452-464.

[RS - 11]

Developmental Toxicity

Test Substance:	sec-Butanol (sBA)

CAS #:	78-92-2
Purity:	≥ 99 %
Method:	Comparable to an OECD 414 guideline study.
Type:	Developmental Toxicity
GLP:	Yes
Year:	1989
Species:	Rat
Strain:	Sprague-Dawley
Route of Administration:	Inhalation
Doses/Concentration:	0, 3500, 5000 or 7000 ppm
Sex:	Female
Exposure Period:	Gestation Days 1-20
Frequency of Treatment:	7 hr/day
Control Group:	Yes
Duration of Test:	20 Days
Statistical Methods:	For the maternal data, multivariate analysis (with baseline as covariant) was used for weight comparisons across groups. The group differences in food and water intake were analyzed by multivariate analysis of variance. A Kruskal-Wallis test was used for group comparisons of corpora lutea per animal. For the fetal data, analysis of covariance was used to compare fetal weights across groups and sex. Group comparisons of the variables including litter size, percentage alive/litter, percentage normal/litter, and percentage females/litter were made using Kruskal-Wallis test. For the variables including skeletal malformations, skeletal variations, visceral malformations, visceral variations, external malformations, and non-normal fetuses, the number of litters with one or more of the variables of interest was compared between groups using Fisher's exact test. The results of the test were adjusted for multiple comparisons, when appropriate, using the Bonferroni technique. A probability of $p = \leq 0.05$ was required for significance.
#/dose:	15 -16 Mated Females
Vehicle:	None
Results:	Maternal NOEL: < 3500 ppm Maternal NOAEL: 3500 ppm Pup NOEL: 3500 ppm Pup NOAEL: > 7000 ppm
Remarks:	Groups of 15-16 rats were exposed by inhalation to 0, 3,500, 5,000 or 7,000 ppm sBA, 7 hours/day on days 1-19 of gestation; the dams were sacrificed on day 20. At 7,000 ppm, narcosis was observed in all animals. At 5000 ppm, the dams were partially narcotized with locomotion activity impaired. Maternal weight gain and food consumption were significantly reduced in all dose groups. No data

	collected on maternal organ weights, or gross or microscopic lesions. The number of live fetuses was significantly reduced and resorptions were increased in the high exposure group only. Fetal body weights were significantly reduced in the mid- and high dose groups. There was no evidence of teratogenic effects in this study, and there was also no evidence of selective developmental toxicity. The no-effect levels were < 3,500 ppm for maternal toxicity and 3,500 ppm for developmental toxicity.
Conclusion:	sBA is not a teratogen. There was no evidence of teratogenic events nor was there evidence of selective developmental toxicity.
Data Quality:	2- Reliable study with restrictions. Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Reference:	Nelson, B. K., Brightwell, W. S., Khan, A., Burg, J. R., and Goad, P. T. (1989). Lack of selective developmental toxicity of three butanol isomers administered by inhalation to rats. *Fundam Appl Toxicol*, 12:469-479.

[RS - 12]

Developmental Toxicity

Test Substance:	sec-Butanol (sBA)
CAS #:	78-92-2
Purity:	≥ 99 %
Method:	Comparable to an OECD 421 guideline study.
Type:	Developmental Toxicity: Part of a Two-Generation Reproduction Study with Measurement of Developmental Toxicity Endpoints.
GLP:	Pre-GLP
Year:	1975 Report and 1977 Abstract publication
Species:	Rat
Strain:	FDRL-Wistar Stock
Sex:	Females
Route of Administration:	Drinking Water
Doses/Concentration:	F_0 Generation - second breeding. 0, 0.3, 1.0, or 2.0% solutions (0, 538, 1644, and 3384 mg/kg-day for males and 0, 594, 1771, and 3122 mg/kg-day for females)
Exposure Period:	8 Weeks premating (Males and Females) and during gestation (Females).
Frequency of Treatment:	Daily **-** ad libitum
Control Group:	Yes - Water
Vehicle:	Drinking Water
Duration of Test:	20 Days

#/sex/dose:	30/sex/group
Results:	Maternal NOEL: 1% (1771 mg/kg/day) Maternal NOAEL: 1% (1771 mg/kg/day) Pup NOEL: 1% (1771 mg/kg/day)
Remarks:	TERATOLOGY SCREEN RESULT: The F_0 rats were mated to obtain a second series of pregnant dams destined to provide teratologic evaluation of the treatments. Pregnancy rates and survival of these females were unaffected. All findings sBA at both 0.3 and 1.0% in the drinking water were negative with respect to signs of toxicity in terms of both growth and reproductive efficiency The body weights of the dams were not depressed. Examination of the uterine contents on the 20th day of gestation revealed that sBA was somewhat fetotoxic at the 2.0% dosage level, as shown by the decreased pup weights (3.74 g vs. 4.14 g in controls). However, that this is a minimal response is shown by the fact that none of the other parameters in the reproductive toxicity phase of this study (nidation, early or late fetal deaths) were affected. The 2.0% group showed apparent increases in missing sternebrae, wavy ribs, and incomplete vertebra ossification when compared with both the 0.3 and 1.0% groups. However, because the incidences for these findings in the control group were comparable, these effects could not be determined to be compound-related. The skeletal abnormalities seen in the sBA groups were consistent in type and frequency with the spontaneous incidence observed in this rat colony. There were no significant soft tissue findings in the 2% treated group.
Conclusion	Not a teratogen.
Data Quality	2 - Reliable study with restrictions. No circumstances occurred that would have affected the quality or integrity of the data. Comparable to a guideline study and test procedures were in accordance with generally accepted scientific standards and described in sufficient detail.
References:	Report: Cox, G.E., D.E. Bailey and K. Morgareidge. (1975). Toxicity studies in rats with 2-butanol including growth, reproduction and teratologic observations. LaB No. 2093. Food and Drug Research Laboratories, Inc., Waverly, NY. Abstract: Gallo, M.A., Oser, B.L., Cox, G.E., and Bailey, D.E. (1997). Studies on the long-term toxicity of 2-butanol. Toxicology and Applied Pharmacology, 41:135.

[RS - 13]

Developmental Toxicity

Test Substance:	Methyl Ethyl Ketone (MEK)
CAS #:	78-93-3
Purity:	99.9%
Method:	Comparable to an OECD 414 guideline study
Type:	Developmental Toxicity
GLP:	Unknown

Year:	1991
Species:	Mouse
Strain:	Swiss Mice [(COBS) (Crl:CD-1)(ICR)BR Swiss Albino]
Route of Administration:	Inhalation
Doses/Concentration:	0, 400, 1000 or 3000 ppm
Sex:	Female
Exposure Period:	7 hr/day
Frequency of Treatment:	Gestation Days 6-15
Control Group:	Yes
Duration of Test:	18 Days
Statistical Methods:	SAS general linear model procedure with ANOVA for unbalanced data. B-Wts or arcsine transformations of proportional incidence data via one-way ANOVA. A Tukey's *t* test (2-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. 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.
#/dose:	10 virgin and 33 plug-positive
Vehicle:	None
Results:	Maternal NOEL: 1000 ppm Pup NOEL: 1000 ppm
Remarks:	Groups of 10 virgin and 25 plug-positive (presumed pregnant), 12-week old females were exposed by inhalation to 400, 1000 or 3000 ppm MEK, 7 hours/day on days 6-15 of gestation; the dams were sacrificed on day 18 and the virgin females were killed 3 days after the last exposure. There were 35 mice in the control group. The day of plug detection was considered day 0 of pregnancy. Animals were housed in wire racks with automatic waterers. Mice were maintained on commercial laboratory chow (NIH-07 diet) and in a room controlled for temperature, humidity, and light cycle. Neither food nor water was provided during the exposure. Body weights were recorded pretest and at intervals of 3-5 days throughout the study. Exposures were conducted in a 2.3 m^3 stainless steel, cubic dynamic exposure chambers and chamber environmental conditions were monitored at 4-hour intervals. MEK vapors were generated by a rotary evaporation system and forced into a conditioned air stream with low-pressure nitrogen prior to entry into the chamber. Uniform distribution of the vapors in the chamber was confirmed. There were indications of maternal toxicity shown by concentration-related increases in relative liver and kidney weights, which were significant in the 3000-ppm dams. Mild concentration-related decrease in fetal body weight was observed for both male and females; however, this was statistically significant only for males at

	3000 ppm. There were no statistically significant increases in the number of malformed fetuses per litter, although there were several atypical malformations not often found in control litters. There was a significant finding of increased incidence of misaligned sternebrae, a skeletal variation, at 3000 ppm. No developmental or maternal effects were observed at vapor concentrations of 1000 ppm or less. The authors concluded that MEK vapors caused developmental toxicity and a low incidence of malformations at concentrations that caused maternal toxicity (i.e., 3000 ppm). No maternal or developmental toxicity was observed at concentrations of 1000 ppm MEK or below.
Conclusion:	MEK is not a teratogen.
Data Quality:	2- Reliable study with restrictions. Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Reference:	Schwetz, B.A., T.J. Mast, R.J. Weigel, J.A. Dill, and R.E. Morrissey. (1991). "Developmental Toxicity of Inhaled Methyl Ethyl Ketone in Swiss Mice," *Toxicol. Appl. Pharmacol*., 16, 742-748.

[RS-14]

Immunotoxicity

Test Substance:	Acetone
CAS #:	67-64-1
Purity:	99+ % by gas-liquid chromatography
Type:	Immunotoxicity study via antibody response to sheep red blood cells (SRBC)
GLP:	Yes
Year:	2003
Species/Strain:	Mouse/ CD-1
Sex:	Males
#/dose:	8/Group
Vehicle:	Drinking water
Route of Administration:	Acetone mixed with municipal water once per week
Duration of Test:	29 Days
Exposure Period:	28 Days
Post-exposure Period:	0 days; Evaluation on day 29 following 28-day exposure period
Frequency and Duration of Exposure:	Continuous (*ad libitum* in drinking water) for 28 days
Exposure Concentration Levels:	0.6, 3 or 6 mg/ml; Target concentrations were selected based on prior studies conducted in mice. All solutions were verified to be within 5% of the target concentrations.
Control and Treated Groups:	8/group administered water only for 28 days (vehicle control) 8/group administered water only for 28 days, and cyclophosphamide (positive control for immunosuppression) 8/group administered 100 mg acetone/kg/day for 28 days 8/group administered 500 mg acetone/kg/day for 28 days

	8/group administered 1000 mg acetone/kg/day for 28 days
Dosage:	Time-weighted average dosages (mg/kg/day) based on water consumption and actual body weights were: Vehicle Control 0 Positive Control 0 100 mg/kg/day 121 500 mg/kg/day 621 1000 mg/kg/day 1144 1000 mg/kg/day equals guideline limit dose.
Statistical Methods:	Means and standard deviations for body and organ weights, antibody response and most hematology were analyzed using a Bartlett's test followed by ANOVA. If analyses indicated a significant difference by the ANOVA, the treatment groups were compared to the drinking water control using a Dunnett's test. WBC differentials and RBC indices were not statistically compared.
Remarks (Test Conditions):	Twice each day a cage-side examination was conducted and to the extent possible the following parameters were evaluated: skin, fur, mucous membranes, respiration, nervous system function (including tremors and convulsions), animal behavior, moribundity, mortality and the availability of feed and water. Body weights were obtained prior to study start and weekly thereafter. Water consumption was determined weekly for each mouse. Test material intake was calculated using solution concentrations, body weights and water consumption data. Four days prior to sacrifice, all mice were immunized with a single intravenous injection of 1×10^8 SRBC via the lateral tail vein. Approximately 24 hours after the last dosing, serum was collected via retro-orbital bleeds and spleens and thymuses were removed and weighed. A single cell suspension was prepared for each spleen and the number of splenocytes counted. Splenocytes were combined with SRBC, guinea pig compliment and agar to conduct an Antibody-Plaque Forming Cell (AFC) assay. In addition, hematology profiles (hematocrit, RBC count, platelet count, RBC indices [MCH, MCV and MCHC], hemoglobin concentration, total WBC count and WBC differential were evaluated.
Results:	Consumption values of acetone-supplemented water were not different from municipal drinking water with one exception. During the first week, the mice provided water containing approximately 6 mg/ml acetone (1,000 mg/kg/day) drank an average of 1.1 gram less water than did mice from the vehicle control group. However, this level of water consumption was not appreciably less than that measured over days -5 to 1 and did not compromise the targeted acetone exposure of 1,000 mg/kg/day (average acetone consumption for days 1-8 = 1,179 mg/kg/day). Body weights were unremarkable throughout the 28 day study and no mortalities occurred in any group. There were no signs of toxicity noted during daily health observations. Hematology parameters were unaffected by acetone consumption and showed no treatment-related effects. The percentage of eosinophils appeared to be lower than controls in some groups of mice treated with acetone but the results were not dose-related. All values were within the range of historical controls.

	Pair-wise comparisons following acetone treatment for 28 consecutive days did not identify statistical differences from controls for spleen or thymus weights from acetone-treated animals. The mean thymus weights of mice administered acetone at 1,144 mg/kg/day were about 25% lower than controls but were not statistically different from control thymus weights. Any suggestion of a treatment-related effect on thymus weights was not supported by a treatment-related effect for WBC counts or lymphocyte differentials. In this study, any change in thymus weight and selected hematology parameters at the highest dose of acetone were also not consistent with previous studies. Dietz *et al.* evaluated similar end points (including thymus weights) in B6C3F1 mice following higher acetone exposures for an extended exposure period *via* drinking water and reported no effects on thymus weights, eosinophils or WBC counts. It is possible that the reduced thymus weights merely reflect the beginning of an overt stress response as aside from MHC II expression, the thymus is known to be the most sensitive marker in the immune system for stress conditions. No effects were noted for spleen cellularity or AFC response following acetone exposures. The AFC responses ranged from 1088 – 1401 AFC/10^6 splenocytes following water or acetone administration, and were not statistically different from control values.
Conclusions:	*Ex vivo* tests that challenge immune cells to respond functionally (*e.g.*, AFC response) are generally more convincing indicators of immunotoxicity and in this study, no treatment related effect of acetone on the SRBC antibody response was observed. The eosinophils in two acetone treated groups appeared to be lower than the controls but demonstrated no dose-related trend, hence this observation does not appear to be treatment-related. Furthermore, these data were within the range of historical values for negative controls and were not consistent with hematology data reported in a previous study. Acetone treatment did not produce any alterations in lymphoid organ weights (spleen or thymus) that were statistically different from controls. Acetone administration under the conditions of this study did not produce immunotoxicity in CD-1 mice.
Data Quality:	1 - Reliable study without Restrictions.
Reference:	Woolhiser, M.R., P.K. Andersen, and J.M. Waechter, Jr. (2003). Acetone: 4-Week Drinking Water Immunotoxicity Study in CD-1 Mice. Report of The Dow Chemical Company.

[RS - 15]

Genetic Tox *In Vivo*

Test Substance:	Methyl Ethyl Ketone (MEK)
CAS #:	78-93-3
Purity:	99.9%
Method:	OECD 474 equivalent
Type:	In Vivo Mammalian Bone Marrow Erythrocyte Micronucleus Assay Intraperitoneal Dosing Method

GLP:	Unknown
Year:	1988
Species:	Mouse
Strain:	Crl:CD-1 (Kingston, NY)
Sex:	Males and Females
Number:	5/sex/dose
Route of Administration:	Intraperitoneal injection
Dose/time:	1.96 ml/kg Single injection (dose equal to the MEK LD_{20} reported as ml test article / kg body weight when administered in a total volume of 10 ml test article-vehicle mixture / kg body weight).
Test Period:	12, 24 and 48 hours
Vehicle:	Corn Oil (10 ml/kg)
Positive Control:	0.25 mg/kg Triethylene melamine (TEM)
Remarks:	The test substance and the vehicle were administered as a single dose by intraperitoneal injection. The vehicle was dosed at a volume equal to the test substance volume. The positive control was administered as a single dose at a volume equal to the test substance volume. Animals from the appropriate groups were sacrificed at approximately 12, 24 and 48 hours. Animals dosed with triethylene melamine were sacrificed at 24 hours only. Immediately following sacrifice, the femur was exposed and the bone marrow was aspirated into a syringe containing fetal calf serum. The cells were washed, centrifuged, and resuspended. Slide smears of the bone marrow were made for each animal and stained with May-Gruenwald-Giemsa stain. Coded slides were then evaluated for presence of micronuclei (1000 polychromatic erythrocytes/animal were evaluated). A 1-way analysis of variance and Duncan's multiple range test ($p \leq 0.05$) were used to assess the statistical significance of any observed effects.
Results:	None of the dose groups were statistically different from the vehicle control. The positive control (0.25 mg/kg TEM) induced a statistically significant increase in the mean number of micronucleated polychromatic erythrocytes ($p \leq 0.01$) which indicates that the positive control was clastogenic and the test system responded in an appropriate manner. Vehicle carrier control values for the mean percent of polychromatic erythrocytes and for the mean percent of micronucleated polychromatic erythrocytes responded in an appropriate manner.
Remarks:	Not mutagenic
Conclusion:	MEK did not induce a statistically significant increase in the mean number of micronucleated polychromatic erythrocytes in the bone marrow of CD-1 mice. Therefore, it is not considered mutagenic under the conditions of this assay.
Data Quality:	1 - Reliable without Restrictions. No circumstances occurred that would have affected the quality or integrity of the data.
Reference:	O'Donoghue, J.L., Haworth, S.R., Curren, R.D., Kirby, P.E., Lawlor, T., Moran, E.J., Phillips, R.D., Putnam, D.L., Rogers-Back, A.M.,

	Slesinski, R.S., and Thilagar, A. (1988). Mutagenicity studies on ketone solvents: methyl ethyl ketone, methyl isobutyl ketone, and isophorone. Mutation Research, 206:149-161.

[RS - 16]

Metabolism and Pharmacokinetics

Test Substances:	2-Butanol (sec-Butanol; sBA) and metabolites 2-Butanone (Methyl ethyl ketone; MEK), 3-Hydroxy-2-Butanone (3H-2B), and 2,3-Butanediol (2,3-BD).
CAS #:	78-92-2 (sBA); 78-93-3 (MEK)
Purity:	Not Identified.
Method:	Experimental Model Development
Type:	Metabolism and Pharmacokinetic Evaluation
GLP:	Unknown
Year:	1981
Species:	Sprague-Dawley
Route of Administration:	Oral Gavage / i.v.
Doses Groups / Concentration:	sBA: 2.2 ml/kg or 1776 mg/kg as a 22% aqueous solution (oral). MEK: 2.1ml/kg or 1690 mg/kg as a 21% aqueous solution (oral). 2,3-BD : 0.68 ml/kg or 676 mg/kg as a 6.8 % aqueous solution (oral or i.v.). 3H-2B: 400 or 800 mg/kg as a 60% aqueous solution (i.v.)
Sex:	Male
Frequency of Treatment:	Single Dose (oral or i.v.)
Duration of Test:	30 Hours
Statistical Methods:	Student's *t*-test was used for statistical evaluation of differences between two means. In the pharmacokinetic model, the differential equations were solved numerically by a Hammings Predictor-Correction method with a Runge-Kutta starter.
#/Dose Group:	Not Identified.
Vehicle:	Aqueous Solution
Results:	In the sBA-treatment phase of the study, blood concentrations of sBA and its metabolites MEK, 3H-2B, and 2,3-BD were measured. Blood sBA concentrations of 0.59 mg/ml peaked at 2 hours and declined to less than 0.05 mg/ml at 16 hours. As the sBA concentration fell, the metabolite concentrations of MEK, 3H-2B, and 2,3-BD concentrations rose to maximums at 8, 12, and 18hr, respectively. The peak concentration of MEK was 0.78 mg/ml, while that of 2,3-BD was 0.21 mg/ml. 3H-2B reached a peak concentration of 0.04 mg/ml. Total AUC values for sBA, MEK, 3H-2B, and 2,3-BD were 3254 ± 258, 9868 ± 566, 443 ± 93, and 3167 ± 503 mg-hr/l, respectively. Following an oral dose of MEK, blood concentrations of MEK and its metabolites sBA, 3H-2B, and 2,3-BD were measured. Blood MEK

	concentrations of 0.95 mg/ml peaked at 4 hours and declined to less than 0.07 mg/ml at 18 hours. As the MEK concentration fell, the end metabolite 2,3-BD rose to a maximum concentration of 0.26 mg/ml at 18 hours. Peak concentrations of sBA and 3H-2B were 0.033 and 0.027 mg/ml, respectively. These were detected at 6 and 8 hr after the MEK administration. Total AUC values for MEK, sBA, 3H-2B, and 2,3-BD were 10,899 ± 824, 414 ± 38, 382 ± 38, and 3863 ± 238 mg-hr/l, respectively.
Remarks:	Dietz et al. (1981) selected doses for MEK and sBA based on the earlier pharmacokinetic analysis (Traiger and Bruckner, 1976) that established approximately 96% of an administered dose of sBA was oxidized *in vivo* to MEK. Thus 1960 mg/kg (2.1 ml/kg) of MEK estimates the amount of MEK formed in vivo from a dose of 1776 mg/kg (2.2 ml/kg) of sBA. Male rats were given oral doses of sBA, MEK, 2-3 B-D (or i.v.), or 3H-2B (i.v.) and serial blood samples were collected for up to 30 hours following treatment.
Conclusion:	In the development of the model, the authors confirmed that a limited amount of sBA could be recovered as glucuronide in the urine. Most of the alcohol appears to undergo oxidation via alcohol dehydrogenase to its corresponding ketone, MEK. The results showed a limited amount of the ketone undergoes a backward reduction to its parent alcohol, sBA. 3H-2B and 2,3-BD are found to be common metabolites of sBA and MEK. The model was able to simulate blood concentrations and elimination of all 4 compounds after oral administration of sBA, and the results after i.v. of 3H-2B and 2,3-BD. AUC analysis suggested that the quantities of 3H-2B and 2,3-BD formed from oral doses of sBA and MEK are comparable. The results supported the estimation in that no significant difference in the AUC of MEK was observed after dosing with either 1776 mg/kg of sBA or 1690 mg/kg of MEK (10,899 ± 824 vs. 9868 ± 566 mg-hr /liter, respectively).
Data Quality:	1 - Reliable study. No circumstances occurred that would have affected the quality or integrity of the data. Test procedures were in accordance with generally accepted scientific standards and described in sufficient detail.
Reference:	Dietz, F.K., Rodrigues-Giaxola, M., Traiger, G.J., Stella, V.J., and Himmelstein, K.J., (1981). Pharmacokinetics of 2-Butanol and its Metabolites in the Rat. Journal of Pharmacokinetics and Biopharmaceutics, Vol. 9 (5): 553-576.

[RS - 17]

Metabolism and Pharmacokinetics

Test Substances:	2-Butanone (Methyl ethyl ketone; MEK)
CAS #:	78-93-3 (MEK)
Purity:	98% with traces of 2-butanol
Method:	Experimental
Type:	Metabolism and Pharmacokinetic Evaluation

GLP:	Unknown
Year:	1976
Species:	Guinea Pig
Route of Administration:	I.P.
Dosage:	450 mg/kg body weight
Sex:	Male
Frequency of Treatment:	Single injection
Duration of Test:	16 Hr.
#/Dose Group:	4 at each blood - sampling interval
Vehicle:	Corn oil (25% solution)
Results:	MEK: 2-Butanol, 3-hydroxy-2-butanone, and 2,3-butanediol were identified as metabolites in the serum of guinea pigs injected i.p. with MEK. The half-life of MEK in serum was 270 min. The clearance time of MEK was 12 Hr. 2,3-Butanediol was cleared in 16 hours, as were the other two metabolites. The metabolism was described as oxidation via hydroxylation of the ω -1 carbon forming 3-hydroxy-2-butanone as the metabolite of MEK. Reduction occurred at the carbonyl group as expected forming the secondary alcohol, 2-butanol from MEK.
Remarks:	Male guinea pigs ranging in weight from 250 - 450 grams were given a single i.p. dose of 450mg/kg MEK (study also investigated MnBK and MiBK - data not addressed here). Blood was collected by heart puncture from 4 animals at each of the following times after dose administration: 1, 2, 4, 6, 8, 12, and 16 Hr. Only 1 sample was collected from each guinea pig. Serum was separated and refrigerated until assayed within 48 Hr. The concentrations of the ketones and their metabolites were measured in duplicate by direct on-column injection of undiluted serum into a Varian 2100 Gas Chromatograph equipped with a flame ionization detector. Ketones and metabolites were quantitated from calibration curves prepared from pure standards. Greater than 90% of each ketone was distributed in the plasma fraction. Half-lives were estimated by extrapolating the linear portion of the decay curve to zero time.
Conclusion:	This study showed the initial metabolism of MEK follows both oxidative and reductive pathways to produce 3-hydroxy-2-butanone, 2,3-butanediol and 2-butanol.
Data Quality:	1 - Reliable study. No circumstances occurred that would have affected the quality or integrity of the data. Test procedures were in accordance with generally accepted scientific standards and described in sufficient detail.
Reference:	DiVincenzo, G.D., Kaplan, C.J., and Dedinas, J., (1976). Characterization of the Metabolites of Methyl *n*-Butyl Ketone, Methyl iso-Butyl Ketone, and Methyl Ethyl Ketone in Guinea Pig Serum and their Clearance. Toxicology and Applied Pharmacology, 36:511-522.

[RS - 18]

Metabolism and Pharmacokinetics

Test Substances:	2-Butanone (Methyl ethyl ketone; MEK)
CAS #:	78-93-3 (MEK)
Purity:	Analytical Grade
Method:	Experimental
Type:	Metabolism and Pharmacokinetic Evaluation
GLP:	Unknown
Year:	1988
Species:	Human
Route of Administration:	Inhalation
Dosage:	200 ppm (8.2mmol/m^3)
Sex:	Male
Frequency of Treatment:	2 Exposure periods at least 1 wk between
Duration of Test:	4 Hr. Exposure
# in Test Group:	9
Vehicle:	None
Results:	Pulmonary retention of MEK in the lungs remained constant throughout exposure with or without exercise. Relative uptake was 53% ± 2%. Estimated mean total pulmonary uptakes were 11.4 mmol (ventilation volume 11 liters/min at rest) and 14.3 mmol (ventilation volume 35 liters/min during the exercise). Blood MEK concentrations increased rapidly during the first hour of exposure (markedly faster when associated with exercise). Thereafter, concentrations increased slowly and linearly through 4 hr with sedentary activity and steeply during the exercise period at the end of the 4 hr exposure period. Two elimination phases were detected for MEK in blood. The calculated half-time for the faster phase of elimination (0-45 min post-exposure) was 30 min and about 81 min for the slower phase (60-320 min post-exposure). Owing to remarkable solubility of MEK, only 2-3% of absorbed dose was eliminated by exhalation. Urinary excretion of unchanged MEK was 0.1% and excretion of the metabolite 2H3B was about 0.1%. The authors speculated that the greater part of absorbed MEK is probably converted to products of intermediary metabolism, e.g., to acetate or acetoacetate via 3H2B .
Remarks:	Nine healthy male volunteers, 18-34 years of age (mean 23.7), weight 65-81 kg (mean 74.3), height 172-190 cm (mean 181.8) and calculated surface area 1.81 - 2.09 m^2 (mean 1.97) were exposed for 4 Hr to 200ppm MEK on 2 separate days at least 1 week apart. Venous blood samples were collected at 1-hr intervals during exposure and over 120 to 210 minutes post-exposure. In a supplementary study, follow-up elimination blood samples were collected in 2 persons until the next morning. One of the exposures constituted sedentary activity and the other encompassed three 100 W ergometric exercise periods over

	minutes 5-15, 95-105 and 225-235 during a total exposure of 240 minutes. Exhaled air samples were collected with a 2-way respirator mouthpiece into 4-liter polyester laminated aluminum-foil bags and analyzed immediately. Samples were collected at one-hour intervals during exposure and over 120-210 minutes thereafter. Urine samples were obtained at 2-hour intervals during the exposure day and in separate samples until the next morning. Whole venous blood was analyzed by gas chromatography, as were air samples. Peaks were compared to calibration curves prepared of known blood or air concentrations of MEK. 2-3BD in urine was analyzed according to a modification of the method of Robinson and Reive. The 2 peaks in the chromatograph (d,l-forms and meso-form) were summed for calculations.
Conclusion:	Two elimination phases were detected for MEK in blood. The $T_{½}$ for the faster phase of elimination was 30 min and about 81 min for the slower phase. 2-3% of absorbed dose of MEK was eliminated by exhalation. Urinary excretion of unchanged MEK was 0.1% and excretion of the metabolite 2H3B was about 0.1%.
Data Quality:	1 - Reliable study. No circumstances occurred that would have affected the quality or integrity of the data. Test procedures were in accordance with generally accepted scientific standards and described in sufficient detail.
Reference:	Liira, J., Riihimaki, V., and Pfaffli, P., (1988). Kinetics of methyl ethyl ketone in man: absorption, distribution and elimination in inhalation exposure. Int.Arch. Occup. Environ. Health 60: 195-200.

[RS - 19]

Repeated Dose Inhalation Neurotoxicity

Test Substance:	Methyl Ethyl Ketone (MEK)
CAS #:	78-93-3
Purity:	99.98%
Method:	Pre-Guideline Research Inhalation Neurotoxicity Study
Type:	6-Month Repeated Dose Inhalation Neurotoxicity Study
GLP:	No
Year:	1980
Species/Strain:	Sprague-Dawley
Sex:	Male
#/ dose:	6
Vehicle:	None
Route of Administration:	Inhalation
Duration of Test:	6 Months; 22 Hours/Day; 7 Days/Week.
Doses:	0, 500 ppm (1475 mg/m^3)

Results:	500ppm exposure for 6 Months, 22 Hours/Day and 7 Days/Week did not produce evidence of neurotoxicity.
Remarks:	Six male Sprague-Dawley rats (250-275g initial weight) were exposed to 0 or 500 ppm MEK for 6 Months, 22 Hours/Day and 7 Days/Week. Chamber concentrations were maintained within ± 5% of the desired nominal level. The MEK group served as a negative solvent control in a study of several other solvents. The rats were fed standard laboratory rat chow ad libitum daily. Vitamin analyses (A, B, B_2, B_6, B_{12}, C, and E) were performed on samples of food that were exposed for 24 hours to MEK vapors to ensure there were no significant modifications to the diet that might induce decrements in neurological function. There were no significant differences between vitamin content of foods exposed to MEK or air. Body weights and clinical conditions were recorded weekly. All groups, including control, had subnormal weight gains during the first eight weeks of the study followed by a normal growth phase during the remaining four months. Chamber airflow was filtered prior to delivery to the exposure system (33 liter glass bell jars). Passing a portion of the filtered, compressed air through a fritted bubbler produced the saturated vapors of MEK. Appropriate chamber concentrations were then achieved by diluting the saturated air with hydrocarbon-free air. Atmospheres were monitored each hour for 15-minute periods and analyzed with a flame ionization detector (FID). MEK vapor concentrations were confirmed with a gas chromatograph. Two animals from each group were randomly selected from each group following 2, 4 or 6 months and were submitted to detailed neuropathologic examination. The animals were perfused with 4% paraformaldehyde followed by phosphate-buffered 5% glutaraldehyde (pH 7.4). Tissue was sampled from regions of maximum vulnerability determined in previous experimental studies of hydrocarbon neuropathy and included cerebellar vermis, cervicomedullary junction, lumbar cord, dorsal and ventral spinal roots, and spinal ganglia, sciatic notch, and three levels of tibial nerve. The tibial nerves were subjected to the "teased" single fiber technique of evaluation. None of the MEK-exposed animals showed significant clinical or histopathological differences from the control animals. No changes were found in the sections of nervous system tissues after eight weeks exposure but, by four months, age associated changes were found in the medulla oblongata and there was some evidence of chronic traumatic damage in the plantar nerves. Single fibers isolated from the branches of the tibial nerve supplying the calf musculature also appeared normal.
Conclusion:	Methyl ethyl ketone failed to produce any morphologic changes in the central or peripheral nervous system of rats continuously exposed to 500 ppm MEK for six months.
Data Quality:	2 - Reliable study with restrictions. Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Reference:	Egan, G., P. Spencer, H. Schaumburg, K.J. Murray, M. Bischoff, and R. Scala, (1980). “n-Hexane-’Free’ Hexane Mixture Fails to Produce Nervous System Damage,” *Neurotoxicology*, 1, 515-524.

[RS - 20]

Repeated Dose Inhalation Neurotoxicity

Test Substance:	Methyl Ethyl Ketone (MEK)
CAS #:	78-93-3
Purity:	> 99.5%
Method:	90-Day Subchronic Toxicity with Neurotoxicity Evaluation
Type:	EPA Guideline Repeated Dose Inhalation Study
GLP:	Yes
Year:	1981
Species/Strain:	Fischer 344
Sex:	Male and Female
#/sex/dose:	15 (10/sex - principals - for routine pathology and 5/sex - dedicated - for special neuropathology)
Vehicle:	None
Route of Administration:	Inhalation
Duration of Test:	90 days; 6 Hours/Day; 5 Days/Week.
Doses:	0, 1250, 2500, or 5000 ppm - Vapor
Results:	The 90-day exposures had no adverse effect on the clinical health or growth of male or female rats except for a depression of mean body weight in the 5000-ppm exposure group. No animals died during the study. No signs of nasal irritation were observed during the study. There were no treatment-related effects in food consumption or ophthalmologic studies in any of the rats exposed to MEK vapors. The 5000-ppm animals had a slight but significant increase in liver weight, liver weight/body weight ratio and liver weight/brain weight ratio at the time of necropsy. Serum glutamic-pyruvic transaminase (SGPT) activity in the 2500-ppm female rats was elevated while the 5000-ppm female rats exhibited significantly decreased SGPT activity. In addition, alkaline phosphatase, potassium, and glucose values for the 5000-ppm female rats were increased. Special neuropathological and routine pathological studies did not reveal any lesions that could be attributed to MEK exposure.
Remarks:	An extensive pathologic investigation was conducted and no lesions were found that could be attributed to MEK exposure. There was no indication that repeated exposure to relatively high levels of MEK had any effect on reproductive tissues. The examined tissues included testes, epididymides, seminal vesicles, vagina, cervix, uterus, oviducts, and ovaries. Special neuropathological studies including specimens of the sciatic and tibial nerves and medulla were Epon-embedded and nerves were evaluated by the "teased fiber" method. Routine pathological studies including examination of reproductive organs (examined tissues included testes, epididymides, seminal vesicles, vagina, cervix, uterus, oviducts, and ovaries) showed no lesions attributed to MEK exposure.
Conclusion:	MEK has a low order of toxicity based on the 90-day repeated-dose

	exposures and neither special neuropathological nor routine pathological evaluations revealed any lesions that could be attributed to MEK exposure. The NOAEL is 5000 ppm.
Data Quality:	1 - Reliable study with restrictions. Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Reference:	Cavender, F.L., Casey, H.W., Salem, H., Swenberg, J.A., and Gralla, E.J. (1983). A 90-day vapor inhalation toxicity study of methyl ethyl ketone. Fund. Appl. Toxicol. 3:264-270. Toxigenics. (1981). 90-Day vapor inhalation study of methyl ethyl ketone in albino rats. Toxigenics' Study 420-0305. Toxigenics, Inc., 1800 East Pershing Road, Decatur, IL 62526.

[RS - 21]

Neurotoxicity - Behavioral Test Performance

Test Substance:	Methyl ethyl ketone (MEK; 2-Butanone)
CAS #:	78-93-3
Purity:	Unknown
Method:	Experimental Human Volunteer Exposure (Non-regulatory)
Type:	Assess the behavioral performance effects of chemical exposure.
GLP:	Unknown
Year:	1984
Species:	Human
Route of Administration:	Inhalation Exposure - MEK and/or Toluene; Oral Cocktail for Ethanol
Dose Groups / Concentrations:	100 ppm Toluene vs. Toluene-placebo; 200 ppm MEK vs. MEK-placebo; 50 ppm Toluene and 100 ppm MEK vs.Toluene/MEK-placebo; and, 0.80 ml/kg Absolute Ethanol vs. Ethanol-placebo.
Sex:	Both
Exposure Period:	4 Hr exposure for MEK and/or Toluene.
Frequency of Treatment:	Single
Control Group:	Yes; Ethanol at 0.08% blood levels as a positive control.
Duration of Test:	Approximately 8 hr of testing.
Statistical Methods:	Multivariate analysis of covariance was used. Pre-exposure scores served as baseline values and were used as the covariate in adjusting for differences in the pretreatment scores. A type III sums of squares analysis was used in computing mean squares to adjust for loss of participants and its affect on data sets. Measurements were considered to be statistically significant when demonstrated on both the multivariate and univariate statistic at $P = 0.05$.
#/Dose Group:	20

Vehicle:	None
Results:	MEK (200 ppm) exposure, biochemical and behavioral performance changes - Average MEK concentration in the 2 m x 2m x 2m test chamber over the course of the 4-hr exposure was 188.9 ppm (S.D. = 9.1 ppm) and the breath levels for MEK during the exposures averaged 7.3 ppm (S.D. = 1.2 ppm). Ninety minutes after the exposure terminated, breath levels had fallen to 1.8 ppm (S.D. = 0.8 ppm). Results from the 2 blood samples taken about 2 and 4 hrs after the exposure began, showed concentrations of 3.1 ppm (S.D. = 1.2 ppm) and 3.7 ppm (S.D. = 1.6 ppm), respectively. There were no significant effects from exposure to MEK as all probabilities exceeded the 5% criterion.
Remarks:	Participants (144 total; 47 female; 18 -38 years of age) were recruited over 18 months and assigned to one of 8 treatment combinations that comprised a series of 4 independent 2-group studies to assess the sensitivity of the neurobehavioral tests. Subjects were required to pass an extensive physical exam that included neurological screening. Volunteers were requested to abstain from the use of alcohol and any medication for 24 hr prior to the experiment. Individuals receiving prescription medicine, pregnant females, hypertensives, and persons with serious disorders were dismissed. All procedures were in accordance with American Psychological Association's ethical principles in the conduct of research and guidelines of the NIOSH Human Subject Review Board. Studies were conducted in single blind and the methodology for all studies was generally the same. Participants were tested repeatedly for alertness during the approximately 8 hours of testing. Three different behavioral tasks with 28 measurements per individual were evaluated: 7 measurements in the 2-hr-30-min pre-exposure period; 14 during the 4-hr exposure; and, 7 in the 71-min post exposure period. To determine body burden, four alveolar breath samples were collected: at the end of pre-exposure; either 1, 1.5, or 2 hr into exposure; at the end of exposure; and, 90-min post exposure. Venus blood was drawn 2 hr after exposure began and for MEK-exposed individuals, immediately at the end of the 4-hr exposure. Two of the performance tests, reaction time and visual-vigilance, were administered throughout the pre-exposure, exposure and post-exposure periods. The pattern discrimination test was run only during the pre-exposure and exposure periods. The pre-exposure data served as baseline data for comparison purposes and the period was preceded by a 15-minute training session on the tasks. The order of test presentation was identical for each participant. The placebo consisted of a 2-min, 25 ppm exposure or "charge" of each chemical/combination or a "blind" cocktail in the ethanol condition.
Conclusion:	MEK at 200 ppm produced no interpretable significant effects in any of the behavioral performance tests used in this study.
Data Quality:	1- Study well documented, meets generally accepted scientific principles, acceptable for assessment.
Reference:	Dick, R.B., Setzer, J.V., Wait, R., Hayden, M.B., Taylor, B.J., Tolos, B., and Putz-Anderson, V., (1984). Effects of acute exposure to toluene and methyl ethyl ketone on psychomotor performance. Int. Arch. Occup. Environ. Health. 54:91-109.

[RS - 22]

Neurotoxicity - Behavioral Test Performance

Test Substance:	Methyl ethyl ketone (MEK; 2-Butanone)
CAS #:	78-93-3
Purity:	99.46%
Method:	Experimental Human Volunteer Exposure (Non-regulatory)
Type:	Assess the behavioral performance effects of chemical exposure.
GLP:	Unknown
Year:	1988
Species:	Human
Route of Administration:	Inhalation Exposure - MEK and/or Acetone; Oral Cocktail for Ethanol
Dose Groups / Concentration:	250 ppm Acetone vs. Placebo (2-min 25-ppm Acetone/MEK mixture exposures twice in 4 hr); 200 ppm MEK vs. Acetone/MEK Placebo; 125 ppm Acetone and 100 ppm MEK vs. Acetone/MEK-Placebo; and, 0.84 ml/kg Absolute (95%) Ethanol vs. Ethanol-placebo (drink mixer without alcohol).
Sex:	Both
Exposure Period:	4 Hr exposure for MEK and/or Acetone.
Frequency of Treatment:	Single
Control Group:	Yes; Ethanol at 0.84 ml/kg (0.07-0.08% blood alcohol) as a positive control and 2 Placebos (chemical exposure and ethanol).
Duration of Test:	10 hr Test regimen; computer-controlled.
Statistical Methods:	SAS version 5.15 programs were used to analyze the data with multivariate analysis of covariance. Measurements were considered to be statistically significant when demonstrated on both the multivariate and univariate statistic at *P* = 0.05 for rejection of the null hypothesis.
#/Dose Group:	12 males and 13 females
Vehicle:	None
Results:	MEK (200 ppm) exposure, biochemical and behavioral performance changes - Average MEK concentration in the test chamber (2.5mW x 5.3mL x 2.2mH) over the course of the 4-hr exposure was 186.3 ppm (S.D. = 4.8 ppm). Breath levels for MEK were not detected pre-exposure or at 20 hr post exposure. During the exposures, the averages were 11.4 ppm (S.D. = 3.0 ppm) at 2 hr and 11.9 ppm (S.D. = 3.0 ppm) at 4 hr. Ninety minutes after the exposures terminated, breath levels had fallen to 0.7 ppm (S.D. = 1.1 ppm). Results from the 2 blood samples taken about 2 and 4 hrs after the exposure began, showed concentrations of 3.1 µg/ml (S.D. = 1.1 µg/ml) and 3.5 µg/ml (S.D. = 1.5 µg/ml), respectively. Ninety minutes after the exposures terminated, blood levels had fallen to 1.0 µg/ml (S.D. = 0.6 µg/ml). Significant correlation coefficients were obtained between blood and breath measurements; 0.78 (*P* = <0.001). There were no significant effects from exposure to MEK in the psychomotor, sensorimotor or POMS tests. There were no detectable levels of MEK in the blood or breath the morning following exposure, and more than half of the subjects had non-detectable levels of MEK in the breath samples taken 90 min post-exposure.
Remarks:	Participants (137 total; 66 female; 18 -32 years of age) were recruited over 1 year. Subjects were required to pass an extensive physical exam that included neurological screening. Volunteers were requested to abstain from the use of alcohol and any medication (unless approved by the medical officer) for 24 hr prior to the 2 days of testing. Preexisting medical conditions (viz. pregnancy, diabetes, hypertension)

	or evidence of recent or chronic drug/alcohol use (verified by urinalysis and breath analysis) were grounds for exclusion from testing or subsequent data analysis. Subjects were assigned to one of 6 separate treatment combinations: Acetone, MEK, Acetone and MEK, Placebo (chemical), Placebo (ethanol) and Ethanol. Ethanol was used as a treatment condition to verify test sensitivity and for magnitude of effect comparisons. The chemical and ethanol conditions were analyzed separately because of route administration (inhalation vs. ingestion) differences. Experimental sessions were conducted double blind (subjects and experimenter). All procedures were in accordance with American Psychological Association's ethical principles in the conduct of research and guidelines of the NIOSH Human Subject Review Board. The testing regimen began with a 2-hr practice session on the day prior to the exposure day and ended with a 2.5-hr testing session on the day following exposure. The exposure day testing took 8 hr and was divided into four 2-hr sessions. The 4-hr exposure that occurred in the middle two periods was continuous, except for body burden sampling. Five breath samples and four blood samples were collected from each subject over the three-day test session. During the 4-hr exposure, blood samples were staggered with one-half of the subjects sampled at 2-hr and the others at 4-hr. Subjects were tested for 10 hr with the following neurobehavioral tests: 4 psychomotor (Visual-Vigilance, Dual Task, Choice Reaction Time, and Sternberg short-term Memory Scanning); 1 sensorimotor (Postural Sway); and 1 psychological test (Profile Of Mood States - POMS). In each 2-hr test period, approximately 32 measurements were used for purposes of analysis. To determine body burden, breath samples were collected: at the end of pre-exposure; 2 hr into exposure; at the end of 4-hr exposure; 90-min post exposure, and 20-hr post exposure. Venus blood was drawn: at the end of pre-exposure; 2 hr into exposure; at the end of 4-hr exposure; 90-min post exposure, and 20-hr post exposure.
Conclusion:	Exposures to 200 ppm MEK showed no interpretable statistically significant results in neurobehavioral tests: psychomotor (Visual-Vigilance, Dual Task, Choice Reaction Time, and Sternberg short-term Memory Scanning); sensorimotor (Postural Sway); and a psychological test (Profile Of Mood States - POMS).
Data Quality:	1 - Reliable study. No circumstances occurred that would have affected the quality or integrity of the data. Test procedures were in accordance with generally accepted scientific standards and described in sufficient detail.
References:	Dick, R.B., Brown, W.D., Setzer, J.V., Taylor, B.J., and Shukla, R. (1988). Effects of short duration exposures to acetone and methyl ethyl ketone. Toxicology Letters. 43: 31-49. Dick, R.B., Setzer, J.V., Taylor, B.J., and Shukla, R. (1989). Neurobehavioral effects of short duration exposures to acetone and methyl ethyl ketone. British Journal of Industrial Medicine. 46:111-121.

[RS - 23]

Neurotoxicity - Behavioral Test Performance

Test Substance:	Methyl ethyl ketone (MEK; 2-Butanone)
CAS #:	78-93-3

Purity:	99.5%
Method:	Experimental Human Volunteer Exposure (Non-regulatory)
Type:	Assess the behavioral performance effects of chemical exposure.
GLP:	Unknown
Year:	1992
Species:	Human
Route of Administration:	Inhalation Exposure - MEK and/or Methyl Isobutyl Ketone (MIBK); Oral Cocktail for Ethanol
Doses Groups / Concentration:	100 ppm MIBK vs. Chemical Control Placebo (5-min; 25-ppm MEK - MIBK mixture exposures at the beginning of each 2-hr exposure period); 200 ppm MEK vs. Chemical Control Placebo; 50 ppm MIBK and 100 ppm MEK vs. Chemical Control Placebo; and, 0.84 ml/kg Absolute (95%) Ethanol vs. Ethanol-placebo (drink mixer without alcohol).
Sex:	Both
Exposure Period:	4 Hr exposure for MEK and/or MIBK.
Frequency of Treatment:	Single
Control Group:	Yes; Ethanol at 0.84 ml/kg (0.07-0.08% blood alcohol) as a positive control and 2 Placebos (chemical exposure and ethanol).
Duration of Test:	Approximately 8 hr of testing.
Statistical Methods:	Multivariate analysis of covariance was used. Pre-exposure scores served as baseline values and were used as the covariate in adjusting for differences in the pretreatment scores. Measurements were considered to be statistically significant when demonstrated on both the multivariate and univariate statistic at $P = 0.05$.
#/Dose Group:	13 males and 10 females
Vehicle:	None
Results:	MEK (200 ppm) exposure, biochemical and behavioral performance changes - Average MEK concentration in the test chamber (2.5-mW x 5.3-mL x 2.2-mH) over the course of the 4-hr exposure was 186.3 ppm (S.D. = 6.8 ppm). Breath levels for MEK (male and female combined) were not detected pre-exposure or at 20 hr post exposure. During the exposures, the averages were 18.4 ppm (S.D. = 5.2 ppm) at 2 hr and 19.7 ppm (S.D. = 6.8 ppm) at 4 hr. Ninety minutes after the exposures terminated, breath levels had fallen to 1.3 ppm (S.D. = 0.9 ppm). Results from the blood samples (male and female combined) taken about 2 and 4 hrs after the exposure began, showed concentrations of 3.0 µg/ml (S.D. = 0.9 µg/ml) and 3.7 µg/ml (S.D. = 1.1 µg/ml), respectively. Ninety minutes after the exposures terminated, blood levels had fallen to 0.9 µg/ml (S.D. = 0.4 µg/ml). There were no significant effects from exposure to MEK in the psychomotor, sensorimotor or POMS tests. There were no detectable levels of MEK in the blood or breath the morning following exposure.
Remarks:	Participants (143 total; 75 female; 18 -32 years of age) were recruited over 1 year. Smokers and subjects with work histories of solvent exposure were eliminated. Subjects were required to pass an extensive

	physical exam that included neurological screening. Volunteers were requested to abstain from the use of alcohol and any medication (unless approved by the medical officer) for 24 hr prior to the 2 days of testing. Medical disqualification criteria included obesity, pregnancy, diabetes, hypertension, elevated values on liver function tests, abnormal EKG, or evidence of recent or chronic drug/alcohol use (verified by urinalysis and breath analysis on day of exposure). Subjects were randomly assigned to one of 6 separate treatment combinations: MEK, MIBK, MIBK and MEK, Placebo (chemical), Placebo (ethanol) and Ethanol. Ethanol was used as a treatment condition to verify neurobehavioral test sensitivity and for magnitude of effect comparisons. The chemical and ethanol conditions were analyzed separately because of route administration (inhalation vs. ingestion) differences. A one-way ANOVA showed no significant age differences between the six treatment groups. Experimental sessions were conducted double blind (e.g., only the chamber operator had knowledge of the exposure conditions.). All procedures were in accordance with American Psychological Association's ethical principles in the conduct of research and guidelines of the NIOSH Human Subject Review Board. The experimental test sessions took place on 3 consecutive days. The testing regimen began with a 2-hr practice session on the day prior to the exposure day and ended with a 2-hr testing session on the morning of the day following exposure. The exposure day testing took 8 hr and was divided into four 2-hr sessions; 2-hr pre-exposure, 4-hr exposure period divided into two 2-hr periods, and a 2-hr post exposure period. Five breath samples and five venous blood samples were collected from each subject over the three-day test session. During the 4-hr exposure, blood samples were staggered with one-half of the subjects sampled at 2-hr and the others at 4-hr. Subjects were tested during each of the 2-hr test periods with the following neurobehavioral tests: 5 psychomotor (Choice Reaction Time [CRT], Simple Reaction Time [SRT], Visual-Vigilance, Dual Task [auditory tone discrimination and tracking], and Sternberg short-term Memory Scanning); 1 neurophysiological test (eye blink reflex); 1 sensorimotor (Postural Sway); and 1 psychological test (Profile Of Mood States - POMS). Additionally, two subjective questionnaires asked subjects to rate sensory and irritant effects (presence of odor, strong odor, objectionable odor, headache, nausea, throat dryness or coughing, tearing, and unpleasant exposure) and to identify the exposure conditions and rate the neurobehavioral tests for irritation. In each 2-hr test period, measurements were used for purposes of analysis. To determine body burden, breath samples were collected: at the end of pre-exposure; 2 hr into first exposure period; at the end of 4-hr exposure period; 90-min post exposure, and 20-hr post exposure. Venus blood was drawn: at the end of pre-exposure; 2 hr into exposure; at the end of 4-hr exposure; 90-min post exposure, and 20-hr post exposure.
Conclusion:	Exposures to 200 ppm MEK showed no interpretable statistically significant results in neurobehavioral tests: psychomotor (CRT, SRT, Visual-Vigilance, Dual Task, and memory scanning); sensorimotor (Postural Sway); and a psychological test (Profile Of Mood States - POMS). In the subjective tests, only presence of strong odor was significant (48% of responders for MEK).

Data Quality:	1 - Reliable study. No circumstances occurred that would have affected the quality or integrity of the data. Test procedures were in accordance with generally accepted scientific standards and described in sufficient detail.
Reference:	Dick, R.B., Krieg, Jr., E.F., Setzer, J.V., and Taylor, B.J., (1992). Neurobehavioral effects from acute exposures to methyl isobutyl ketone and methyl ethyl ketone. Fundamental and Applied Toxicology. 19:453-473.