FOREWORD INTRODUCTION

4-METHYLPENTAN-2-OL

CAS N°: 108-11-2

SIDS Initial Assessment Report

For

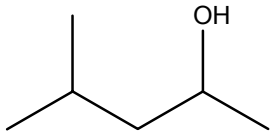
SIAM 21

Washington, D.C., USA, 18-21October 2005

1. Chemical Name:	4-Methylpentan-2-ol (Methyl Isobutyl Carbinol)
2. CAS Number:	108-11-2
3. Sponsor Country:	United States
4. Shared Partnership with:	
5. Roles/Responsibilities of the Partners:	
• Name of industry sponsor /consortium	Elizabeth Hunt Lesser Ketones Manufacturing Association 17260 Vannes Court Hamilton, VA 20158 Phone: (540) 751-2093
• Process used	The IUCLID Data Set has been revised and the SIAR prepared by a consortium of chemical industry producers in 2005. Data searches included published scientific literature, databases and handbooks as well as the internal files of the member companies of the consortium
6. Sponsorship History	
• How was the chemical or category brought into the OECD HPV Chemicals Programme?	The Lesser Ketones Manufacturing Association submitted a test plan and robust summaries for this chemical to the United States Environmental Protection Agency (U.S. EPA) in August 2002, under the International Council of Chemical Associations (ICCA) Global Initiative on High Production Volume (HPV)_ Chemicals Program.
7. Review Process Prior to the SIAM:	Members of a consortium of chemical industry producers conducted a comprehensive literature search. Documents were prepared by the Lesser Ketones Manufacturing Association and reviewed by industry toxicologists prior to submission to the U.S. EPA. The U.S. EPA conducted reviews of submitted data and offered comments to industry. The U.S. EPA submitted documents to OECD for consideration at SIAM 21.
8. Quality check process:	The quality of existing data was determined using guidance provided in the Manual for Investigation of HPV Chemical, Chapter 3: Data Evaluation (OECD, 2002).
9. Date of Submission:	20 August 2002
10. Date of last Update:	19 February 2007
11. Comments:	The data provided herein and in the dossier represent available data from the Lesser Ketones Manufacturing Association member companies as well as from any literature references

identified in searches; the last of which was conducted in November 2004. The searches included but were not necessarily limited to the following: Toxline/Toxlit, Chemlist, SANSS, TSCATS, Aquire, Biolog, CESAR, Datalog, Envirofate, Ishow, NIOSHTIC SUBSET, Phytotox, Syracuse Research Database and NLM Consumer Database.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	108-11-2
Chemical Name	4-Methylpentan-2-ol
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Analogue Justification

The metabolism and clearance of 4-methylpentan-2-ol (methyl isobutyl carbinol; MIBC) is rapid (Cmax and t½ approximately 30 min and 2 hr, respectively). MIBC is metabolized to 4-hydroxy-4-methyl-2-pentanone (HMP) through methyl isobutyl ketone (MIBK). Dosing with MIBC or MIBK results in similar internal exposure to MIBK and HMP and minimal exposure to MIBC. Thus, the data for MIBK and HMP adequately support the evaluation of MIBC systemic toxicity.

Human Health

Studies with experimental animals indicate that MIBC is of low toxicity by the oral, dermal and inhalation routes of exposure. MIBC has typical organic solvent effects in rats following acute inhalation exposures with anesthetic effects occurring at 10 mg/L (2360 ppm) and death following an 8-hour exposure to 8.4 mg/L (2000 ppm). The acute oral and dermal LD_{50} values for MIBC are 2260 - 2970 mg/kg and 2870 mg/kg, respectively.

In standard primary irritation studies, MIBC was slightly irritating to skin and moderately to severely irritating to the eye. Human volunteers exposed to MIBC vapors at 50 ppm experienced eye irritation in most subjects with nose and throat irritation experienced at higher concentrations. The maximum tolerable concentration was considered to be 25 ppm. A skin sensitization study in animals was negative and indicates that MIBC is not likely to be a sensitizer in humans.

Repeated dose studies with MIBC and its primary metabolites, MIBK and HMP, indicated that systemic toxicity is minimal. The NOAEC for subchronic inhalation exposure was 886 ppm (3.70 mg/L) for MIBC (6-weeks with rats) and 1000 ppm (4.09 mg/L) for MIBK (14-weeks with rats and mice). There were no organ-specific toxic effects for either chemical. The NOAEL for the ultimate metabolite, HMP, via gavage dosing for 45 days was 30 mg/kg/day for males (based on hyaline droplet nephropathy) and 100 mg/kg/day for females. The LOAEL for this study was 100 mg/kg/day for males and 300 mg/kg/day for females.

MIBC and HMP were not mutagenic to bacterial cells (bacterial reverse mutation assay) *in vitro* with or without metabolic activation. In a mammalian cell cytogenetic assay (rat liver cells), MIBC was negative with and without metabolic activation. HMP was negative in an *in vitro* chromosomal assay. Based on the negative results in the bacterial mutagenicity and mammalian cell cytogenetic assays with MIBC and bacterial mutagenicity and chromosomal aberration assays with HMP, MIBC is unlikely to be mutagenic in humans.

MIBC showed no effects on reproductive organs following 6 weeks of inhalation exposure to concentrations as high as 3.70 mg/L (886 ppm). MIBK showed no reproductive effects in a two-generation study with inhalation exposures up to 8.18 mg/L (2000 ppm). Slight changes in reproductive performance (decreased fertility and implantations) and pup viability following high oral exposure to HMP (1000 mg/kg/day) in an OECD TG 422 study may have occurred in the presence of maternal toxicity (reduced weight gain, statistically significant changes in hematology, clinical biochemistry and relative organ weights; renal and hepatic histopathological lesions). No teratogenic effects were observed for rats or mice at MIBK inhalation concentrations as high as 3000 ppm (12.3 mg/L) and no fetal toxicity was observed without the presence of maternal toxicity; the NOAEC for maternal and fetal toxicity was 1000 ppm (4.09 mg/L) due to clinical signs of toxicity including neuromuscular effects (both species), and statistically

significant changes in body weight, relative kidney weights and decreased food consumption (rats only) and increased liver weight (mice only), and decreased fetal body weight with evidence of delayed ossification. Based on the available animal data, MIBC is not expected to be a human reproductive or developmental toxicant.

Environment

The melting point of MIBC is – 90°C and the boiling point is 131.7°C. The vapor pressure is 4.97 hPa at 20°C. The water solubility of MIBC is 16.4 g/L (20°C) and density is 0.81 g/cm^3 at 25°C. The calculated log Kow is 1.68. MIBC is predicted to be photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of approximately 10 hours (calculated). MIBC does not have hydrolyzable groups and therefore hydrolysis is not a degradation pathway. Distribution modeling using Mackay Level I indicated that partitioning will occur to air (37.8%), water (59.6%), and soil (2.5%) phases. Fugacity model Level III predicted greatest distribution ($\geq$ 86%) to the primary compartment of release. When equal releases were assumed, the predicted distribution was: 3.6% (air), 45% (water), 51% (soil) and <1% (sediment). A low bioaccumulation potential is expected based on the partition coefficient and other physical/chemical parameters. MIBC is readily biodegradable attaining 94% degradation within 20 days and meeting the "10-day window".

The 96-hour LC_{50} for rainbow trout (*Oncorhynchus mykiss*) is 359 mg/L (measured), the 48-hour EC_{50} for *Daphnia magna* is 337 mg/L (measured) and the 96-hour EC_{50} value for growth rate of algae (*Pseudokirchneriella subcapitata*) is 334 mg/L (measured) and for biomass is 147 mg/L (measured) .

Exposure

The estimated total volume of MIBC production in North America in 1998 was 25,000 tonnes. MIBC is primarily used (~70%) in the production of lube oil additives. MIBC (~20% of the total production) is used as a flotation frother for treating copper ores and coal with usual concentrations less than 1000 ppm and in many cases in the hundreds of ppm range (100 - 600 ppm). The remaining production is primarily for its use as an additive to surface coatings as a solvent to maintain binder softness until the binder fuses.

The use as a solvent and as flotation frothers result in environmental releases at very low concentrations. Human exposure to MIBC is very limited based on its use patterns. With the exception of tar sand mining frothers, MIBC is used in closed systems and only catastrophic failure results in any appreciable exposure. In tar sand mining, exposure (in the ppm range) is typically limited to the equipment operators. MIBC used as an intermediate in the manufacture of lube oil additives is blended with other alcohols and reacted. Normally these reactors are closed systems and exposure is limited to upsets or catastrophic failure of the reactor. In its primary use as an intermediate for corrosion inhibitor production, significant residual MIBC is not anticipated. As noted above, in mining operations, low ppm vapor exposure may occur in operators. Minimal exposure to vapors from the use of MIBC as a solvent in coating applications may also occur. The ACGIH TLV-TWA for MIBC is 25 ppm (104 mg/m^3) and the TLV-STEL is 40 ppm (167 mg/m^3). The German MAK value is 25 ppm.
Based on its pattern of use, consumer exposure to MIBC is expected to be negligible. Environmental exposure to MIBC can occur during mining processes or through accidental release.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemical is currently a low priority for further work. The chemical possesses properties indicating a potential hazard for human health (eye irritation, narcosis at high inhalation concentrations) These hazards do not warrant further work as they are related to acute toxicity which may become evident only at high exposure levels. They should nevertheless be noted by chemical safety professionals and users.

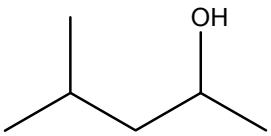
Environment: The chemical is currently a low priority for further work due to its low hazard profile.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 108-11-2
IUPAC Name: 4-Methylpentan-2-ol
Molecular Formula: $C_6H_{14}O$
Structural Formula:



Molecular Weight: 102.17
Synonyms: Methyl Isobutyl Carbinol (MIBC)
4-Methyl-2-pentanol
1,3-Dimethylbutanol
2-Methyl-4-pentanol
2-Pentanol, 4-methyl-
4-Methyl-2-amyl alcohol
4-Methyl-2-pentyl alcohol
Isobutylmethylcarbinol
Isobutylmethylmethanol
Methyl amyl alcohol

1.2 Purity/Impurities/Additives

Purity of MIBC is >98%

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Reference
Physical state	Liquid	
Melting point	-90 ºC (measured)	Verschueren, 2001
Boiling point	131.7 ºC (measured)	Rowley et al., 2004
Density	0.81 g/cm^3 @ 25ºC (measured)	Rowley et al., 2004
Vapour pressure	4.97 hPa @ 20ºC (measured)	Rowley et al., 2004
Water solubility	16.4 g/L @ 20°C in water (measured)	Riddick et al., 1986
Partition coefficient n-octanol/water (log value)	1.68 (calculated)	U.S. EPA, 2000a
Henry's law constant	4.5 Pa x m3 / mol (calculated)	U.S. EPA, 2000b

1.4 Analog Justification

MIBC is rapidly metabolized to methyl isobutyl ketone (MIBK) and subsequently to the primary metabolite of MIBK, 4-hydroxy-4-methyl-2-pentanone (HMP). Therefore, data for MIBK have been used for some mammalian toxicity endpoints. To substantiate that MIBC metabolism proceeds through MIBK to HMP and to establish whether this metabolism allows for the use of MIBK and HMP toxicity data to be used for MIBC, toxicokinetic studies in rats were done (Guillaumat, 2002; Gingell et al., 2003). Details of the studies are included in Section 3.1.1. The results indicated that metabolism and clearance of MIBC is rapid through MIBK to HMP concluding that dosing with MIBC or MIBK results in similar internal exposure to MIBK and HMP and minimal exposure to MIBC.

Based on the similar internal exposure following doses of MIBC or MIBK, it is clear that the use of selected studies from the extensive toxicity database for MIBK as well as the data for HMP, is appropriate for the evaluation of potential hazards from MIBC.

2 GENERAL INFORMATION ON EXPOSURE

2.1 Production Volumes and Use Pattern

The estimated total volume of MIBC production in North America in 1998 was 25,000 tonnes (Bizzari, 1999). Methyl isobutyl carbinol (MIBC) is a flammable, colorless, stable liquid. It is sold as technical grade with a minimum of 98% purity. MIBC is produced either as a recovered coproduct during methyl isobutyl ketone (MIBK) production or directly by hydrogenation of MIBK. MIBK, itself, is produced from acetone in a 3-step reaction. The first step involves the aldol condensation of two molecules of acetone in liquid phase to diacetone alcohol. Diacetone alcohol is then dehydrated under acidic conditions to mesityl oxide. Lastly, mesityl oxide is hydrogenated using a palladium catalyst to MIBK (Bizzari, 1999).

MIBC is primarily used (~70%) in the production of lube oil additives, specifically zinc dialkyldithiophosphate, for antiwear and corrosion inhibitors. The second largest use of MIBC (~20%) is as a flotation frother for treating copper ores and coal (Bizzari, 1999) and tar sand mining. In mining frother applications, MIBC is used in the ppm range, with usual concentrations less than 1000 ppm and in many cases in the hundreds of ppm range (100 - 600 ppm). The remaining production is primarily for its use as an additive to surface coatings as a solvent to maintain binder softness until the binder fuses.

2.2 Environmental Exposure and Fate

2.2.1 Sources of Environmental Exposure

Environmental exposure to MIBC can occur during mining processes and accidental releases. In many applications, MIBC is used in closed systems and environmental releases are considered unlikely and only result from accidental release. In its use as a mining frother, MIBC may be introduced into one or more environmental compartments at low concentrations. Photodegradation and biodegradation limit the potential exposure of environmental species and humans in these cases.

2.2.2 Photodegradation

The indirect photodegradation of MIBC by reaction with hydroxyl radicals in the atmosphere is estimated to occur with a half-life of approximately 10 hours (12-hr day; 1.5E06 OH/cm^3) (U.S. EPA, 2000c).

2.2.3 Stability in Water

MIBC does not react with water; the only functionality other than carbon-carbon and carbon-hydrogen bonds is the hydroxyl group, which does not hydrolyze.

2.2.4 Transport between Environmental Compartments

The theoretical distribution of MIBC has been estimated using the fugacity model of Mackay, Level I (Canadian Environmental Modeling Centre, 1999). According to this model, MIBC released into the environment partitions to air, water, and soil phases with 37.8%, 59.6% and 2.5%, in the respective compartments.

The environmental distribution of MIBC has also been examined using the Level III fugacity model (U.S. EPA, 2000b). MIBC is used in several different processes. Therefore, potential release scenarios were examined as outlined in the following table:

Table 2 Environmental Distribution

Distribution	% Predicted in Air	% Predicted in Water	% Predicted in Soil	% Predicted in Sediment
Equal (Air, Water, Soil)	3.6	45	51	<1
100% to Air	86	11	2.4	<0.1
100% to Water	<1	99	<0.1	<1
100% to Soil	<1	8.9	90	<0.1

2.2.5 Biodegradation

In a biodegradation assay according to Standard Methods for Examination of Water and Wastewater, 13th Edition, American Pub. Health Assoc., MIBC was readily biodegradable with 94% biodegradation after 20 days and meeting the 10-day window (Price *et al*., 1974).

2.2.6 Bioaccumulation

No experimental data on bioaccumulation are available. With a calculated log K_{ow} of 1.68, a low bioaccumulation potential is expected.

2.3 Human Exposure

2.3.1 Occupational Exposure

With the exception of the use in tar sand mining, frothers are used in closed systems and only catastrophic failure results in any appreciable exposure. In tar sand mining, the MIBC is added to the tar sand and the sand is spread out and allowed to dry. The majority of MIBC from this use is

volatilized to the air. Exposure (in the ppm range) is typically limited to the equipment operator pushing the sand. MIBC used as an intermediate in the manufacture of lube oil additives is blended with other alcohols and reacted. Normally these reactors are closed systems and exposure is limited to upsets or catastrophic failure of the reactor.

The ACGIH TLV-TWA for MIBC is 25 ppm (104 mg/m^3) and the TLV-STEL is 40 ppm (167 mg/m^3). The German MAK value is 25 ppm.

2.3.2 Consumer Exposure

In its primary use as an intermediate for corrosion inhibitor production, significant residual MIBC is not anticipated. As noted above, in mining operations, low ppm vapor exposure may occur in operators. Minimal exposure to vapors from the use of MIBC as a solvent in coating applications may also occur. Overall, consumer exposure to MIBC is expected to be negligible.

3 HUMAN HEALTH HAZARDS

Analog Justification for Use of Methyl Isobutyl Ketone (MIBK) and 4-hydroxy-4-methyl-2-pentanone (HMP) Data: As detailed in Section 1.4, MIBC is rapidly metabolized to methyl isobutyl ketone (MIBK) and subsequently to the primary metabolite of MIBK, 4-hydroxy-4-methyl-2-pentanone (HMP). Therefore, data for MIBK have been used for some mammalian toxicity endpoints.

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Analogue Justification for the use of Methyl Isobutyl Ketone (MIBK) and 4-hydroxy-4-methyl-2-pentanone (HMP)

The mammalian metabolism of secondary alcohols proceeds primarily through their respective ketones. It has been demonstrated (Granvil et al., 1994) that MIBC is metabolized to methyl isobutyl ketone (MIBK: CAS No. 108-10-1) and subsequently to the primary metabolite of MIBK, 4-hydroxy-4-methyl-2-pentanone (HMP; CAS No. 123-42-2) in rats. In this study, no MIBC was detected in blood of rats following oral dosing although low concentrations of MIBC were found following inhalation exposure. Based on these preliminary findings, a study to confirm metabolism of MIBC to MIBK and allow the use of the extensive toxicity database for MIBK to support the hazard assessment of MIBC was conducted. This study is reported below.

Studies in Animals

In vivo studies

Toxicokinetic studies have been done (Guillaumat, 2002; Gingell et al., 2003) in male Sprague-Dawley rats orally dosed with MIBC or MIBK at a dose of 5 mmol/kg in corn oil (approximately 500 mg/kg). Following oral dosing of MIBC to rats, absorption is rapid with Cmax occurring at approximately 0.25 to 0.5 hours post-dosing. The half-life for MIBC in blood is approximately 2.3 hours. MIBC is rapidly metabolized to methyl isobutyl ketone (MIBK) and subsequently to the primary metabolite of MIBK, 4-hydroxy-4-methyl-2-pentanone (HMP). MIBC metabolism is shown below:

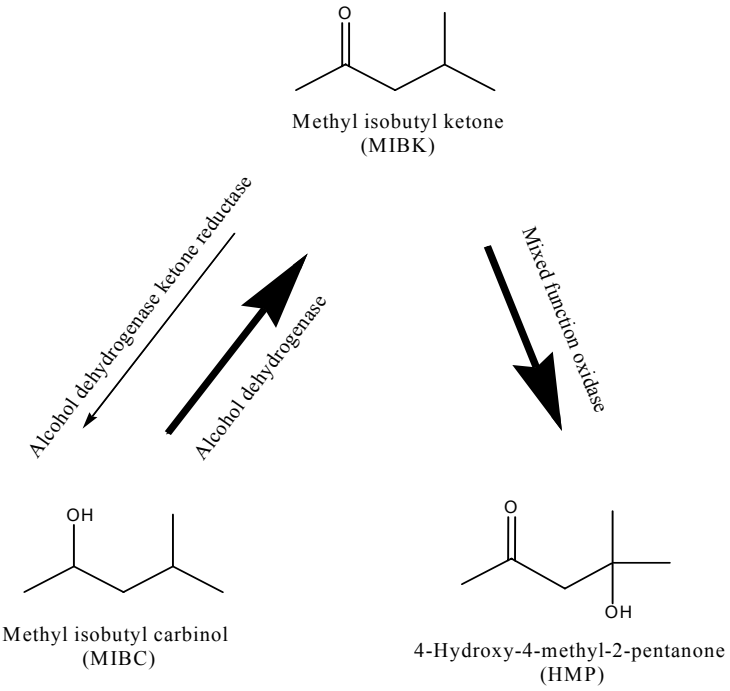


Figure 1: Metabolic Scheme for MIBC and MIBK

Plasma samples were collected at 0.125, 0.25, 0.5, 0.75, 1, 1.5, 3, 4.5, 6, 9 and 12 hours post-dosing. Plasma concentrations of MIBC, MIBK and HMP were measured at each time point. The plots of plasma concentration versus time for the three compounds, MIBC, MIBK, and HMP, following a single oral dose of MIBC or MIBK are shown in Figures 2 and 3, respectively.

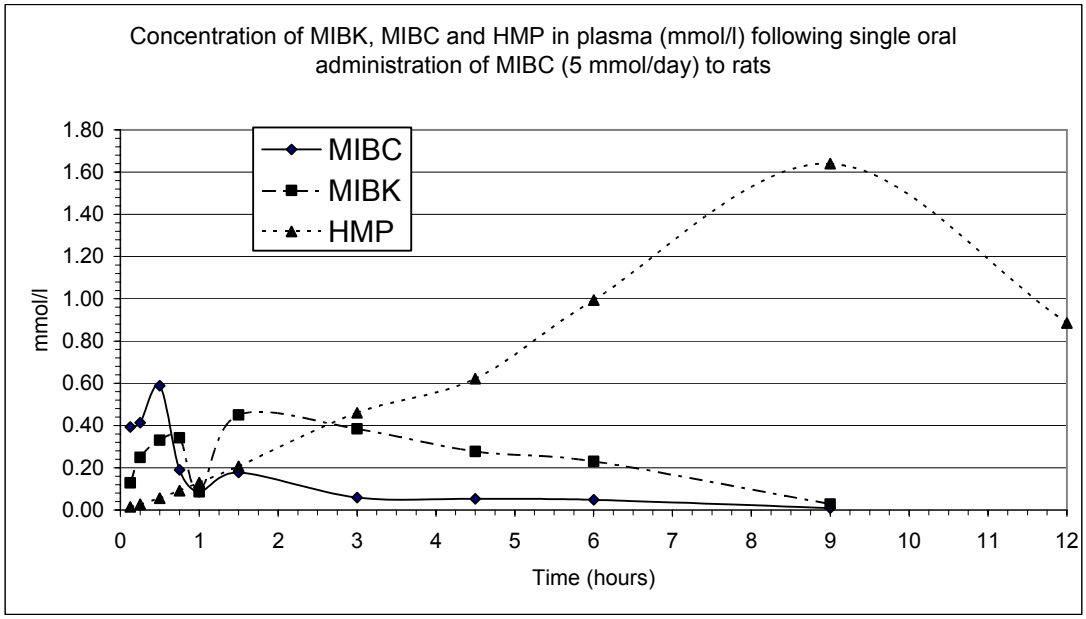


Figure 2: Metabolism and Clearance of an MIBC Dose

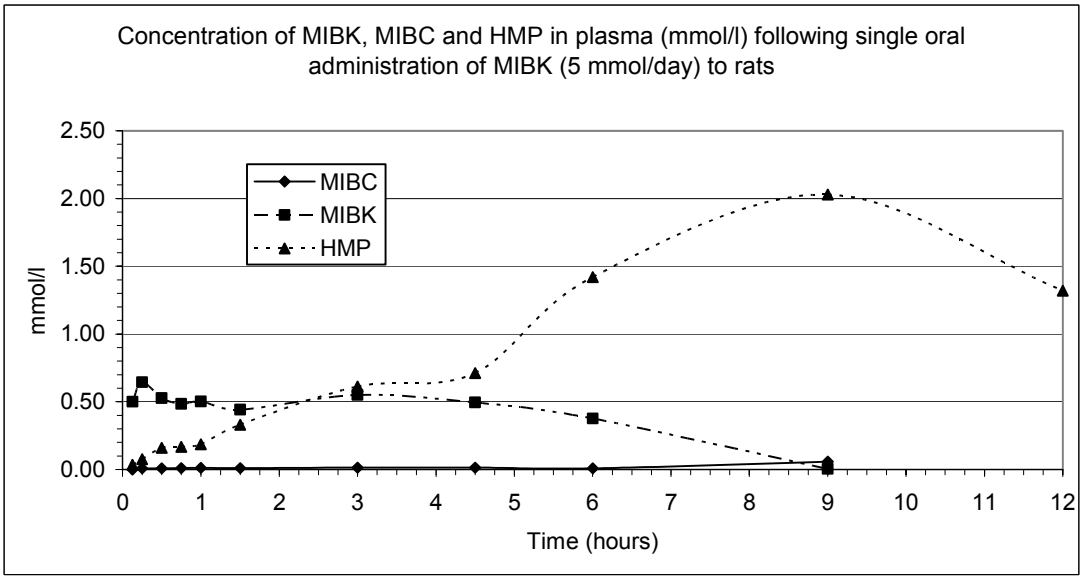


Figure 3: Metabolism and Clearance of an MIBK Dose

Selected pharmacokinetic parameters (non-compartmental) are listed in the following table:

Table 3 Selected Pharmacokinetic Parameters after Oral Administration of MIBK or MIBC

Test Substance	Analyte	C_{max} [mmole/L]	Time of C_{max} [hr]	Half Life [hr]	AUC $_{0\text{-}12hr}$ [mmole*hr/L]	% Total AUC
MIBK	MIBC	0.014	NA	4.657	0.089	0.05
	MIBK	0.644	0.25	2.529	3.558	20
	HMP	2.030	9	4.831	13.756	79
Total AUC					17.436	
MIBC	MIBC	0.588	0.5	2.256	0.819	6
	MIBK	0.450	1.5	1.571	2.268	17
	HMP	1.64	9	3.377	10.408	77
Total AUC					13.495	

NA = Not applicable; no peak concentration could be determined due to the low concentrations at each measurement.

Following oral dosing of either MIBC or MIBK, absorption is rapid with Cmax for both compounds occurring at approximately 0.25 to 0.5 hours post-dosing. The half-life for both compounds in blood was short (approximately 2.3 and 2.5 hours, respectively). MIBC was not detectable by 9 hours following MIBC dosing. Total exposure (based on $AUC_{0\text{-}12}$) to MIBK following dosing with either MIBC or MIBK was similar (2.3 and 3.6 mmol*h/l, respectively) as was exposure to HMP (10.4 and 13.8 mmol*h/l, respectively). Compared to MIBK and HMP, internal exposure to MIBC was minimal following dosing with MIBC (0.8 mmol*h/l), representing approximately 6% of the exposure to the three compounds over 12 hours. Therefore, the internal exposure to MIBC is minimal following MIBC dosing, and oral dosing of MIBC or MIBK results in similar internal exposure to MIBK and HMP.

The extent of metabolism of MIBC to MIBK can be determined by comparing the combined AUC for MIBK plus HMP, after administration of MIBC, to the combined AUC for these same materials after administration of MIBK. This analysis indicates the proportion of MIBC metabolized through MIBK to HMP is 12.676/17.314, or 73% of the administered dose of 5 mole/kg. This value should be considered to be a lower estimate. It is likely that some MIBC is not absorbed or is rapidly excreted as a glucuronide or sulfate conjugate in the urine after oral bolus administration. This would decrease the amount available for metabolism to MIBK and HMP in the blood, as compared to that available after MIBK.

Conclusion

Based on the similar internal exposure following doses of MIBC or MIBK, it is clear that the use of the extensive toxicity database for MIBK as well as the data for HMP, is appropriate for the evaluation of potential hazards from MIBC.

3.1.2 Acute Toxicity

Studies in Animals

Inhalation

Groups of six rats were exposed to saturated vapors (approximately 19 mg/L) for up to two hours or to 2000 ppm (8.4 mg/L) for eight hours. No mortality was observed after the 2-hour exposure to 19 mg/L and five of six rats died following the 8-hour exposure (Smyth *et al*., 1951; Reliability = 2). In a second study, groups of 5 rats/sex were exposed to 10 or 16 mg/L of MIBC (2360 or 3776 ppm) for 4 hours. All animals were anesthetized within the first hour of exposure and regained consciousness within 30 minutes or two hours of cessation of the exposure at 10 or 16 mg/L, respectively. One female died at 16 mg/L, and the 4-hour LC_{50} for MIBC was > 16 mg/L (Blair, 1981; Reliability = 2).

Dermal

The acute dermal LD_{50} was 3.56 ml/kg equivalent to approximately 2870 mg/kg (Smyth *et al.,* 1951; Reliability = 2). Undiluted MIBC was applied to the backs of six rabbits under occlusive conditions for 24 hours. Additional details of the results of the study were not included in the publication.

Oral

The acute oral LD_{50} for MIBC is between 2260 and 2970 mg/kg in male rats (Smyth *et al*., 1951; Reliability = 2). The study used six animals per group. Additional details of the study were not included in the publication.

Conclusion

MIBC has minimal acute toxicity by oral and dermal routes of exposure. Anesthetic effects, typical of organic solvents, can be expected at high vapor concentrations.

3.1.3 Irritation

Skin Irritation

Studies in Animals

MIBC was slightly irritating to rabbit skin following a 24-hour occluded exposure to undiluted chemical (Smyth *et al*., 1951; Reliability = 2). Details of the study were not included in the publication.

Eye Irritation

Studies in Animals

The available studies (Reliability = 2) evaluating eye irritation of MIBC are summarized in the following table:

Table 4 Eye Irritation

Species	Exposure Conditions	Result	Reference
Rabbit	0.02 ml; 24 hours; not rinsed	Highly irritating*	Smyth *et al.,* 1951
Rabbit	0.1 ml; 24 hours not rinsed	Moderately irritating**	McOmie and Anderson, 1949; Shell Chemical Corporation, 1957

*MIBC caused an irritation grade 5, defined as severe injury with necrosis, visible on fluorescein staining, covering approximately 75% of the cornea, or more severe necrosis over a smaller area.

**Conjunctivitis, edema and corneal injury that resolved by day 7 were observed.

Studies in Humans

Inhalation

A study with human volunteers (12/sex) indicated that vapor exposure to MIBC at 50 ppm for 15 minutes resulted in eye irritation in most subjects with nose and throat irritation experienced at higher concentrations. The maximum tolerable concentration was considered to be 25 ppm (Silverman et al., 1946).

Conclusion

Neat MIBC is slightly irritating to the skin of rabbits; atmospheric exposure produced nose and throat irritation in humans. Upon eye contact in humans, MIBC may cause moderate to severe irritation with corneal injury.

3.1.4 Sensitisation

Studies in Animals

Skin

MIBC has been tested in an OECD TG 406 Skin Sensitization study (maximization test) with guinea pigs (Elf Atochem, 1997; Reliability = 1). Induction was accomplished by an intradermal injection of a 1% solution of MIBC in Freund's adjuvant on day 1 followed by a topical application of neat MIBC on day 8 (covered for 48 hours) to 10 animals/sex/group (5/sex in the control). On day 22, a challenge dose of neat MIBC was applied topically (covered for 24 hours). Skin reactions were evaluated 24 and 48 hours after the challenge dose and no sensitization was observed.

Conclusion

MIBC gave no evidence of sensitizing potential based on a maximization test in guinea pigs.

3.1.5 Repeated Dose Toxicity

Studies in Animals

A 6-week inhalation study with MIBC is available. In addition, a 14-week inhalation study with MIBK and an OECD TG 422 study with HMP are summarized below and included in the IUCLID Dossier for MIBC.

Inhalation

A 6-week inhalation toxicity study with MIBC (Reliability = 2) was conducted with rats using a protocol similar to OECD TG 407 (Blair, 1982). In this study, groups of 12 rats/sex were exposed (whole body) to MIBC vapor at concentrations of 0, 0.211, 0.825, or 3.70 mg/L (0, 50.5, 198, or 886 ppm) six hours per day, five days per week. There were no deaths, clinical signs of toxicity, body weight effects, or hematological changes. Increased levels of ketone bodies in the urine were observed in females at all concentrations and in males at 0.825 and 3.70 mg/L. Plasma alkaline phosphatase was increased in females and kidney weights increased in males at the high concentration. Proteinurea was also detected at the high concentration in males. There were no exposure-related histopathological effects (including kidneys) observed in this study. The increases in ketone bodies, kidney weight differences and blood chemistry differences were not considered adverse toxicological effects. Although the authors did not define the NOAEC for this study, the Lesser Ketones Manufacturing Association has considered it to be the highest exposure concentration of 3.70 mg/L (886 ppm).

A 14-week vapor inhalation toxicity study (equivalent to OECD TG 413) with MIBK (Reliability = 1) has been reported (Phillips *et al*., 1987). In this study, male and female rats and mice (14 per species/sex/group) were exposed to atmospheres of 0, 50, 250, or 1000 ppm MIBK (0, 0.204, 1.02, 4.09 mg/L), 6 hr/day, 5 days/week for 14 weeks. Doses were selected based on a range-finding study reported in the same publication. No adverse effects on clinical health or growth of the rats or mice were observed. Minimal increases in liver weight were observed in males of both species at 1000 ppm and in male mice at 250 ppm. There were no histopathologic changes observed with these minimal weight gains and the changes were considered to be of no toxicological relevance. Male rats in the 250 and 1000 ppm groups also had an increase in hyaline droplets within the proximal tubule cells of the kidney. Kidney effects of MIBK are consistent with the binding to alpha-2u-globulin that results in male rat-specific hyaline droplet inclusions. The NOAEC was considered to be 1000 ppm (4.09 mg/L) for both species.

Oral

A repeated dose study according to OECD TG 422 was conducted with the ultimate metabolite of MIBC, HMP (Ministry of Health and Welfare: Japan, 1997; Reliability = 1). In this study, 10 rats/sex/group were dosed by gavage with 0, 30, 100, 300, or 1000 mg/kg/day of HMP in distilled water for approximately 45 days. Decreased locomotor activity and stimulation response were observed at 300 and 1000 mg/kg/day for both sexes. Altered blood parameters, dilatation of the distal tubules of the kidneys, hepatocellular hypertrophy, and vacuolization of the zona fasciculata of the adrenals were observed in males from the 1000 mg/kg/day group. Females at 300 mg/kg/day showed dilatation of the distal tubules and fatty degeneration of the proximal tubular epithelium in the kidneys. At 1000 mg/kg/day, female body weight gain was reduced, liver weight was increased, hepatocellular hypertrophy was noted, and kidney lesions similar to those at 300 mg/kg/day were also recorded. In addition, increased incidence and/or severity of hyaline droplets in the tubular epithelium was noted in males at 100 mg/kg/day and greater. The LOAEL for this study was 100 mg/kg/day for males and 300 mg/kg/day for females. The NOAEL was 30 mg/kg/day for males (based on hyaline droplet nephropathy) and 100 mg/kg/day for females.

Conclusion

The NOAEC for MIBC via repeated inhalation exposure (6 hours/day for 6 weeks) was 3.7 mg/L (886 ppm) in Wistar rats. For its primary metabolite, MIBK, the NOAEC via the inhalation route was 4.1 mg/L (1000 ppm) in B6C3F1 mice and Fischer 344 rats. The NOAEL for the ultimate metabolite, HMP, via gavage dosing for 45 days is 30 mg/kg bw/day in Sprague-Dawley rats based on hyaline droplet nephropathy, a male-rat specific lesion not pertinent to human hazard

assessment. The NOAEL for females was 100 mg/kg bw/day, and the only effect seen in the males at this dose was the rat-specific kidney lesion.

3.1.6 Mutagenicity

Studies in Animals

In vitro Studies

A series of bacterial mutation assays with Reliability of 2 have been conducted with MIBC. These are summarized in the following table:

Table 5 Bacterial Mutation Assays

Test System	Assay	Concentrations	Result	Reference
Salmonella typhimurium strains: TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation	31.25 – 4000 µg/plate	Negative with and without metabolic activation	Clare, 1983
S. typhimurium strains: TA98, TA100, TA1535, TA1537, TA1538	Reverse mutation	1 – 5000 µg/plate	Negative with and without metabolic activation; 5000 µg/plate was cytotoxic to all strains	Shimizu et al., 1985
Escherichia coli WP2 *uvr* A pkm 101	Reverse mutation	31.25 – 4000 µg/plate	Negative with and without metabolic activation	Clare, 1983
E. coli WP2 *uvr* A	Reverse mutation	1 – 5000 µg/plate	Negative with and without metabolic activation; 5000 µg/plate was cytotoxic	Shimizu et al., 1985
Saccharomyces cerevisiae JD1	Gene mutation	0.01 – 5.0 mg/ml	Negative with and without metabolic activation; 5.0 mg/ml was cytotoxic	Clare, 1983

MIBC was tested in a cytogenetic assay using rat liver RL4 cells without metabolic activation; rat liver RL4 cells are metabolically competent. Concentrations of 0, 0.5, 1.0 and 2.0 mg/ml were tested. MIBC was found to be negative in this assay (Clare, 1983).

Genetic toxicity *in vitro* with HMP

HMP was negative in the Bacterial Reverse Mutation Assay with and without metabolic activation (Ministry of Health and Welfare: Japan, 1997; Reliability = 1). Four strains of *Salmonella typhimurium* and one strain of *Escherichia coli* were tested at concentrations from 313 to 5000 µg/plate. HMP was also tested for chromosomal aberrations in CHL/IU cells according to OECD TG 473. The test was conducted at concentrations ranging from 0.30 to 1.2 mg/ml; cytotoxicity was not observed at 1.2 mg/ml. Polyploidy (1.25 and 1.00%) was increased significantly at 0.60 and 1.2 mg/mL. However the authors concluded that these were not cytogenetic effects because a trend test showed no dose-dependence. The study concluded that HMP was not mutagenic in this assay.

Conclusion

MIBC is not mutagenic in bacterial and mammalian cell cytogenetic assays. The ultimate metabolite, HMP, is not mutagenic in bacteria and gives a negative result in a chromosomal aberration study.

3.1.7 Carcinogenicity

No studies were identified.

3.1.8 Toxicity for Reproduction

Studies in Animals

Effects on Fertility

Reproductive organs were examined in the 6-week MIBC inhalation toxicity study with rats (described in the Repeated Dose Toxicity Section 3.1.5 above) and no effects were observed up to the highest concentration tested of 3.70 mg/L (886 ppm) (Blair, 1982).

A high-quality inhalation 2-generation reproduction study with rats has been conducted with MIBK (Nemec, 2004; Reliability = 1). The study was conducted in compliance with US EPA OPPTS Guideline 870-3800. Exposures were 0, 500, 1000 and 2000 ppm (0, 2.04, 4.09, and 8.18 mg/L) for 6 hr/day, 7 days/week. Treatment began 70 days prior to mating for the F0 and F1 generations, continuing to the end of the mating period for males and to day 20 of gestation for females; treatment of females resumed at day 5 of lactation. Group sizes were 30/sex. A transient reduced acoustic startle response was observed for the F0 and F1 adults during exposure at 1000 and 2000 ppm consistent with a sedative effect. The effect was not observed one hour after exposure. CNS depression was observed in pups upon initiation of exposures on Day 22 (one F1 pup died on Day 22). Therefore, exposures were terminated and restarted on Day 28. Other minor effects on parental animals, including decreased body weight gain and slight decreased food consumption during the first 2 weeks of exposure, occurred only at the high concentration in both generations. Increased male kidney weights associated with hyaline droplet inclusions were observed at all concentrations of MIBK. There were no effects on reproductive parameters, developmental landmarks, or andrology measurements. The NOAEC for systemic toxicity was 1000 ppm (4.09 mg/L) based on slight body weight and feed consumption reductions at 2000 ppm (excluding the increased male kidney weights). The NOAEC for reproductive toxicity was 2000 ppm (8.18 mg/L).

The OECD TG 422 study conducted for HMP described in Section 3.1.5 indicated no statistically significant changes in any reproductive parameters at any dose. Animals were treated for 45 days, beginning 14 days prior to mating. The authors indicated that there was a tendency at 1000 mg/kg/day for lower reproductive indices (fertility and implants) as well as a trend toward reduced live pup births and other pup viability parameters. A clear NOAEL was established at 300 mg/kg/day (Ministry of Health and Welfare: Japan, 1997; Reliability = 1).

Developmental Toxicity

A high quality, standard guideline, two-species developmental toxicity study with MIBK has been reported (Tyl et al., 1987; Reliability = 1). Female rats and mice (35 animals/group) were exposed to MIBK vapor concentrations of 0, 300, 1000, or 3000 ppm (0, 1.23, 4.09, or 12.3 mg/L) on Gestational Days (gd) 6 through 15. The high concentration resulted in maternal toxicity in both species including clinical signs of toxicity including neuromuscular effects (both species), and statistically significant changes in body weight, relative kidney weights and decreased food

consumption (rats only) and increased liver weight (mice only).. Reduced fetal body weight per litter and reduced skeletal ossification were observed in rats at the high concentration. An increased incidence of dead fetuses, reduced fetal body weight per litter and reductions in skeletal ossification were observed in mice from the high concentration group. No embryotoxicity or teratogenicity was observed in either species. The NOAEC for maternal and fetal toxicity was 1000 ppm (4.09 mg/L).

The OECD TG 422 study conducted for HMP described in Section 3.1.5 indicated a tendency for decrease of developmental parameters such as total number of pups born, delivery index, live birth index, number of pups alive and viability index on day 4 of lactation at the highest dose of 1000 mg/kg/day. Animals were treated for 45 days, beginning 14 days prior to mating. A clear NOAEL was established at 300 mg/kg/day (Ministry of Health and Welfare: Japan, 1997; Reliability = 1).

Conclusion

Based on results of animal studies evaluating exposure to MIBC and MIBK vapors, no reproductive toxicity is anticipated for MIBC via the inhalation route of exposure. Slight changes in reproductive performance and pup viability following high oral exposure to HMP may have occurred in the presence of maternal toxicity.

Based on studies with MIBK and HMP, MIBC is not anticipated to be selectively toxic to the embryo or fetus and is not teratogenic via inhalation exposure.

3.2 Initial Assessment for Human Health

The metabolism and clearance of 4-methylpentan-2-ol (methyl isobutyl carbinol; MIBC) is rapid. MIBC is metabolized to 4-hydroxy-4-methyl-2-pentanone (HMP) through methyl isobutyl ketone (MIBK). Dosing with MIBC or MIBK results in similar internal exposure to MIBK and HMP and minimal exposure to MIBC. Thus, the data for MIBK and HMP adequately support the evaluation of MIBC systemic toxicity.

Studies with experimental animals indicate that MIBC is of low toxicity by the oral, dermal and inhalation routes of exposure. The acute oral and dermal LD_{50} values for MIBC are 2260 - 2970 mg/kg and 2870 mg/kg, respectively. MIBC had typical organic solvent effects following acute inhalation exposures with anesthetic effects occurring at 10 mg/L and death following an 8-hour exposure to 8.4 mg/L. In standard primary irritation studies, MIBC was slightly irritating to skin and moderately to severely irritating to the eye. A skin sensitization study in animals was negative and indicates that MIBC is not likely to be a sensitizer in humans.

Repeated dose studies with MIBC and its primary metabolite, methyl isobutyl ketone (MIBK), indicate that systemic toxicity is minimal. The NOAEC for subchronic inhalation exposure was 198 ppm (0.825 mg/L) for MIBC (6-weeks with rats) and 1000 ppm (4.09 mg/L) for MIBK (14-weeks with rats and mice).

There were no toxicologically significant organ-specific toxic effects for either chemical. The NOAEL for the ultimate metabolite, HMP, via gavage dosing for 45 days was 30 mg/kg/day based on hyaline droplet nephropathy, a male-rat specific lesion not pertinent to human hazard assessment. The NOAEL for females was 100 mg/kg/day.

MIBC and HMP were not mutagenic to bacterial cells (bacterial reverse mutation assay) *in vitro* with or without metabolic activation. In a mammalian cell cytogenetic assay (rat liver cells), MIBC was negative with and without metabolic activation. HMP was negative in an *in vitro* chromosomal assay. Based on the negative results in the bacterial mutagenicity and mammalian cell cytogenetic assays with MIBC and bacterial mutagenicity and chromosomal aberration assays with HMP, MIBC is unlikely to be mutagenic.

MIBC showed no effects on reproductive organs following 6 weeks of inhalation exposure to concentrations as high as 3.70 mg/L (886 ppm). MIBK showed no reproductive effects in a two-generation study with inhalation exposures up to 8.18 mg/L (2000 ppm). Slight changes in reproductive performance and pup viability following high oral exposure to HMP (1000 mg/kg/day) in an OECD TG 422 study may have occurred in the presence of maternal toxicity. No teratogenic effects were observed at MIBK inhalation concentrations as high as 3000 ppm (12.3mg/L) and no fetal toxicity was observed without the presence of maternal toxicity; the NOAEC for maternal and fetal toxicity was 1000 ppm (4.09 mg/L) due to clinical signs of toxicity including neuromuscular effects (both species), and statistically significant changes in body weight, relative kidney weights and decreased food consumption (rats only) and increased liver weight (mice only) and decreased fetal body weight with evidence of delayed ossification. Based on the available data, MIBC is not a reproductive or developmental toxin.

Human volunteers exposed to MIBC vapors at 50 ppm experienced eye irritation in most subjects with nose and throat irritation experienced at higher concentrations. The maximum tolerable concentration was considered to be 25 ppm.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Acute Toxicity Test Results

Acute toxicity to fish (Marino et al., 2003a; Reliability = 1) yielded a 96-hour LC_{50} for Rainbow trout (*Oncorhynchus mykiss*) of 359 mg/L. The NOEC was 105 mg/L. The study followed OECD TG 203 using a static renewal design. Nominal exposure concentrations ranged from 105 to 625 mg/L. The mean measured concentrations were 95.5 to 615 mg/L. Mortality occurred in the two highest concentrations (448 and 615 mg/L, measured). The LC_{50} was determined based on measured concentrations.

Acute toxicity to *Daphnia magna* (Marino et al., 2003b; Reliability = 1) yielded a 48-hour EC_{50} of 337 mg/L. The NOEC was 288 mg/L. The study followed OECD TG 202 using a static renewal design. Nominal exposure concentrations ranged from 105 to 625 mg/L. The mean measured concentrations were 96.6 to 481 mg/L. Immobilization occurred in the two highest concentrations (378 and 481 mg/L, measured). The EC_{50} was determined based on measured concentrations.

Acute toxicity to the green algae, *Pseudokirchneriella subcapitata* (Hancock et al., 2003; Reliability = 1) yielded 72- and 96-hour ErC_{50} values of 264 and 334 mg/L, respectively (NOECs of 75.5 mg/L for both time periods) and 72- and 96-hour EbC_{50} values of 139 and 147 mg/L, respectively (NOECs of 41.6 mg/L and 75.5 mg/L, respectively). The study followed OECD TG 201. Nominal exposure concentrations ranged from 31.3 to 1000 mg/L. The mean measured concentrations ranged from 15.5 to 624 mg/L and the measured/nominal ratio ranged from approximately 50 to 67%. Inhibition of growth occurred in the four highest concentrations (75.5, 155, 326 and 624 mg/L, measured). The EC_{50} values were determined based on measured concentrations.

Conclusion

Based on the available data, MIBC exhibits a low acute hazard potential for toxicity to aquatic organisms.

4.2 Terrestrial Effects

No studies were identified.

4.3 Initial Assessment for the Environment

The melting point of MIBC is – 90°C, the boiling point is 131.7°C and the vapor pressure is 4.97 hPa at 20ºC. The water solubility is 16.4 g/L (20°C) and density is 0.81 g/cm^3 at 25°C. The calculated log Kow is 1.68. MIBC is predicted to be photodegraded by reaction with hydroxyl radicals in the atmosphere with a half-life of approximately 10 hours (calculated). MIBC does not have hydrolyzable groups and therefore hydrolysis is not a degradation pathway. Distribution modeling using Mackay Level I indicated that partitioning will occur to air, water, and soil phases at 37.8%, 59.6% and 2.5%, respectively. Fugacity model Level III predicted greatest distribution (≥ 86%) to the primary compartment of release. When equal releases were assumed, the predicted distribution was: 3.6% (air), 45% (water), 51% (soil) and <1% (sediment). A low bioaccumulation potential is expected based on the partition coefficient and other physical/chemical parameters. MIBC is readily biodegradable attaining 94% degradation within 20 days and meeting the "10-day window". MIBC has a low acute hazard potential for toxicity to aquatic organisms. The 96-hour LC_{50} for rainbow trout (*Oncorhynchus mykiss*) was 359 mg/L (measured), the 48-hour EC_{50} for *Daphnia magna* was 337 mg/L (measured) and the 96-hour EC_{50} value for growth rate of algae (*Pseudokirchneriella subcapitata*) was 334 mg/L (measured) and for biomass was 147 mg/L (measured).

5 RECOMMENDATIONS

Human Health: This chemical is currently a low priority for further work. The chemical possesses properties indicating a potential hazard for human health (eye irritation, narcosis at high inhalation concentrations) These hazards do not warrant further work as they are related to acute toxicity which may become evident only at high exposure levels. They should nevertheless be noted by chemical safety professionals and users.

Environment: The chemical is currently a low priority for further work due to its low hazard profile.

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I U C L I D

Data Set

Existing Chemical	:	ID: 108-11-2
CAS No.	:	108-11-2
EINECS Name	:	4-methylpentan-2-ol
EC No.	:	203-551-7
TSCA Name	:	2-Pentanol, 4-methyl-
Molecular Formula	:	C6H14O

Producer related part

Company	:	Lesser Ketones Manufacturing Association
Creation date	:	16.12.2005

Substance related part

Company	:	Lesser Ketones Manufacturing Association
Creation date	:	16.12.2005
Status	:	
Memo	:	Final for SIDS
Printing date	:	16.12.2005
Revision date	:	
Date of last update	:	16.12.2005
Number of pages	:	75
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 6, 7, 8, 10
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 APPLICANT AND COMPANY INFORMATION

1.0.2 LOCATION OF PRODUCTION SITE, IMPORTER OR FORMULATOR

1.0.3 IDENTITY OF RECIPIENTS

1.0.4 DETAILS ON CATEGORY/TEMPLATE

1.1.0 SUBSTANCE IDENTIFICATION

IUPAC Name	:	Methyl isobutyl carbinol
Smiles Code	:	
Molecular formula	:	C6 H14 0
Molecular weight	:	102
Petrol class	:	

08.05.2002

1.1.1 GENERAL SUBSTANCE INFORMATION

Purity type	:	typical for marketed substance
Substance type	:	organic
Physical status	:	liquid
Purity	:	> 98 % w/w
Colour	:	colorless
Odour	:	mild

Remark : The test substance used in the studies included in this dossier was > 98% methyl isobutyl carbinol and represented the commercial product. Studies with MIBC in this dossier that did not define MIBC purity are assumed to have used the commercial grade of > 98%.

Reliability : The LOAEL for this study was 100 mg/kg/day for males and 300 mg/kg/day for females.The NOAEL was 30 mg/kg/day for males (based on hyaline droplet nephropathy) and 100 mg/kg/day for females.

02.08.2002

1.1.2 SPECTRA

1.2 SYNONYMS AND TRADENAMES

2-Methyl-4-pentanol

02.07.2002

4-Methyl-2-pentanol

02.07.2002

Methyl isobutyl carbinol

02.07.2002

Methylamyl alcohol

02.07.2002

MIBC

02.07.2002

1.3 IMPURITIES

Purity : typical for marketed substance
CAS-No :
EC-No :
EINECS-Name :
Molecular formula :
Value :

Remark : No impurities were identified in the test substances used in studies that are included in this IUCLID dossier

02.07.2002

1.4 ADDITIVES

1.5 TOTAL QUANTITY

Remark : The estimated total volume of MIBC production in North America in 1998 was 25,000 tonnes (Bizzari, 1999). Methyl isobutyl carbinol (MIBC) is a flammable, colorless, stable liquid.

09.12.2005 (2)

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.6.3 PACKAGING

1.7 USE PATTERN

Remark : MIBC is sold as technical grade with a minimum of 98% purity. MIBC is produced either as a recovered coproduct

during methyl isobutyl ketone (MIBK) production or directly by hydrogenation of MIBK.
MIBC is primarily used (~70%) in the production of lube oil additives, specifically zinc dialkyldithiophosphate, for antiwear and corrosion inhibitors. The second largest use of MIBC (~20%) is as a flotation frother for treating copper ores and coal (Bizzari, 1999). In mining frother applications, MIBC is used in the ppm range, with usual concentrations less than 1000 ppm and in many cases in the hundreds of ppm range (100 - 600 ppm). The remaining production is primarily for its use as an additive to surface coatings as a solvent to maintain binder softness until the binder fuses.

09.12.2005 (2)

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

Origin of substance : Natural origin
Type :

Remark : MIBC is produced either as a recovered coproduct during methyl isobutyl ketone (MIBK) production or directly by hydrogenation of MIBK. MIBK is produced from acetone in a 3-step reaction. The first step involves the aldol condensation of two molecules of acetone in liquid phase to diacetone alcohol. Diacetone alcohol is then dehydrated under acidic conditions to mesityl oxide. Lastly, mesityl oxide is hydrogenated using a palladium catalyst to MIBK.

09.12.2005 (2)

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

Remark : The ACGIH TLV-TWA for MIBC is 25 ppm (104 mg/m3) and the TLV-STEL is 40 ppm (167 mg/m3). The German MAK value is 25 ppm.

19.04.2005

1.8.2 ACCEPTABLE RESIDUES LEVELS

1.8.3 WATER POLLUTION

1.8.4 MAJOR ACCIDENT HAZARDS

1.8.5 AIR POLLUTION

1.8.6 LISTINGS E.G. CHEMICAL INVENTORIES

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Remark : In many applications, MIBC is used in closed systems and environmental releases are considered unlikely and only result from accidental release. In a few applications, e.g. use as a mining frother, MIBC may be introduced into one or more environmental compartments at low concentrations. Rapid photodegradation and biodegradation limit the potential exposure of environmental species and humans in these cases

With the exception of the use in tar sand mining, frothers are used in closed systems and only catastrophic failure results in any appreciable exposure. In tar sand mining, the MIBC is added to the tar sand and the sand is spread out and allowed to dry. The majority of MIBC from this use is volatilized to the air. Exposure (in the ppm range) is typically limited to the equipment operator pushing the sand. MIBC used as an intermediate in the manufacture of lube oil additives is blended with other alcohols and reacted. Normally these reactors are closed systems and exposure is limited to upsets or catastrophic failure of the reactor.

In its primary use as an intermediate for corrosion inhibitor production, significant residual MIBC is not anticipated. As noted above, in mining operations, low ppm vapor exposure may occur in operators. Minimal exposure to vapors from the use of MIBC as a solvent in coating applications may also occur. Overall, consumer exposure to MIBC is expected to be negligible.

31.10.2005

1.11 ADDITIONAL REMARKS

1.12 LAST LITERATURE SEARCH

1.13 REVIEWS

2.1 MELTING POINT

Value : = -90 °C
Sublimation :
Method :
Year : 2001
GLP :
Test substance :

Reliability : (2) valid with restrictions
Acceptable value from published Handbook
Flag : Critical study for SIDS endpoint
27.07.2004 (53)

2.2 BOILING POINT

Value : = 131.7 °C at 1011 hPa

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
08.05.2002 (46)

Value : = 125 °C at
Decomposition :
Method : other: EPIWIN (v 3.11) MPBPVP Submodel (v 1.41)
Year : 2004
GLP :
Test substance :

Remark : The experimental database value documented in the model data is 131.6 degrees C
Reliability : (2) valid with restrictions
Acceptable value from the Model and consistent with Experimental Database.
10.06.2004 (52)

2.3 DENSITY

Type : density
Value : ca. .81 g/cm³ at 25 °C

Reliability : (2) valid with restrictions
24.06.2004 (46)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = 4.97 hPa at 20 °C

Reliability : (2) valid with restrictions
Acceptable value from published source (DIPPR)

Flag : Critical study for SIDS endpoint
08.05.2002 (46)

Value : = 3.72 hPa at 25 °C
Decomposition :
Method : other (calculated): EPIWIN (v 3.11) MPBPVP Submodel (v 1.41)
Year : 2004
GLP :
Test substance :

Remark : The experimental database value documented in the model data is 7.0 hPa at 25 degrees C
Reliability : (2) valid with restrictions
10.06.2004 (52)

2.5 PARTITION COEFFICIENT

Partition coefficient : octanol-water
Log pow : = 1.68 at °C
pH value :
Method : other (calculated): EPIWIN (v 3.11) KOWWIN Submodel (v 1.67)
Year : 2004
GLP :
Test substance :

Reliability : (2) valid with restrictions
Acceptable value from Model
Flag : Critical study for SIDS endpoint
10.06.2004 (50)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 16.4 g/l at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 1986
GLP :
Test substance :

Reliability : (2) valid with restrictions
Acceptable value from published Handbook
Flag : Critical study for SIDS endpoint
24.06.2004 (37)

Solubility in : Water
Value : = 16.7 g/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :

pKa : at 25 °C
Description :
Stable :
Deg. product :
Method :
Year : 1968
GLP :
Test substance :

Reliability : (2) valid with restrictions
Acceptable value from published Handbook
Flag : Critical study for SIDS endpoint
08.12.2005 (20)

Solubility in : Water
Value : = 15720 mg/l at 25 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :
Deg. product :
Method : other: EPIWIN (v 3.11) WSKOWWIN Submodel (v 1.41)
Year : 2004
GLP :
Test substance :

Reliability : (2) valid with restrictions
08.12.2005 (48)

Solubility in : Water
Value : at 20 °C
pH value :
concentration : at °C
Temperature effects :
Examine different pol. :
pKa : at 25 °C
Description :
Stable :

Result : Slightly soluble
Reliability : (2) valid with restrictions
08.12.2005 (19)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : = 40.9 °C
Type :

06.05.2002 (46)

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 DISSOCIATION CONSTANT

2.13 VISCOSITY

2.14 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	**air**
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
DIRECT PHOTOLYSIS		
Halflife t1/2	:	= 10 hour(s)
Degradation	:	% after
Quantum yield	:	
Deg. product	:	
Method	:	other (calculated): EPIWIN (v3.11) AOPWIN Submodel (v 1.91)
Year	:	2004
GLP	:	
Test substance	:	
Remark	:	The EPIWIN model (v 3.11) was run using the following measured physical chemical properties: Water Solubility (mg/L) : 16400 Vapor Pressure (mm Hg) : 3.74 Boiling Point (deg C) : 131.70 Melting Point (deg C) : -90.00 OVERALL OH Rate Constant = 13 E-12 cm3/molecule-sec HALF-LIFE = 0.836 Days (12-hr day; 1.5E06 OH/cm3) HALF-LIFE = 10.0 Hrs
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

09.12.2005 (49)

Type	:	**air**
Light source	:	other
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
Deg. product	:	
Method	:	
Year	:	1972
GLP	:	no data
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	The study measured reactivity with smog components in irradiation chambers. According to the authors, alcohol decompostion in smog chambers involves initial attack at a bond of the alpha-carbon atom. Therefore, this measurement provides a relative estimate of photodegradation.
Remark	:	The rate of nitrogen dioxide formation in the reaction chamber relative to toluene was 1.4 . The rate of hydrocarbon disappearance relative to toluene was 1.2. The oxidant maximum relative to toluene was 1.45

08.12.2005 (24)

Type	:	**air**
Light source	:	Sun light
Light spectrum	:	nm

Relative intensity	:	based on intensity of sunlight
Conc. of substance	:	at 15 °C
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1000000 molecule/cm³
Rate constant	:	= .0000000000036632 cm³/(molecule*sec)
Degradation	:	= 50 % after 2.2 day(s)
Deg. product	:	
Method	:	OECD Guide-line draft "Photochemical Oxidative Degradation in the Atmosphere"
Year	:	
GLP	:	no data
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Reliability	:	(4) not assignable Not assignable because original document was not reviewed. Entry from CB IUCLID submitted by Shell Nederland Chemie B.V. Hoogvliet-Rotterdam. It is retained in the IUCLID based on the understanding that the original entries were to be retained.

08.12.2005

3.1.2 STABILITY IN WATER

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	**fugacity model level I**
Media	:	
Air	:	37.8 % (Fugacity Model Level I)
Water	:	59.6 % (Fugacity Model Level I)
Soil	:	2.5 % (Fugacity Model Level I)
Biota	:	% (Fugacity Model Level II/III)
Soil	:	% (Fugacity Model Level II/III)
Method	:	other: calculated
Year	:	2004
Method	:	Level I Fugacity Model (v. 2.11)
Remark	:	Input Parameters for Level I Model: Chemical Type = 1, Indicates chemical can partition into all environmental compartments Molecular Mass (g/mol): 102.17 Data Temperature (deg C): 20 LogKow: 1.68 Water Solubility (g/m3): 16400

Water Solubility (mol/m3): 160.5168
Henry's Law Constant (Pa.m3/mol): 3.096249
Vapor Pressure (Pa): 497
Melting Point (deg C): -90
Amount of Chemical (kg): 100000
Amount of Chemical (mol): 978760.9
Fugacity Pa: 9.027075E-06
Total of VZ Products: 1.08425E+11

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
08.12.2005 (7)

Type : **volatility**
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other
Year : 1982

Remark : The calculated Henry's Law Constant is 3.44 Pa*m3/mole.

Based on this the volatilisation half-life of
4-Methyl-2-pentanol from a stream with a depth of 1 m and a
current of 1 m/s and a wind velocity of 3 m/s is calculated
to be 28.6 hours
08.12.2005 (25)

Type : **volatility**
Media : water - air
Air : % (Fugacity Model Level I)
Water : % (Fugacity Model Level I)
Soil : % (Fugacity Model Level I)
Biota : % (Fugacity Model Level II/III)
Soil : % (Fugacity Model Level II/III)
Method : other
Year :

Remark : The calculated dimensionless Henry's constant = 1.84 X 10-3

The paper gives the inverse of Henry's constant as 10^2.72.
08.12.2005 (21)

3.3.2 DISTRIBUTION

Media : **other: soil, air and water (emissions to each compartment = 1000 kg/hr)**
Method : Calculation according Mackay, Level III
Year : 2004

Result : Concentration (%)
Air : 3.6
Water : 44.9
Soil : 51.3
Sediment : <1.0

Level III Fugacity Model (Full-Output):
==========

Chem Name : 2-Pentanol, 4-methyl-
Molecular Wt: 102.18
Henry's LC : 4.45e-005 atm-m3/mole (Henry database)
Vapor Press : 3.74 mm Hg (user-entered)
Log Kow : 1.68 (Kowwin program)
Soil Koc : 19.6 (calc by model)

Mass Amount	Half-Life	Emissions
(percent)	(hr)	(kg/hr)
Air 3.63	20.1	1000
Water 44.9	360	1000
Soil 51.3	360	1000
Sediment 0.105	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	6.64e-011	959	278	32	9.25
Water	7.49e-010	662	344	22.1	11.5
Soil	1.23e-008	757	0	25.2	0
Sediment	5.94e-010	0.386	0.016	0.0129	0.000535

Persistence Time: 255 hr
Reaction Time: 322 hr
Advection Time: 1.23e+003 hr
Percent Reacted: 79.3
Percent Advected: 20.7

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 20.07
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 3.133 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Remark : The EPIWIN model (v 3.11) was run using the following measured physical chemical properties:

Water Solubility (mg/L) : 16400
Vapor Pressure (mm Hg) : 3.74
Boiling Point (deg C) : 131.70
Melting Point (deg C) : -90.00

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
09.12.2005 (51)

Media : **other: air (emission = 1000 kg/hr; emission to other compartments = 0 kg/hr)**
Method : Calculation according Mackay, Level III
Year : 2004

Result :

Concentration (%)
Air : 86.1
Water : 11.4

Soil : 2.4
Sediment: <0.1

Level III Fugacity Model (Full-Output):
==========

Chem Name : 2-Pentanol, 4-methyl-
Molecular Wt: 102.18
Henry's LC : 4.45e-005 atm-m3/mole (Henry database)
Vapor Press : 3.74 mm Hg (user-entered)
Log Kow : 1.68 (Kowwin program)
Soil Koc : 19.6 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	86.1	20.1	1000
Water	11.4	360	0
Soil	2.44	360	0
Sediment	0.0265	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	5.32e-011	768	222	76.8	22.2
Water	6.4e-012	5.66	2.94	0.566	0.294
Soil	1.98e-011	1.21	0	0.121	0
Sediment	5.07e-012	0.0033	0.000137	0.00033	1.37e-005

Persistence Time: 25.8 hr
Reaction Time: 33.3 hr
Advection Time: 115 hr
Percent Reacted: 77.5
Percent Advected: 22.5

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 20.07
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 3.133 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+00

Remark : The EPIWIN model (v 3.11) was run using the following measured physical chemical properties:

Water Solubility (mg/L) : 16400
Vapor Pressure (mm Hg) : 3.74
Boiling Point (deg C) : 131.70
Melting Point (deg C) : -90.00

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
09.12.2005 (51)

Media : **other: water (emission = 1000 kg/hr; emission to other compartments = 0 kg/hr)**
Method : Calculation according Mackay, Level III
Year : 2004

Result : Concentration (%)
Air : <1.0

Water : 98.9
Soil : <0.1
Sediment: <1.0

Level III Fugacity Model (Full-Output):
==========

Chem Name : 2-Pentanol, 4-methyl-
Molecular Wt: 102.18
Henry's LC : 4.45e-005 atm-m3/mole (Henry database)
Vapor Press : 3.74 mm Hg (user-entered)
Log Kow : 1.68 (Kowwin program)
Soil Koc : 19.6 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.846	20.1	0
Water	98.9	360	1000
Soil	0.024	360	0
Sediment	0.231	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	6.18e-012	89.3	25.9	8.93	2.59
Water	6.58e-010	582	302	58.2	30.2
Soil	2.3e-012	0.141	0	0.0141	0
Sediment	5.22e-010	0.339	0.0141	0.0339	0.00141

Persistence Time: 306 hr
Reaction Time: 455 hr
Advection Time: 931 hr
Percent Reacted: 67.2
Percent Advected: 32.8

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 20.07
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 3.133 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Remark : The EPIWIN model (v 3.11) was run using the following measured physical chemical properties:

Water Solubility (mg/L) : 16400
Vapor Pressure (mm Hg) : 3.74
Boiling Point (deg C) : 131.70
Melting Point (deg C) : -90.00

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
09.12.2005 (51)

Media : **other: soil (emission = 1000 kg/hr; emission to other compartments = 0 kg/hr)**
Method : Calculation according Mackay, Level III
Year : 2004

Result : Concentration (%)
Air : <1.0
Water : 8.9
Soil : 90.4
Sediment: <0.1

Level III Fugacity Model (Full-Output):
==========

Chem Name : 2-Pentanol, 4-methyl-
Molecular Wt: 102.18
Henry's LC : 4.45e-005 atm-m3/mole (Henry database)
Vapor Press : 3.74 mm Hg (user-entered)
Log Kow : 1.68 (Kowwin program)
Soil Koc : 19.6 (calc by model)

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	0.677	20.1	0
Water	8.93	360	0
Soil	90.4	360	1000
Sediment	0.0208	1.44e+003	0

	Fugacity (atm)	Reaction (kg/hr)	Advection (kg/hr)	Reaction (percent)	Advection (percent)
Air	7.03e-012	102	29.4	10.2	2.94
Water	8.45e-011	74.7	38.8	7.47	3.88
Soil	1.23e-008	755	0	75.5	0
Sediment	6.7e-011	0.0435	0.00181	0.00435	0.000181

Persistence Time: 434 hr
Reaction Time: 466 hr
Advection Time: 6.37e+003 hr
Percent Reacted: 93.2
Percent Advected: 6.82

Half-Lives (hr), (based upon Biowin (Ultimate) and Aopwin):
Air: 20.07
Water: 360
Soil: 360
Sediment: 1440
Biowin estimate: 3.133 (weeks)

Advection Times (hr):
Air: 100
Water: 1000
Sediment: 5e+004

Remark : The EPIWIN model (v 3.11) was run using the following measured physical chemical properties:

Water Solubility (mg/L) : 16400
Vapor Pressure (mm Hg) : 3.74
Boiling Point (deg C) : 131.70
Melting Point (deg C) : -90.00

Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
09.12.2005 (51)

3.4 MODE OF DEGRADATION IN ACTUAL USE

Remark : In air 4-methyl-2-pentanol is degradaded by reaction with OH-radicals.
In water the substance is biodegraded.
The integrated environmental half-life is estimated to be less than one week.

09.12.2005 (22)

3.5 BIODEGRADATION

Type : **aerobic**
Inoculum : predominantly domestic sewage, non-adapted
Concentration : 3 mg/l related to DOC (Dissolved Organic Carbon)
related to
Contact time :
Degradation : = 94 (±) % after 20 day(s)
Result : readily biodegradable
Kinetic of testsubst. : 5 day(s) = 50 %
10 day(s) = 72 %
15 day(s) = 90 %
20 day(s) = 94 %
%
Deg. product :
Method : other: Standard Methods for Examination of Water and Wastewater, 13th Edition, American Pub. Health Assoc. New York, NY (1971)
Year : 1974
GLP : no data
Test substance : other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%

Test condition : As described in reference
Remark : The test method utilized was: "Standard Methods for the Examination of Water and Wastewater." 1971. 13th edition, Amer. Pub. Health Assn., New York, NY. A settled domestic wastewater was filtered through glass wool and then added (3 ml/bottle) as seed material to clean 300 ml BOD bottles. The dilution water was sparged with pure oxygen to produce an available DO level of 30 to 35 mg/l and added to the seed material to completely fill the bottles. The pure chemical was added to each bottle (3.0 µl/bottle) to provide a concentration of approximately 10 mg/l (MIBC ThOD = 2.82 mg/mg). At least two of the concentrations were tested in duplicate. Dissolved oxygen content was measured approximately five times throughout the test using a commercial DO meter filled with an agitated probe. When the DO level dropped below 4.0 mg/l, the contents were reaerated. Samples (2 ml) were analyzed routinely for nitrites and nitrates throughout the study because ammonia nitrogen and organic nitrogen contained in the test system could be oxidized to form these two compounds. No attempt was made to inhibit nitrification. Appropriately seeded blanks and glucose standards were prepared during each test run using the same dilution water used for the test samples.
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint
08.12.2005 (36)

Type : **aerobic**
Inoculum : other: activated sludge from synthetic waste

Method : Alcohol added to flask at 16 mg/l, no information on inoculum concentration, alcohol degradation time course measured by GC.
Remark : This study investigated the relationship of biodegradation rate constants for aliphatic alcohols, including 2-methyl-4-pentanol, to their octanol water partition coefficients. The biodegradation rate constant for 2-methyl-4-pentanol was 0.0477.
Reliability : (4) not assignable
08.12.2005 (55)

3.6 BOD5, COD OR BOD5/COD RATIO

BOD5
Method : **other: Standard Methods for Examination of Water and Waste Water No. 219, APHA**
Year : 1971
Concentration : related to
BOD5 : mg/l
GLP : no data
COD
Method : other: ASTM D 1252-67
Year : 1974
COD : = 2600 mg/g substance
GLP : no data
RATIO BOD5 / COD
BOD5/COD : = .91

Remark : ThOD is 2.82 g/g, BOD5 is 2.37 g/g = 84% ThOD
COD is 2.60 g/g = 92% ThOD
Reliability : (2) valid with restrictions
08.12.2005 (5)

BOD5
Method : **other**
Year :
Concentration : related to
BOD5 : mg/l
GLP :

Remark : In this examination of structural features associated with biodegradation of chemicals a BOD5 value of 43% ThOD was reported for 2-pentanol, 4-methyl using an acclimated innoculum.
Reliability : (4) not assignable
08.12.2005 (32)

COD
Method : other: APHA standard methods for examination of water and wastewater
Year : 1971
COD : = 2640 mg/g substance
GLP : no data

Reliability : (2) valid with restrictions
08.12.2005 (36)

3.7 BIOACCUMULATION

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	**other: static renewal**
Species	:	Oncorhynchus mykiss (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
NOEC	:	= 105
LC50	:	= 359 measured/nominal
Limit test	:	no
Analytical monitoring	:	yes
Method	:	other: OECD 203; EEC 92/69/EEC, C.1; TSCA 40 CFR 797.1440
Year	:	2003
GLP	:	yes
Test substance	:	other TS

Test substance : Methyl isobutyl carbinol; Lot No. AA0155V178 (received from Union Carbide Corp., Texas City, TX; 99.9%.

Method : A 96-hour static probe study was conducted at nominal concentrations of 0, 31.3, 62.5, 125, 250, 500 and 1000 mg/L (10 fish/concentration). All fish died at 500 and 1000 mg/L. No mortality was observed at or below 250 mg/L. Due to variability in the measured concentrations of the test substance between days 2 and 4 of the study, the definitive study was conducted under static renewal conditions at nominal concentrations of 105, 150, 214, 306, 438, and 625 mg/L.

The definitive test used a total of 10 fish (5 fish per replicate, in each of two replicates) exposed to each test concentration, as well as a control (100% dilution water). Mortality (no response to touching of the caudal peduncle and no opercular movement) and sublethal effects (e.g., erratic swimming) were recorded at 24, 48, 72 and 96 hours, and any dead fish were removed. Behavioral and gross pathological effects were recorded. The following summarizes the test conditions

Parameter	Condition
Test type	Static renewal
Species	Oncorhynchus mykiss
Supplier	Thomas Fish Co., Anderson, CA
Test duration	96 hours
Temperature	15 ± 2°C
Light cycle	16-hour light/8-hour dark
Feeding prior to test (Aquatic Diet Number 1)	Standard lab diet
Feeding regime	None (during preceding 48 hour and during testing)
Test chamber	12 L glass beakers
Water volume	10.0 L
Acclimation / Health	14-day acclimation < 5% mortality in 7 days prior to test.
Age/wt of test organisms	Juvenile (4.3 ± 0.3 cm; 0.694 ± 0.160 g)
Definitive test concentrations	0, 105, 150, 214, 306, 438, and 625 mg/L
No. replicate /concentration	2
Number of fish per replicate	5

Aeration Not required
(>=60% DO maintained)
Dilution water Laboratory
Dilution Water (LDW):

Original source Lake Huron
Renewal Day 0 and ~48 hours

Statistical analyses: The U.S. EPA Trimmed Spearman-Karber (TSK) Program, Version 1.5 was used to calculate the LC50 values and corresponding percent trim values. This method was used because of the limited test concentrations resulting in mortality between 0 and 100% that would allow for use of the preferred probit analyses.

Analytical: Test concentrations were analyzed on days 0, 2 and 4 using a gas chromatography/flame ionization detection (GC/FID) method and external standard quantitation.

Test condition : Species: O. mykiss
Age: Juvenile
Weight: 0.694 ± 0.160 g (end of study)
Length: 4.3 ± 0.3 cm
Loading: < 1 g/L
Test medium: Laboratory Dilution Water
Water quality parameters as measured during the test):
Temperature = 14.0 - 15.7 degrees C (Days 0, 1, 2, 3, 4);
Dissolved oxygen = 6.2 - 11.4 mg/L (Days 0, 1, 2, 3, 4);
pH = 7.1 - 7.8 (Days 0, 1, 2, 3, 4);

Total hardness
Control 60, 62 mg/L CaCO3;
306 and 625 mg/L 70, 62 mg/L CaCO3
Total alkalinity
Control 43, 36 mg/L CaCO3;
306 and 625 mg/L 40, 41 mg/L CaCO3
Conductivity
Control 173, 187 umho/cm
306 and 625 mg/L 172, 174 umho/cm

Result : Analytical Results (in mg/L):

Nominal Conc. Corrected (mg/L)	Hours 0	48	48	96
Averages		Spent	Renewed	
Control	<LOQ	<LOQ	<LOQ	<LOQ	<LOQ
105	98.6	90.8	94.6	98.1	95.5
(91.0% of nominal)					
150	152	137	133	141	141
(94.0% of nominal)					
214	198	194	198	188	195
(91.1% of nominal)					
306	306	278	279	287	288
(94.1% of nominal)					
438	474	421			
448 (102% of nominal)					

625 655 575
615 (98.4% of nominal)

LOQ = Limit of quantitation = 11.4 mg/L

Cumulative Mortality (total number of fish in each group = 10):

Concentration (mg/L)*	Number of deaths Time (hours) 24	48	72	96
0	0	0	0	0
95.5	0	0	0	0
141	0	0	0	0
195	0	0	0	0
288	0	0	0	0
448	10	10	10	10
615	10	10	10	10

Mean measured concentration

Sublethal effects including partial loss of equilibrium, hyperactivity, and lethargy were noted at 141 mg/L and above.

Number of fish with effects (total no. of fish in each group = 10):

Concentration (mg/L)*	Time (hours) 24	48	72	96
0	0	0	0	0
95.5	0	0	0	0
141	0	0	1	1
195	2	3	1	1
288	4	5	5	6
448	10	10	10	10
615	10	10	10	10

*Mean measured concentration

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
08.12.2005 (28)

Type : **static**
Species : Carassius auratus (Fish, fresh water)
Exposure period : 24 hour(s)
Unit : mg/l
LC50 : = 360
Limit test :
Analytical monitoring : yes
Method : other
Year : 1979
GLP : yes
Test substance : other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%

Method : Goldfish (Carassius auratus) of uniform length (6.2 ± 0.7 cm) and weight (3.3 ± 1.0 g) were used. The test substance

was tested at a series of concentrations. Six fish were exposed at 20 ± 1 ºC in 25 l of solution contained in all-glass tanks. The duration of the test was 24 hours because the volatility of the MIBC prohibited adequate aeration (oxygen concentration maintained at > 4 mg/l)for longer periods without loss of more than 10% of the test substance. The concentration of the MIBC was determined and after the test. If the pH of the test solution was outside of the range 6 to 8, it was adjusted to 7.0 with NaOH or H2SO4. Solutions were made in tap water with the following characteristics (all units are mg/l): Cl- = 65; NO2- = 0; NO3- = 4; SO4- = 35; PO4- = 0.15; HCO3- = 25; SiO2 = 25; NH4+ = 0; Fe = 0.05; Mn = 0; Ca2+ = 100; Mg 2+ = 8; alkali as Na+ = 30 and pH = 7.8. The LC50 value was obtained by interpolation from a graph of logarithm of the concentration versus the percentage mortality.

Remark : Test method: APHA np. 231.
Reliability : (3) invalid
The exposure period was only 24 hours long.

08.12.2005 (6)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : semistatic
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
NOEC : = 288 measured/nominal
EC50 : = 337 calculated
Analytical monitoring : yes
Method : other: OECD 202; Directive 92/69/EEC, C.2.; TSCA 40 CFR 797.1300
Year : 2003
GLP : yes
Test substance : other TS

Test substance : Methyl isobutyl carbinol; Lot No. AA0155V178 (received from Union Carbide Corp., Texas City, TX; 99.9%
Method : A 48-hour static probe study was conducted at nominal concentrations of 0, 31.3, 62.5, 125, 250, 500 and 1000 mg/L (10 daphnia/concentration). All daphnia were immobile at 500 and 1000 mg/L at 24 and 48 hours. No immobility was observed at or below 250 mg/L. Due to reduction in the measured concentrations of the test substance on day 2 of the study (as low as 65% of nominal), the definitive study was conducted under static renewal conditions at nominal concentrations of 105, 150, 214, 306, 438, and 625 mg/L.

The definitive test used a total of 20 daphnia (10 daphnia per replicate, in each of two replicates) exposed to each test concentration, as well as a control (100% dilution water). Daphnia were impartially added to each test vessel within 30 minutes of initial test solution sampling. Immobility (inability to swim with in 15 seconds after gentle agitation of the test container) were recorded at 24 and 48 hours. Daphnia were not fed during the test. The following summarizes the test conditions

Parameter	Condition
Test type	Static renewal

Species	Daphnia magna Straus
Supplier	Originally from Aquatic Biosystems, Fort Collins, CO
Test duration	48 hours
Temperature	20 ± 2°C
Light cycle	16-hour light/8-hour dark
Illumination	2050 ± 350 lux (cool-white fluorescent)
Feeding prior to test	Mixture of algae and yeast-ceraphyll trout
Feeding regime during testing)	Five times weekly before the test; None
Test chamber	250 ml glass beakers
Water volume	200 ml
Age of test organisms	Instars; < 24 hours old
Definitive test concentrations	0, 105, 150, 214, 306, 438, and 625 mg/L
No. replicate /concentration	2
Number of daphnia per replicate	10
Dilution water	Adjusted (for hardness) Laboratory

Dilution Water (ALDW)

Original source: Lake Huron
Renewal Day 0 and ~24 hours

Statistical analyses: An insufficient biological response (variable, non-linear, and insufficient immobility at the highest dose level) was observed following 24 hours of exposure. Therefore the 24-hour EC50 was empirically determined and conservatively estimated that it would be no less than the 48-hour EC50 value. The U.S. EPA Trimmed Spearman-Karber (TSK) Program, Version 1.5 was used to calculate the 48-hour LC50 values and corresponding percent trim values. This method was used because of the limited biological response that did not allow for use of the preferred probit analyses.

Analytical: Test concentrations were analyzed at 0, 24 and 48 hours using a gas chromatography/flame ionization detection (GC/FID) method and external standard quantitation.

Test condition : Species: D. magna
Age: < 24 hours
Test medium: Adjusted (for hardness) Laboratory Dilution Water
Water quality parameters as measured during the test):
Temperature = 19.9 - 20.9 degrees C (Days 0, 1, 2);
Dissolved oxygen = 8.2 - 9.9 mg/L (Days 0, 1, 2);
pH = 7.3 - 7.6 (Days 0, 1, 2);
residual chlorine was <10 ppb (limit of detection).

Total hardness	
Control	148, 150 mg/L CaCO3;
625 mg/L	148, 146 mg/L CaCO3
Total alkalinity	
Control	35, 36 mg/L CaCO3;
625 mg/L	38, 38 mg/L CaCO3
Conductivity	
Control	391, 391 umho/cm

625 mg/L 393, 392 umho/cm

Result : Analytical Results (in mg/L):

Nominal Conc. Corrected (mg/L)	Hours 0	24	24	48
Averages		Spent	Renewed	
Control	<LOQ	<LOQ	<LOQ	<LOQ
105	114	89.4	93.6	89.2	96.6
(92.0% of nominal)				
150	160	116	148	126	138
(92.0% of nominal)				
214	223	181	208	194	202
(94.4% of nominal)				
306	344	241	286	280	288
(94.1% of nominal)				
438	469	328	392	323	378
(86.3% of nominal)				
625	672	230	610	413	481
(77.0% of nominal)				

LOQ = Limit of quantitation = 10.5 mg/L

All immobility following 24 hours came from one replicate vessel in each of the affected concentrations and was reflective of the variability observed in the measured concentrations of the spent solutions at 14 hours [measured concentrations of 281 and 179 mg/L for the 625 mg/L (nominal) concentration and 400 and 256 mg/L for the 438 mg/L (nominal) solutions].

Cumulative Immobility (total number of daphnia in each group = 20):

Concentration (mg/L)*	Number Immobile Time (hours) 24	48
0	0	0
96.6	0	1**
138	0	0
202	0	0
288	0	0
378	10	18
481	2	19

*Mean measured concentration
**Immobility considered unrelated to treatment and not included in EC50

Reliability : (1) valid without restriction Guideline study
Guideline study

Flag : Critical study for SIDS endpoint
08.12.2005 (27)

Type :
Species : Daphnia magna (Crustacea)
Exposure period : 24 hour(s)
Unit : mg/l
EC0 : < 80

EC50	:	= 283.5
EC100	:	= 730
Analytical monitoring	:	no data
Method	:	other: ISO 6341
Year	:	1988
GLP	:	no data
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Test condition	:	The daphnia were maintained in a synthetique medium and feed algae (Scenedesmus subspicatus). The pH was 8.18, and the oxygen concentration was 8.7 mg/l at the lowest concentration producing 100% immobilisation. The EC50 for potassium dichromate (positive control) = 0.95 mg/l and the negative controls showed a 5% immobilisation rate.
Reliability	:	(3) invalid The exposure period was only 24 hours. The exposure period was only 24 hours.

09.12.2005 (1)

Type	:	static
Species	:	Artemia salina (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
LC50	:	= 370
Analytical monitoring	:	no data
Method	:	other
Year	:	1974
GLP	:	no data
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Remark	:	Method as described in reference.
Reliability	:	(3) invalid The exposure period was only 24 hours. The exposure period was only 24 hours.

08.12.2005 (36)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	**other algae: Pseudokirchneriella subcapitata**
Endpoint	:	other: biomass and growth rate
Exposure period	:	96 hour(s)
Unit	:	mg/l
Limit test	:	no
Analytical monitoring	:	yes
Method	:	other: OECD 201; Directive 92/69/EEC, C.3.; TSCA 40 CFR 797.1500
Year	:	2003
GLP	:	yes
Test substance	:	other TS
Test substance	:	Methyl isobutyl carbinol; Lot No. AA0155V178 (received from Union Carbide Corp., Texas City, TX; 99.9%
Method	:	A 96-hour probe study was conducted at nominal concentrations of 0, 8.00, 40.0, 200, and 1000 mg/L (10 daphnia/concentration). Percent inhibition compared to controls was 3, 7, 33 and 99%, respectively. Based on these results, the definitive study was conducted at nominal concentrations of 0, 31.3, 62.5, 125, 250, 500 and 1000 mg/L.

The definitive test used an inoculum of approximately 10,000 cells/ml in each replicate (4 replicates/concentration). The algal inoculum was prepared from a 3-day old stock culture. The growth rate and biomass were determined at 72 and 96 hours.

Parameter	Condition
Test species	Pseudokirchneriella subcapitata (formerly Selenastrum capricornutum
Test duration	96 hours
Temperature	24.5-24.6°C
pH at initiation	6.8 - 7.0
pH at termination	7.1 - 9.5 (with algae); 6.8 - 7.0 (blank)
Illumination	7283 ± 422 lux
Test chamber	250 ml Erlenmeyer flasks with Shimadzu closures
Water volume	100 ml
Supplier	Originally from U. Toronto Algal Collection
Age of test organisms	3-day old stock culture
Definitive test concentrations	0, 31.3, 62.5, 125, 250, 500 and 1000 mg/L
No. replicate /concentration	4 (3 with algae, 1 without algae)
No. replicate/control	7 (6 with algae, 1 without algae)
Inoculum	10,000 cells/ml
Growth medium	EPA Algal Assay Bottle Test Medium

Statistical analyses: The EC25 and EC50 values for cell density were determined by a least squares linear regression of cell density against the log of the concentration at 72 and 96 hours for test concentrations where a clear dose-relationship was observed. The ErC50 was calculated by regressing the percent reduction in mean specific growth rate for each dose group compared to the control group against the natural logarithm of the concentrations for the 0- to 72-hour and 0- to 9-hour exposure periods where a clear dose-response relationship was observed. The EbC50 value was calculated by regression of the differences in area under the growth curves for each dose group compared to the control against the log of the concentrations for 72 and 96 hours where a clear dose-response relationship was observed. Prior to evaluation of the NOEC, the data were tested for normality using the Shapiro-Wilk's test and for homogeneity of variance using the Bartlett's Test. To meet the assumptions of normality, and/or homogeneity of variance, the 72-hour cell density and 96-hour biomass data were log transformed and the NOECs for cell density, growth rate, and biomass were calculated using the analysis of variance and Dunnett's test.

Analytical: Test concentrations were analyzed at 0 and 4 days using a gas chromatography/flame ionization detection (GC/FID) method and external standard quantitation.

Result : Analytical Results (in mg/L):

Nominal Conc.

(mg/L)	Day 0 Mean*	Day 4 Pooled/assays**	Day 4 Blank (no Algae)	(% of nominal)
Control	<LOQ	<LOQ	<LOQ	<LOQ
31.3	24.2	6.81	6.18	15.5 (49.5%)
62.5	65.3	17.8	18.6	41.6 (66.6%)
125	123	27.9	32.3	75.5 (60.4%)
250	246	63.0	68.0	155 (62.0%)
500	521	130	114	326 (65.2%)
1000	1007	241	287	624 (62.4%)

LOQ = Limit of quantitation = 2.3 mg/L
*Mean of the Day 0 and Day 4 samples
**Samples from 3 test vessels/concentration were pooled

The following table provides a summary of cell density, area under growth curves and growth rate for the definitive test:

Nominal Conc. (mg/L)	Average Cell Counts (x 10,000) 24 h	48 h	72 h	96 h	Inhibition of Biomass (%)
0	6.0	35	146	410	
31.3	5.8	33	148	400	2
62.5	5.3	31	134	371	10
125	5.3	25	123	344*	16
250	4.0	15	75*	238*	42
500	1.1	3.2	10*	45*	89
1000	0.9	2.4	1.5*	2.2	99

* = Significantly different from controls; p = 0.05

The following values were calculated or estimated:

Endpoint	Mean Measured MIBC (mg/L)
72-Hour Cell Density	
EC25	76.3
EC50	147
NOEC	75.5
72-Hour Specific Growth Rate	
ErC50	264
NOEC	75.5
72-Hour Biomass	
EbC50	139
NOEC	41.6
96-Hour Cell Density	
EC25	77.8
EC50	153
NOEC	41.6
96-Hour Specific Growth Rate	
ErC50	334
NOEC	75.5
96-Hour Biomass	
EbC50	147
NOEC	75.5

Microscopic evaluation of the cells at the end of the incubation period revealed no morphological abnormalities.

Reliability : (1) valid without restriction
Guideline study
Flag : Critical study for SIDS endpoint
08.12.2005 (18)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

Memo : Toxicity to larval stages of the clawed toad Xenopus laevis

Test substance : Report did not define MIBC purity; assumed to have used the commercial grade of > 98%

Test condition : Groups of 10 3-4 week old larvae were exposed in 1 litre of Dutch Standard Water in a covered aquarium for 48 hours at a temperature of 20C. Nominal concentrations of test substance were added to the aquaria at the beginning of the experiment to provide 5 concentration levels. There was no test replication and no analysis of test concentrations.

Result : The 48 hour LC50 for 4-methyl 2-pentanol in the clawed toad Xenopus laevis was 656 mg/l.

08.12.2005 (11)

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

In Vitro/in vivo	:	In vivo
Type	:	Toxicokinetics
Species	:	rat
Number of animals		
Males	:	26
Females	:	
Doses		
Males	:	5 mmoles/kg (approximately 500 mg/kg) of MIBC or MIBK
Females	:	
Vehicle	:	other: corn oil
Route of administration	:	gavage
Exposure time	:	
Product type guidance	:	
Decision on results on acute tox. tests	:	
Adverse effects on prolonged exposure	:	
Half-lives	:	1st: 2.26 hr 2nd: 3rd:
Toxic behaviour	:	
Deg. product	:	
Method	:	
Year	:	2002
GLP	:	yes
Test substance	:	other TS: See TS free text field

Test substance : Methyl isobutyl carbinol (MIBC; CAS RN 108-11-2; 99.7%) and methyl isobutyl ketone (MIBK; CAS RN 108-10-1; 99.9%)

Method : Treatment Procedure

MIBC and MIBK were administered as a solution in corn oil [2.5 mmole/ml] at a dose of 5 mmoles/kg [approximately 500 mg/kg] by oral gavage. Rats were deprived of food for approximately 14 hr before dosing, and the food was re-offered 4 hr after dosing.

Analytical Methods

Blood samples [1 ml] were taken by orbital bleeding from lightly anesthetized rats at 0.125, 0.25, 0.5, 0.75, 1, 1.5, 3, 4.5, 6, 9 and 12 hr after dosing. Three samples were withdrawn from each rat at spaced intervals (e.g. at the 0.125, 0.75, and 3 hour sampling periods). Plasma was stored at -20°C until analyzed by gas chromatography [GC]. MIBC, MIBK and HMP in plasma were determined by gas chromatography-mass spectroscopy [GCMS].

Quantification

Calibration curves for MIBC, MIBK and HMP were linear up to 10 ug/mL plasma. Replicates of calculated values for analytes in plasma were within 15% [20% at the limit of quantitation] or samples were reanalyzed. Preliminary studies indicated that each analyte was quantitatively and reproducibly recovered from spiked blood samples. Pharmacokinetic analysis was performed by a non-compartmental approach using Top computer software, version 2.

Result : No mortality nor clinical signs of toxicity were observed in any of the animals. The only materials detected in the plasma were MIBC, MIBK and 4-hydroxymethyl-4-methyl-2-pentanone (HMP).

MIBK was readily absorbed after oral administration, the Cmax for MIBK occurring at 0.25 hr. The major material in the blood was the metabolite, HMP, with a Cmax of 2.03 mmole/L being reached at 9 hr. MIBC was a very minor component [<0.1% of the total AUC]. MIBC was similarly readily absorbed, the Cmax for MIBC occurring at 0.5 hr. The Cmax for the metabolite MIBK occurred at 1.5 hr. As with the MIBK dose, the major material in the plasma was HMP, the Cmax of 1.64 mmole/L again occurring at 9 hr. MIBC was a minor component [6% of the total AUC] of the materials in the blood after administration of MIBC. Levels of MIBK [20 and 17% of the total AUC] and HMP [79 and 77%], were similar after dosing with MIBK or MIBC respectively.

Approximately 73% of the MIBC dose was metabolized to MIBK and HMP. This value was considered to be a lower estimate. It is likely that some MIBC is not absorbed or is rapidly excreted as a glucuronide or sulfate conjugate in the urine after oral bolus administration. This would decrease the amount available for metabolism to MIBK and HMP in the blood, as compared to that available after MIBK.

The metabolism sheme for MIBC is shown in Figure 1. The plots of plasma concentration versus time for the three compounds, MIBC, MIBK, and HMP, following a single oral dose of MIBC or MIBK are shown in Figures 2 and 3, respectively. Selected pharmacokinetic parameters (non-compartmental) are listed in Table 1.

Attached document : Figure 1.bmp
Figure 2.bmp
Figure 3.bmp
Table 1.bmp

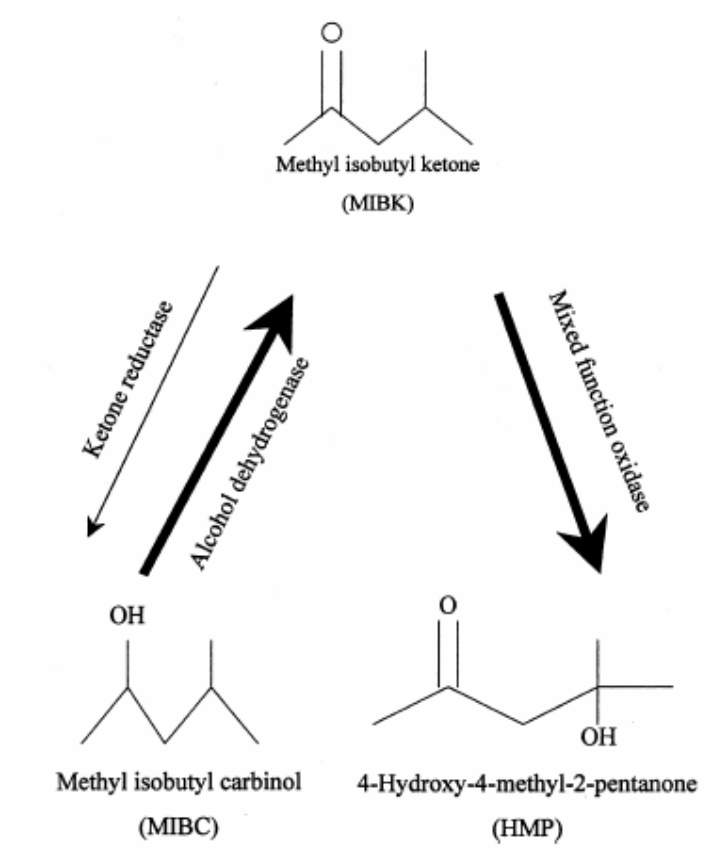

Figure 1 Metabolic Scheme for MIBC and MIBK

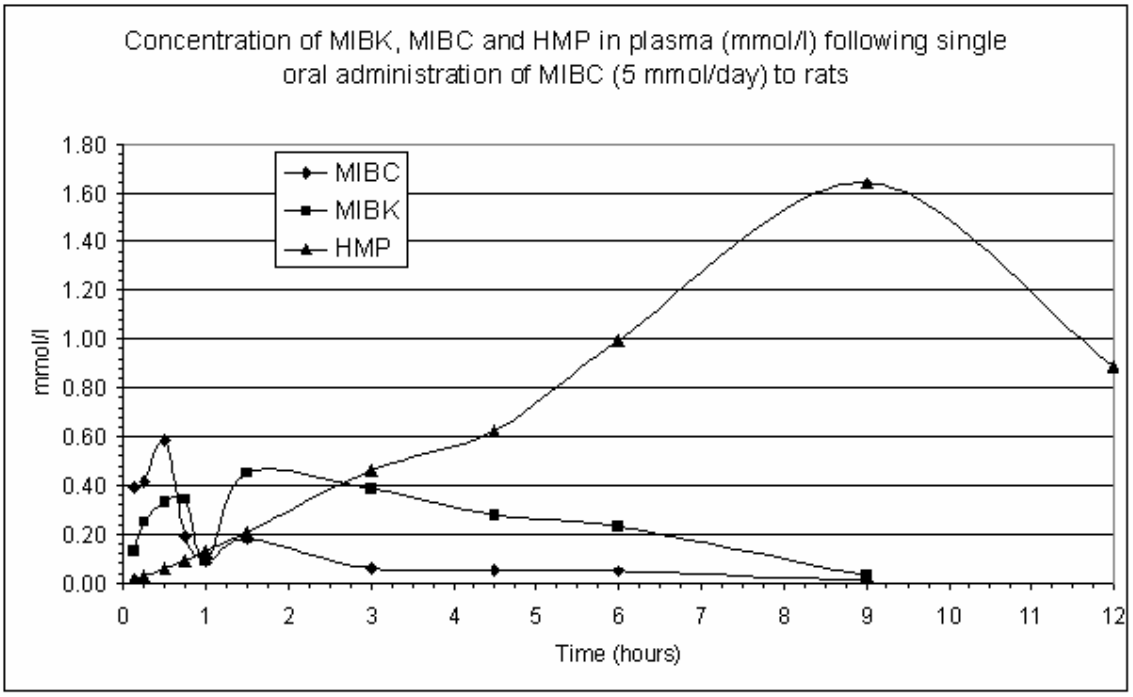

Figure 2 Metabolism and Clearance of an MIBC Dose

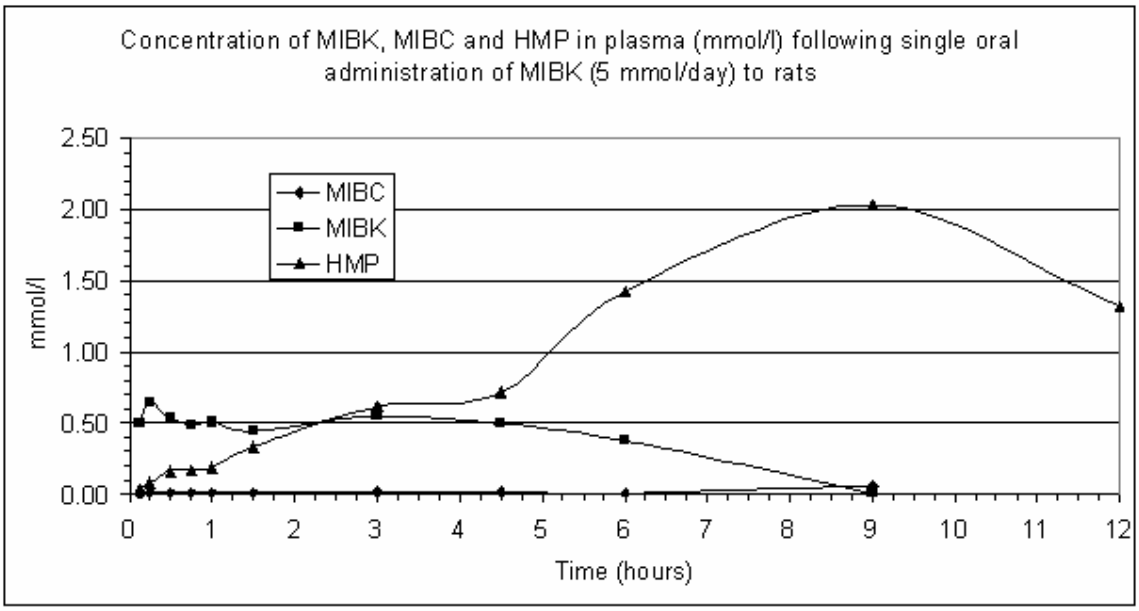

Figure 3 Metabolism and Clearance of an MIBK Dose

Table 1: Pharmacokinetic Parameters after Oral Administration of MIBK or MIBC

Test Substance	Analyte	C_{max} [mmole/ L]	Time of C_{max} [hr]	Half Life [hr]	$AUC_{0\text{-}12hr}$ [mmole*hr/L]	% Total AUC
MIBK	MIBC	0.014	NA	4.657	0.089	0.05
Total AUC	MIBK	0.644	0.25	2.529	3.558	20
	HMP	2.030	9	4.831	13.756	79
					17.436	
MIBC	MIBC	0.588	0.5	2.256	0.819	6
Total AUC	MIBK	0.450	1.5	1.571	2.268	17
	HMP	1.64	9	3.377	10.408	77
					13.495	

Conclusion : These results suggest that any systemic toxicity of MIBC is not likely to be mediated by MIBC itself, but to the metabolites MIBK or HMP.

Remark : Exposure time = single administration

Reliability : (1) valid without restriction
16.12.2005 (15) (17)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rabbit
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle : water
Route of administration : gavage
Exposure time :
Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method :
Year :
GLP :
Test substance : other TS: See TS free text field

Test substance : Technical grade MIBC, British Drug Houses Ltd.

Method : Three chinchilla rabbits were administered 25 mmole methyl isobutyl carbinol (approximately 850 mg/kg bw) in water by gavage. The urinary excretion of glucuronic acid was measured for 24 hr following exposure.

Result : Following gavage, the amount of glucuronic acid in the urine increased by an average of 33.7%, expressed as % of dose (36.5, 37.3, 27.8% of dose for the three rabbits, respectively). There was evidence for the presence of a small quantity of a methyl ketone in the urine (presumed to be isobutyl methyl ketone). Ethanol/ether extraction of urine from four rabbits which had received 3 ml, yielded a glucuronide gum which was characterised as triacetyl beta-4-methylpentyl-2-D-glucuronide, methyl ester.
The metabolism of methyl isobutyl carbinol appears to follow two pathways, oxidation to the corresponding ketone and glucuronide conjugation of the unoxidised portion.

Reliability : (2) valid with restrictions
08.12.2005 (23)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : mouse
Number of animals
Males : 8
Females : 0
Doses
Males : 2.5 mmol/kg bw (approximately 255 mg/kg bw)
Females :
Vehicle : other: corn oil
Route of administration : i.p.
Exposure time :

Product type guidance :
Decision on results on acute tox. tests :
Adverse effects on prolonged exposure :
Half-lives : 1st:
2nd:
3rd:
Toxic behaviour :
Deg. product :
Method :
Year :
GLP :
Test substance : other TS: See TS free text fiel

Test substance : MIBC, Aldrich Chemical Co., Montreal, Quebec; purity not specified.

Method : A group of eight male CD-1 mice were given a single intraperitoneal injection of 2.5 mmol/kg bw (approximately 255 mg/kg bw) in corn oil. Blood and brain samples were collected 15, 30, 60 and 90 min after treatment and assessed for the presence of metabolites.
Result : Unchanged methyl isobutyl carbinol, as well as methyl isobutyl ketone and 4-hydroxy-4-methyl-2-pentanone were detected in both the blood and brain samples of treated mice.
Reliability : (2) valid with restrictions
08.12.2005 (16)

In Vitro/in vivo : In vivo
Type : Metabolism
Species : rat
Number of animals
Males :
Females :
Doses
Males :
Females :
Vehicle :
Method :
Year :
GLP :
Test substance : other TS: See TS free text field

Test substance : Methyl isobutyl ketone (MIBK, CAS RN 108-10-1; 99.5%)

Method : Rats were treated orally with 1.5, 3, or 6 mmol/kg of MIBK or via inhalation for 4 hours/day to concentrations of 100, 400 or 600 ppm for 3 days. Plasma, liver and lung were analyzed for MIBK and its metabolites.
Result : Blood concentrations following oral dosing were 5.3, 8.4, and 16.1 ug/ml and for inhalation exposure they were 5.0, 8.1, and 14.3 ug/ml. Plasma MIBK and 4-hydroxy-4-methyl-2-pentanone (HMP) [identified in the publication as 4-hydroxy MIBK] were found to increase in a dose-related manner with the administered dose of MIBK regardless of dose route. Plasma concentrations of methyl isobutyl carbinol (MIBC) could not be detected following oral dosing but MIBC concentrations of 4.0 and 4.8 ug/ml after 400 and 600 ppm inhalation exposure were determined. No other metabolites were identified.
08.12.2005 (13)

In Vitro/in vivo	:	In vivo
Type	:	Metabolism
Species	:	guinea pig
Number of animals		
Males	:	
Females	:	
Doses		
Males	:	
Females	:	
Vehicle	:	
Method	:	
Year	:	
GLP	:	
Test substance	:	other TS: See TS free text field
Test substance	:	Methyl isobutyl ketone (MIBK, CAS RN 108-10-1; >97%)
Method	:	Guinea pigs were given a single 450 mg/k i.p. dose of MIBK and metabolites in serum were identified.
Result	:	MIBK was converted primarily to 4-hydroxy-4-methyl-2-penatone (HMP). A very low concentration of methyl isobutyl carbinol (MIBC) was detected that could not be quantified.

22.08.2002

5.1.1 ACUTE ORAL TOXICITY

Type	:	**other: range finding LD50**
Value	:	= 2260 - 2970 mg/kg bw
Species	:	rat
Strain	:	Sherman
Sex	:	male
Number of animals	:	
Vehicle	:	no data
Doses	:	
Method	:	other
Year	:	1951
GLP	:	no
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	General procedure: Groups of six male rats weighing from 90 to 120 grams were given single dose by gavage of the test chemical at 10, 1, 0.1 etc. g/kg. The selection of the dose was based on previous experience with other similar chemicals. The samples were diluted or suspended in water. One week later, six additional rats were dosed and the procedure continued until two doses differing by a multiple of ten were found, one of which caused death within 14 days. The LD50 was estimated based on probit analysis.
Remark	:	LD50 value = 2590 mg/kg bw.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

08.12.2005 (43) (44)

Type	:	**LD50**
Value	:	810 - 1210 mg/kg bw
Species	:	mouse

Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	Groups of five fasted mice were administered methyl isobutyl carbinol as a temporary emulsion in 1% Tergitol by stomach tube. The total volume given was 0.2 ml/g bw and the dose levels were 1.0-2.0 ml/kg bw (810-1610 mg/kg bw).
Result	:	Anaesthesia, as determined by loss of righting reflex, was observed in 2/5 mice given 810 mg/kg bw and in all mice exposed to 1210 and 1610 mg/kg bw. One animal receiving 810 mg/kg bw died and most of those given 1210 and 1610 mg/kg bw died. Autopsy revealed hyperemia of the stomach wall and duodenum. No histopathology was carried out.
Reliability	:	(4) not assignable

08.12.2005 (29) (39)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	**LC50**
Value	:	> 19 mg/l
Species	:	rat
Strain	:	Sherman
Sex	:	no data
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	2 hour(s)
Method	:	other
Year	:	1951
GLP	:	no
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	General Procedure: Groups of six male rats were exposed to a flowing stream of air substantially saturated with vapors of the test material prepared by passing the air through a fritted disc bubbler at room tempature for periods of time falling in a geometric series with a constant ratio of 2 to 8 hours. The exposures were repeated on additional groups of rats until an exposure time resulting in death was obtained. Groups of six Sherman rats were exposed to saturated vapours (about 19 mg/l) for increasing exposure times (up to 2 hours), or to 2000 ppm (8.4 mg/l) for 8 hours.
Result	:	Following exposure to the saturated vapours, the maximum exposure time without mortality was 2 hours. Five of the six rats exposed to 8.4 mg/l for 8 hours died within the 14-day observation period.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

08.12.2005 (43) (44)

Type	:	**LC50**
Value	:	> 16 mg/l
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	20
Vehicle	:	
Doses	:	
Exposure time	:	4 hour(s)
Method	:	other
Year	:	
GLP	:	no
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	Groups of five male and five female Wistar rats were exposed to 10 or 16 mg/l (2360 or 3776 ppm respectively) for 4 hours. The animals were observed for clinical signs of toxicity for the first 30 min of exposure and at 15 min intervals thereafter. Following exposure, the animals were observed for 14 days and those surviving subjected to a gross post mortem examination. No histopathological examination was conducted.
Result	:	All animals were anaesthetised within the first hour of exposure, all at 10 mg/l regained consciousness within 30 min of cessation of exposure. At 16 mg/l, all except one female regained consciousness within 2 hours, this female died. All other exposed animals survived and no signs of toxicity were observed over the 14 day period.
Reliability	:	(2) valid with restrictions The study was not conducted to GLP but was subject to QA.
Flag	:	Critical study for SIDS endpoint

08.12.2005 (4)

Type	:	**other: acute toxicity**
Value	:	2000 ppm
Species	:	rat
Strain	:	Sherman
Sex	:	no data
Number of animals	:	6
Vehicle	:	
Doses	:	
Exposure time	:	4 hour(s)
Method	:	other
Year	:	1949
GLP	:	no
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	Six male or female Sherman rats were exposed to 2000 ppm (about 8.4 mg/l) for 4 hours.
Result	:	Two to four of the six rats died.
Remark	:	No analytical check was made on the concentration of the vapor. The concentration was based upon empirical calculation.
Reliability	:	(3) invalid

08.12.2005 (9)

Type	:	**other: acute toxicity**
Value	:	> 20 mg/l

Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	40
Vehicle	:	
Doses	:	
Exposure time	:	8.5 hour(s)
Method	:	other
Year	:	
GLP	:	no
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	Groups of ten mice were exposed to saturated vapours (approximately 20 mg/l or 4720 ppm) for 4, 8.5, 10 or 15 hours.
Result	:	All mice showed signs of respiratory tract irritation within 5 min, somnolence within 1 hr and ataxia and hind-limd paralysis as the exposure continued. Anaesthesia was evident in seven of the mice exposed for 4 hr and in all animals exposed for 8.5 hr or longer, although there were no mortalities at the lower two exposure periods. All surviving mice returned to normal at the end of the 10 day observation period. Six and eight of the mice exposed for 10 and 15 hr respectively died during the exposure period. Gross pathological examination revealed congestion of the lungs with haemorrhage and pneumonia in some animals. The liver and kidney also appeared congested but to a lesser extent. There was no microscopic examination.
Reliability	:	(4) not assignable

08.12.2005 (29) (39) (40)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	**LD50**
Value	:	= 3.56 ml/kg bw
Species	:	rabbit
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	
Doses	:	
Method	:	other
Year	:	1951
GLP	:	no
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	General procedure: Undiluted test material was applied to the clipped skin of the rabbit trunk. The dose was retained under a flexible film of rubber, vinlyl plastic or similar material for 24 hours. Undiluted methyl isobutyl carbinol was applied under covered contact to groups of six rabbits (sex unspecified) for 24 hr. The animals were observed for 14 days.
Result	:	The LD50 was found to be 3.56 ml/kg bw (2870 mg/kg bw) with a standard deviation of 2.72-4.76 ml/kg bw (2190-3840 mg/kg bw).
Reliability	:	(2) valid with restrictions

Flag : Critical study for SIDS endpoint
08.12.2005 (43) (44)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type	:	**LD50**
Value	:	= 812 mg/kg bw
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	
Doses	:	
Route of admin.	:	i.p.
Exposure time	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Remark	:	No further details are available from the citing reference (NIOSH, 1994) and the study could not be identified within Shell.
Reliability	:	(4) not assignable

08.12.2005 (33) (38)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	5
Vehicle	:	
PDII	:	
Result	:	slightly irritating
Classification	:	not irritating
Method	:	Draize Test
Year	:	1944
GLP	:	no
Test substance	:	other TS:Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	Neat methyl isobutyl carbinol was applied under covered contact to the skin of 5 rabbits for 24 hours. On removal of the patch, the reaction seen was scored similarly to that of Draize et al. 1944.
Result	:	Methyl isobutyl carbinol caused an irritation grade 2 reaction, this being equivalent to a trace capillary injection.
Reliability	:	(2) valid with restrictions

08.12.2005 (12) (44)

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Open
Exposure time	:	

Number of animals	:	3
Vehicle	:	
PDII	:	
Result	:	slightly irritating
Classification	:	not irritating
Method	:	other
Year	:	
GLP	:	no
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	The neat material was applied, uncovered, to the skin of three rabbits for a single exposure period of 15 min (10 ml) or for five repeated exposure periods of 5-12 hr over a 15-21 day period.
Result	:	Following single exposure, there was immediate slight erythema progressing to moderate erythema with drying of the skin. No systemic effects were seen. Repeated application resulted in severe drying of the skin with some sloughing and cracking.
Reliability	:	(4) not assignable

08.12.2005 (29) (39) (40)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.02 ml
Exposure time	:	24 hour(s)
Comment	:	not rinsed
Number of animals	:	5
Vehicle	:	
Result	:	highly irritating
Classification	:	irritating
Method	:	other: Carpenter & Smyth
Year	:	1946
GLP	:	no
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Remark	:	Methyl isobutyl carbinol caused an irritation grade 5 reaction when instilled into the eye. A grade 5 reaction is designated when 0.005 ml of the neat material gives a score of up to 5.0 and 0.02 ml of the neat material gives a score of > 5.0; the score of 5.0 representing severe injury with necrosis, visible on fluorescein staining, covering approximately 75 % of the cornea, or more severe necrosis over a smaller area.
Reliability	:	(2) valid with restrictions

08.12.2005 (8) (44)

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure time	:	24 hour(s)
Comment	:	not rinsed
Number of animals	:	3
Vehicle	:	
Result	:	moderately irritating
Classification	:	irritating

Method	:	Draize Test
Year	:	1944
GLP	:	no data
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	Undiluted methyl isobutyl carbinol was instilled into the eye of three rabbits and the reaction was scored after 1, 24 and 72 hr according to the method of Draize et al. 1944.
Result	:	Scores at 1, 24 and 72 hr were 11, 25 and 17 respectively (maximum score 110). Conjunctivitis, oedema and corneal injury were observed but all eyes were grossly normal after 7 days.
Reliability	:	(2) valid with restrictions

09.12.2005 (12) (29) (39) (40)

5.3 SENSITIZATION

Type	:	**Guinea pig maximization test**
Species	:	guinea pig
Concentration	:	1st: Induction 1 % intracutaneous 2nd: Induction undiluted occlusive epicutaneous 3rd: Challenge undiluted occlusive epicutaneous
Number of animals	:	30
Vehicle	:	other: paraffin oil
Result	:	not sensitizing
Classification	:	not sensitizing
Method	:	OECD Guide-line 406 "Skin Sensitization"
Year	:	1997
GLP	:	yes
Test substance	:	other TS:
Test substance	:	Methyl Isobutyl Carbinol: Atofina, batch No. 9609P0519, purity 99.04%
Method	:	Thirty guinea-pigs were allocated to two groups: a control group 1 (five males and five females) and a treated group 2 (ten males and ten females). On day 1, intradermal injections of Freund's complete adjuvant mixed with the test substance (treated group) or the vehicle (control group) were performed in the dorsal region between the shoulders. On day 7, the same region received a topical application of sodium lauryl sulfate in vaseline (10% w/w) in order to induce local irritation. On day 8, this same test site was treated by topical application of the test substance (treated group) or the vehicle (control group) and was covered by an occlusive dressing for 48 hours. On day 22, after a rest period of 12 days, all animals of the treated and control groups were challenged by a topical application of the test substance to the right flank. The left flank served as control and received the vehicle only. Test substance and vehicle were maintained under an occlusive dressing for 24 hours. Skin reactions were evaluated approximately 24 and 48 hours later. Test substance concentrations were as follows: Induction (treated group) -intradermal injections: METHYLISOBUTYLCARBINOL at 1% (w/w) in paraffin oil - topical application: METHYLISOBUTYLCARBINOL undiluted.

Challenge (all groups)
- topical application: METHYLISOBUTYLCARBINOL undiluted.

At the end of the study, animals were killed without examination of internal organs. No skin samples were taken from the challenge application sites.

The sensitivity of the guinea-pigs was checked with a positive sensitizer: 2,4-DINITRO CHLOROBENZENE (DNCB). During the induction period, the positive substance was applied at 0.1% (w/w) (day 1) and 1% (w/w) (day 8). For the challenge application, the DNCB was applied to the right flank at a concentration of 0.5% (w/w).

Result : No clinical signs and no deaths related to treatment were noted during the study. No cutaneous reactions were observed after the challenge application. The sensitivity of the guinea-pigs was satisfactory since 50% of the animals showed a positive reaction with DNCB.

Conclusion : According to the maximization method of Magnusson and Kligman, no cutaneous reactions attributable to the sensitization potential of METHYLISOBUTYLCARBINOL were observed in guinea pigs.

Reliability : (1) valid without restriction

09.12.2005 (14)

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Wistar
Route of admin.	:	inhalation
Exposure period	:	6 weeks
Frequency of treatm.	:	6 hours per day/5 days per week
Post exposure period	:	none
Doses	:	0, 0.211, 0.825, 3.70 mg/l (0, 50.5, 198, 886 ppm)
Control group	:	yes, concurrent no treatment
NOAEL	:	= 3.7 mg/l
NOEL	:	= .825 mg/l
Method	:	other: comparable to OECD Guide-line 407
Year	:	
GLP	:	no
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%

Method : 12 rats/sex/dose were used. The doses equate to 0, 50.5, 198 and 886 ppm respectively. The animals were observed twice daily for changes in general health and behaviour and their body weights measured weekly. At study termination, clinical chemistry and haematology studies and urinalysis were conducted. The brain, heart, kidney, liver, spleen and testes were weighed and tissues from the major organs of all the control-, mid- and top-dose animals, as well as all grossly abnormal tissues, were examined histopathologically. The tissues examined included: mammary glands, lymph nodes, pancreas, stomach, intestine, cecum, spleen, liver, adrenals, kidneys, ovaries, testes, uterus, prostate, seminal vesicles, urinary bladder, thyroid, heart, lungs, nasal cavity larynx, thymus eye and lacrymal gland, salivary

gland, brain, spinal cord, pituitary, tongue, sciatic nerve muscle bone.

Result : There were no deaths, clinical signs of toxicity or effects on the body weights or haematological parameters. Gross and microscopic examination of the organs revealed no significant compound related changes. Urinalysis revealed increased levels of ketone bodies in females at all concentrations and in males at 0.825 mg/l and above and the top concentration, respectively. Plasma alkaline phosphatase was increased in the top-concentration females, as was the kidney weight of males at this same level. Proteinuria was detected in males at the highest concentration, although this
was only determined by a semi-quantitative "Dipstick" method. The values for kidney weight and plasma alkaline phosphatase were:

Concentration (mg/L)	0	0.211	0.825	3.70
Kidney Wt. (g) - Males	2.81	2.91	2.83	3.05*
- Females	1.80	1.78	1.78	1.79
Alk Phos. (i.u.) - Males	118	133	130	131
- Females	78.2	88.7	85.7	91.9*

Statisitcally significant - $P < 0.05$

The NOEC is dictated by the organ weight (kidney) change and and proteinurea in males, and the alkaline phosphatase increase in females at the highest concentration. However, none of these changes were indicative of major adverse toxicological effects.
The authors considered that there was evidence that the ketone bodies might be the result of metabolism of methyl isobutyl carbinol to the corresponding ketone. The presence of protein in the urine is considered evidence of a mild toxic effect at the highest concentration. The method employed was subjective and insufficiently accurate to reliably detect small differences in protein. There were no exposure-related histopathological effects (including kidneys) observed in this study.

The increases in ketone bodies, kidney weight differences and blood chemistry differences were not considered adverse toxicological effects. Although the authors did not define the NOAEC for this study, the Lesser Ketones Manufacturing Association has considered it to be the highest exposure concentration of 3.70 mg/L (886 ppm).

Reliability : (2) valid with restrictions
The study was not conducted to GLP but was subject to QA audit.

Flag : Critical study for SIDS endpoint
08.12.2005 (3)

Type :
Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : inhalation
Exposure period : 14 weeks
Frequency of treatm. : 6 hr/day, 5 days/wk
Post exposure period : None
Doses : 0, 50, 250, 1000 ppm (0.20, 1.02, 4.09 mg/l)

Control group : yes
NOAEL : = 1000 ppm
Method : other: Equivalent to OECD 413
Year : 1987
GLP : yes
Test substance : other TS: Methyl Isobutyl Ketone (CAS RN 108-10-1; >99%)

Test substance : Methyl Isobutyl Ketone (CAS RN 108-10-1; > 99%)
Method : Male and female Fischer 344 rats (14/sex/group) were exposed to atmospheres containing MIBK vapor at 0, 50, 250 or 1000 ppm, 6 hrs/day 5 days/wk for 14 weeks. The control group was exposed to air. Animals were sacrificed the morning after the last dose. In-life observations and measurements included signs of toxicity, ophthalmology, and weekly body weights. Hematology, serum chemistry and urinalysis were performed at necropsy. Complete gross pathological examinations were made at necropsy and the kidneys, heart, liver, lungs, and testes were weighed. The nasal cavity (7 levels), trachea, liver, kidneys, and lungs (4 levels) from all animals were examined histologically. The following tissues were examined from animals in the high exposure and control groups: brain (cerebellum, cerebrum, medulla), spinal cord (two cross- and two longitudinal-sections from each of the following levels: cervical, thoracic, lumbar, sacral), peripheral nerves (sciatic and anterior tibial), eyes, optic nerve, pituitary, thyroid, parathyroid, salivary glands (submaxillary), heart, spleen, pancreas, adrenals, lymph nodes (mesenteric and mandibular), bladder (inflated with formalin), ovaries, uterus, oviducts, vagina, cervix, stomach, small intestine (3 levels), large intestine (3 levels), skeletal muscle (thigh), skin, mammary glands (males and females), bone (sternum), bone marrow, aorta, testes, epididymis, esophagus, thymus, prostate, seminal vesicle, and any gross lesions.

Whole-body exposures were made in glass and stainless steel chambers with a total volume of approximately 4320 l (a subchronic mouse study was conducted simultaneously in the same chambers). Temperature, relative humidity, and airflow were recorded at least four times during each 6-hr exposure. Chamber distribution of MIBK vapor was determined prior to the start of the study and repeated on the highest concentration chamber during exposure. All chambers were analyzed for MIBK concentration twice an hour.

Statistical analyses for continuous variable data were analyzed by Bartlett's test for homogeneity of variance, analysis of variance and Duncan's multiple rang test. When the F value for ANOVA was significant, Duncan's multiple range test was used to denote which groups differed significantly from the controls. If Bartlett's test indicated heterogeneous variance, the F test was employed to compare each exposure group with the air-control group. Student's t-test was used when the F value was not significant. Cochran t-test was used when the F value was significant. Nonparametric data were analyzed by the Kruskal-Wallis or Fisher's exact test. Following identification of significance, the Mann-Whitney U or Wilcoxon two-sample rank test was employed.
Result : The mean analytical chamber concentrations over the course of the study were 50, 252, and 1002 ppm. Body weights were

equivalent to controls for all MIBK exposure concentrations. Changes in hematology, serum chemistry and urinalysis were considered unrelated to treatment or of such minimal magnitude or inconsistent occurrence as to be toxicologically insignificant. Male rats exposed to 1000 ppm MIBK had a slight increase in liver weight and liver to body weight ratio (12.4 vs 11.0 g and 3.5 vs 3.2%, respectively). No gross or microscopic hepatic lesion related to MIBK exposure were observed. The liver weight increase was, therefore, considered of no toxicological relevance. Hyalin droplets within the proximal tubular cells of the kidneys of males exposed to 250 and 1000 ppm MIBK were observed. This finding is consistent with the known binding of MIBK to alpha-2u-globulin and is considered a male-rat specific effect that is not pertinent to human risk assessment. No treatment-related effects were observed in females at any exposure concentration. The NOAEC was considered to be 1000 ppm.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
08.12.2005 (34)

Type :
Species : mouse
Sex : male/female
Strain : B6C3F1
Route of admin. : inhalation
Exposure period : 14 weeks
Frequency of treatm. : 6 hr/day, 5 days/wk
Post exposure period : none
Doses : 0, 50, 250, 1000 ppm (0.20, 1.02, 4.09 mg/l)
Control group : yes
NOAEL : = 1000 ppm
Method : other: Equivalent to OECD 413
Year : 1987
GLP : yes
Test substance : other TS: Methyl Isobutyl Ketone (CAS RN 108-10-1; >99%)

Test substance : Methyl Isobutyl Ketone (CAS RN 108-10-1)
Method : Male and female B6C3F1 mice (14/sex/group) were exposed to atmospheres containing MIBK vapor at 0, 50, 250 or 1000 ppm, 6 hrs/day 5 days/wk for 14 weeks. The control group was exposed to air. Animals were sacrificed the morning after the last dose. In-life observations and measurements included signs of toxicity, ophthalmology, and weekly body weights. Hematology was performed at necropsy. Complete gross pathological examinations were made at necropsy and the kidneys, heart, liver, lungs, and testes were weighed. The nasal cavity (7 levels), trachea, liver, kidneys, and lungs (4 levels) from all animals were examined histologically. The following tissues were examined from animals in the high exposure and control groups: brain (cerebellum, cerebrum, medulla), spinal cord (two cross- and two longitudinal-sections from each of the following levels: cervical, thoracic, lumbar, sacral), peripheral nerves (sciatic and anterior tibial), eyes, optic nerve, pituitary, thyroid, parathyroid, salivary glands (submaxillary), heart, spleen, pancreas, adrenals, lymph nodes (mesenteric and mandibular), bladder (inflated with formalin), ovaries, uterus, oviducts, vagina, cervix, stomach, small intestine (3 levels), large intestine (3 levels), skeletal muscle

(thigh), skin, mammary glands (males and females), gall bladder, bone (sternum), bone marrow, aorta, testes, epididymis, esophagus, thymus, prostate, seminal vesicle, and any gross lesions.

Whole-body exposures were made in glass and stainless steel chambers with a total volume of approximately 4320 l (a subchronic rat study was conducted simultaneously in the same chambers). Temperature, relative humidity, and airflow were recorded at least four times during each 6-hr exposure. Chamber distribution of MIBK vapor was determined prior to the start of the study and repeated on the highest concentration chamber during exposure. All chambers were analyzed for MIBK concentration twice an hour.

Statistical analyses for continuous variable data were analyzed by Bartlett's test for homogeneity of variance, analysis of variance and Duncan's multiple rang test. When the F value for ANOVA was significant, Duncan's multiple range test was used to denote which groups differed significantly from the controls. If Bartlett's test indicated heterogeneous variance, the F test was employed to compare each exposure group with the air-control group. Student's t-test was used when the F value was not significant. Cochran t-test was used when the F value was significant. Nonparametric data were analyzed by the Kruskal-Wallis or Fisher's exact test. Following identification of significance, the Mann-Whitney U or Wilcoxon two-sample rank test was employed.

Result : The mean analytical chamber concentrations over the course of the study were 50, 252, and 1002 ppm. One male mouse from the high exposure group died during the 14th week of exposure. No cause could be attributed for the death. Body weights were equivalent to controls for all MIBK exposure concentrations. There were no treatment related differences in hematology measurements. Male mice exposed to 250 and 1000 ppm MIBK had a slight increase in liver weight and the liver to body weight ratio was increased in the high exposure group. These data are shown below:

Concentration (ppm)		0	50	250	1000
Liver Wt. Male-Absolute (g)		1.50	1.57	1.62	1.66
	Relative (%)	5.08	5.10	5.40	5.60

No gross or microscopic hepatic lesion related to MIBK exposure were observed. The liver weight increase was, therefore, considered of no toxicological relevance. No treatment-related effects were observed in females at any exposure concentration. The NOAEC was considered to be 1000 ppm.

Reliability : (1) valid without restriction
08.12.2005 (34)

Type :
Species : rat
Sex : no data
Strain : no data
Route of admin. : inhalation
Exposure period : 90 days
Frequency of treatm. : no data
Post exposure period : no data

Doses	:	0.425 mg/l (103 ppm); no data on group size
Control group	:	no data specified
NOAEL	:	< .425 mg/l
LOAEL	:	<= .425 mg/l
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Result	:	Hyaline droplet degeneration of the proximal tubules of the kidneys with some tubular necrosis occurred, this tubular damage being reversible on cessation of exposure. This study was also conducted in dogs and monkeys exposed at this same atmospheric concentration. No effects on the kidneys were seen in these species.
Remark	:	No further experimental details are given in the citing reference (Blair et al. 1982).
Reliability	:	(4) not assignable

08.12.2005 (3) (26)

Type	:	
Species	:	mouse
Sex	:	no data
Strain	:	no data
Route of admin.	:	inhalation
Exposure period	:	see remarks
Frequency of treatm.	:	see remarks
Post exposure period	:	no data
Doses	:	20 mg/l (4890 ppm); 9 mice
Control group	:	no data specified
NOAEL	:	< 20 mg/l
LOAEL	:	<= 20 mg/l
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	Mice were exposed twelve times, for 4 hr, to vapour saturated air (approximately 20 mg/l, 4720 ppm).
Result	:	There were no mortalities. At the end of each exposure period, the animals were lightly anaesthetised or in the pre-anaesthesia excitement state.
Reliability	:	(3) invalid

08.12.2005 (29) (39) (40)

Type	:	
Species	:	rabbit
Sex	:	no data
Strain	:	no data
Route of admin.	:	dermal
Exposure period	:	15-21 days
Frequency of treatm.	:	5 x in 15-21 days
Post exposure period	:	no data
Doses	:	2.5 g/kg bw; group of 3 rabbits
Control group	:	no data specified
NOAEL	:	= 2500 mg/kg
LOAEL	:	> 2500 mg/kg
Method	:	other
Year	:	

GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No overt systemic toxicity or changes in the microscopic appearance of the "internal organs" were seen. No further details are available.
Reliability	:	(3) invalid

08.12.2005 (29)

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Crj: CD(SD)
Route of admin.	:	gavage
Exposure period	:	Males; 44 days, Females; from 14 days before mating to day 3 of lactation
Frequency of treatm.	:	daily
Post exposure period	:	1 day
Doses	:	30, 100, 300, 1000 mg/kg/day (in distilled water)
Control group	:	yes, concurrent vehicle
NOAEL	:	= 30 mg/kg bw
LOAEL	:	= 100 mg/kg bw
Method	:	OECD combined study TG422
Year	:	1997
GLP	:	yes
Test substance	:	other TS
Test substance	:	4-Hydroxy-4-Methylpentan-2-one (HMP): CAS RN 123-42-2 Diacetone alcohol Source: Mitsubishi Chemical Lot No. 50831 Purity 99.8%, Kept at 4°C until use
Test condition	:	Age at study initiation was 9 weeks old (338-385 g) formales and 8 weeks old (198 - 225 g) for females. Number ofanimals per sex per dose was 10. Distilled water was used as a vehicle. Functional observation was not performed because the test was conducted by the TG adopted in 1990.
Result	:	NOAEL: Male: 30 mg/kg/day, Female: 100 mg/kg/day LOAEL: Male: 100 mg/kg/day, Female: 300 mg/kg/day Toxic effects: Male: At 100 mg/kg: Increased deposition of hyaline droplets in the proximal tubular epithelium in the kidneys (0: + 10/10, 30 mg: + 10/10, 100 mg: + 2/10, ++ 8/10, 300 mg: ++ 6/10, +++ 4/10, 1,000 mg: + 1/10, ++ 2/10, +++ 7/10) At 300 mg/kg Decreased locomotor activity and less responses to stimulation by knocking sounds or palpation during the early administration period. Increased deposition of hyaline droplets in the proximal tubular epithelium and basophilic tubules in the kidneys. At 1,000 mg/kg Decreased locomotor activity and less responses to stimulation by knocking sounds or palpation during the early administration period. Increases of platelet count, GOT, total protein, total cholesterol, total bilirubin, blood urea nitrogen,

creatinine and calcium, and decreased glucose.

Increases of relative liver and adrenal weights.
Increased deposition of hyaline droplets in the proximal tubular epithelium, basophilic tubules and dilatation of the distal tubules in the kidneys.
Hepatocellular hypertrophy and vacuolization in zona fasciculata of adrenals.

Female:
At 300 mg/kg
Decreased locomotor activity and less responses to stimulation by knocking sounds or palpation during the early administration period.
Slight but not significant dilatation of distal tubules and fatty degeneration of the proximal tubular epithelium in the kidneys.

At. 1,000 mg/kg
Decreased locomotor activity and less responses to stimulation by knocking sounds or palpation during the early administration period.
Decrease in body weight gain during the premating period
Increases of relative liver weight
Slight but no significant dilatation of distal tubules and fatty degeneration of the proximal tubular epithelium in the kidneys. Hepatocellular hypertrophy

Conclusion : The LOAEL for this study was 100 mg/kg/day for males and 300 mg/kg/day for females.The NOAEL was 30 mg/kg/day for males (based on hyaline droplet nephropathy) and 100 mg/kg/day for females.

Remark : Test type: OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test
Duration of test: 45 days
Statistical analysis: Dunnett's or Scheffe's test for continuous data and Chi square test for quantal data
One female at 1,000 mg/kg had to be killed in extremis because of difficulty in delivery.

Reliability : (1) valid without restriction
09.12.2005 (30)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : **Salmonella typhimurium reverse mutation assay**
System of testing : Strains: TA98, 100, 1535, 1537, 1538
Test concentration : 31.25, 62.5, 125, 250, 500, 1000, 2000, 4000 µg/plate
Cytotoxic concentr. : None of the concentrations tested was cytotoxic.
Metabolic activation : with and without
Result : negative
Method : other: comparable to OECD Guide-line 471
Year :
GLP : no
Test substance : other TS

Test substance : Methyl isobutyl carbinol: Tokyo Kasei Kogyo Co. Ltd, Tokyo, Japan; 98% pure.

Method : Arochlor induced rat liver S9 fraction was the metabolic activation system. The bacterial cultures were incubated, in the presence of methyl isobutyl carbinol, at 37 degrees C for 48-72 hr, after which the revertant colonies were

counted. Benzo(a)pyrene, sodium azide and neutral red were used as the positive controls, and dimethyl sulphoxide as the negative, solvent control.

Reliability : (2) valid with restrictions
The study was not conducted to GLP but was subject to QA audit.

Flag : Critical study for SIDS endpoint

08.12.2005 (10)

Type : **Salmonella typhimurium reverse mutation assay**
System of testing : Strains: TA98, 100, 1535, 1537, 1538
Test concentration : 1, 5, 10, 50, 100, 500, 1000, 5000 µg/plate
Cytotoxic concentr. : Inhibition of bacterial growth was seen at 5000 µg/plate
Metabolic activation : with and without
Result : negative
Method : other: Sugimura et al.
Year : 1976
GLP : no data
Test substance : other TS: Tokyo Kasei Kogyo Co. Ltd, Tokyo, Japan; 98% pure.

Method : The tests were conducted according to the preincubation method of Sugimura et al. 1976. The bacteria were preincubated in the presence of the test concentrations at 37 degrees C for 20 min, added to the agar and incubated at 37 degrees C for a further 48 hr. The numbers of revertant colonies were then counted. Each test was performed in duplicate. Dimethyl sulphoxide was used as the diluent and, as well as distilled water, as the negative control. A selection of positive controls were used. Polychlorinated biphenyl-induced male Sprague-Dawley rat liver S9 fraction was the metabolic activation system.

Reliability : (2) valid with restrictions

Flag : Critical study for SIDS endpoint

08.12.2005 (41) (45)

Type : **Bacterial reverse mutation assay**
System of testing : Escherichia coli WP2 uvr A pkm 101
Test concentration : 31.25, 62.5, 125, 250, 500, 1000, 2000, 4000 µg/plate
Cytotoxic concentr. : None of the concentrations tested was cytotoxic.
Metabolic activation : with and without
Result : negative
Method : other: comparable to OECD Guide-line 472
Year :
GLP : no
Test substance : other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%

Method : Dimethyl sulphoxide was used as the diluent. Arochlor induced rat liver S9 fraction was the metabolic activation system. The bacterial cultures were incubated, in the presence of methyl isobutyl carbinol, at 37 degrees C for 48-72 hr, after which the revertant colonies were counted. Potassium dichromate was used as the positive control and dimethyl sulphoxide as the negative, solvent control.

Reliability : (2) valid with restrictions
The study was not conducted to GLP but was subject to QA audit.

Flag : Critical study for SIDS endpoint

08.12.2005 (10)

Type	:	**Bacterial reverse mutation assay**
System of testing	:	Escherichia coli WP2 uvr A
Test concentration	:	1, 5, 10, 50, 100, 500, 1000, 5000 µg/plate
Cytotoxic concentr.	:	Inhibition of bacterial growth was seen at 5000 µg/plate.
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: Sugimura et al.
Year	:	1976
GLP	:	no data
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Test substance	:	Tokyo Kasei Kogyo Co. Ltd, Tokyo, Japan; 98% pure.
Method	:	The tests were conducted according to the preincubation method of Sugimura et al. 1976. The bacteria were preincubated in the presence of the test concentrations at 37 degrees C for 20 min, added to the agar and incubated at 37 degrees C for a further 48 hr. The numbers of revertant colonies were then counted. Each test was performed in duplicate. Dimethyl sulphoxide was used as the diluent and, as well as distilled water, as the negative control. 2-Aminoanthracene and 2-(2-furyl)-3-(5-nitro-2-furyl)acrylamide were used as positive controls. Polychlorinated biphenyl-induced male Sprague-Dawley rat liver S9 fraction was the metabolic activation system.
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint

08.12.2005 (41) (45)

Type	:	**Gene mutation in Saccharomyces cerevisiae**
System of testing	:	Saccharomyces cerevisiae JD1
Test concentration	:	0.01, 0.1, 0.5, 1.0, 5.0 mg/ml
Cytotoxic concentr.	:	Some evidence of reduced cell survival was seen at 5.0 mg/ml
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: comparable to OECD Guide-line 480
Year	:	
GLP	:	no
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	Liquid suspension cultures of log-phase cells were dosed with the test concentrations and incubated for 18 hr at 30 degrees C in the absence of metabolic activation and for 2 hr at 37 degrees C followed by 16 hr at 30 degrees C in the presence of metabolic activation. The cultures were seeded onto the appropriate media for the selection of prototrophic colonies, incubated for 3 days at 30 degrees C and these colonies counted. Dimethyl sulphoxide was used as the diluent and negative control and 4-nitroquinoline-N-oxide and cyclophosphamide as the positive controls. Arochlor-induced rat liver S9 fraction was the metabolic activation system.
Reliability	:	(2) valid with restrictions The study was not conducted to GLP but was subject to QA audit.

08.12.2005 (10)

Type	:	**Cytogenetic assay**
System of testing	:	rat liver (RL4) cells
Test concentration	:	0, 0.5, 1.0, 2.0 mg/ml

Cytotoxic concentr.	:	None of the concentrations tested inhibited cell growth.
Metabolic activation	:	without
Result	:	negative
Method	:	
Year	:	
GLP	:	no
Test substance	:	other TS: Report did not define MIBC purity; assumed to have used the commercial grade of > 98%
Method	:	Monolayer slide cultures of cells were incubated for 24 hr in culture medium containing the test concentrations and metaphase cells were analysed for structural chromosome aberrations. 7,12-Dimethylbenzanthracene was used as the positive control. Dimethyl sulphoxide was used as the diluent and negative control.
Result	:	There was no evidence of an increase in the frequency of structural chromatid or chromosome aberrations.
Remark	:	RL4 cells are metabolically competent.
Reliability	:	(2) valid with restrictions The study was not conducted to GLP but was subject to QA audit.
Flag	:	Critical study for SIDS endpoint

08.12.2005 (10)

Type	:	**Bacterial reverse mutation assay**
System of testing	:	Salmonella typhimurium TA100, TA1535, TA98, TA1537; Escherichia coli WP2 uvrA
Test concentration	:	-S9: 0, 313, 625, 1250, 2500, 5000 ug/plate +S9: 0, 313, 625, 1250, 2500, 5000 ug/plate
Cytotoxic concentr.	:	Toxicity was not observed up to 5000 ug/plate in five strains with or without S9 mix.
Metabolic activation	:	with and without
Result	:	negative
Method	:	
Year	:	1997
GLP	:	yes
Test substance	:	other TS
Test substance	:	4-Hydroxy-4-Methylpentan-2-one (HMP): CAS RN 123-42-2 Diacetone alcohol Produced by Mitsubishi Chemical, Lot No. 50831, Purity: 99.8%, Kept at 4C until use
Method	:	Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD TG 471 Statistical methods: No statistic analysis
Test condition	:	Number of replicates: 2 Plates/test: 3 Procedure: Pre-incubation Solvent: Water Positive controls: -S9 mix, 2-(2-Furyl)-3-(5-nitro-2-furyl) acrylamide (TA100, TA98, WP2), Sodium azide (TA1535) and 9-Aminoacridine (TA1537) +S9 mix, 2-Aminoanthracene (five strains)
Conclusion	:	Bacterial gene mutation is negative with and without metabolic activation (Submitter).
Remark	:	Metabolic Activation: S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone
Reliability	:	(1) valid without restriction

09.12.2005 (30)

Type	:	**Chromosomal aberration test**
System of testing	:	CHL/IU cells

Test concentration	:	
Cytotoxic concentr.	:	Toxicity was not observed up to 1.2 mg/ml in continuous and short-term treatment with or without S9 mix.
Metabolic activation	:	with and without
Result	:	negative
Method	:	
Year	:	1997
GLP	:	yes
Test substance	:	other TS
Test substance	:	4-Hydroxy-4-Methylpentan-2-one (HMP): CAS RN 123-42-2 Diacetone alcohol Produced by Mitsubishi Chemical, Lot No. 50831, Purity: 99.8%, Kept at 4C until use
Method	:	Guidelines for Screening Mutagenicity Testing of Chemicals (Japan) and OECD TG 473 Statistical methods: Fisher's exact analysis
Test condition	:	For continuous treatment, cells were treated for 24 or 48 hrs without S9. For short-term treatment, cells were treated for 6 hrs with and without S9 and cultivated with fresh media for 18 hrs. Plates/test: 2 Solvent: Distilled water Positive controls: Mitomycin C for continuous treatment Cyclophosphamide for short-term treatment
Result	:	Genotoxic effects: clastogenicity polyploidy + ? - + ? - With metabolic activation: [ ] [ ] [X] [ ] [ ] [X] Without metabolic activation: [ ] [ ] [X] [ ] [ ] [X]
Conclusion	:	Chromosomal aberration in CHL/IU cells is negative with and without metabolic activation (Author and Submitter).
Remark	:	Concentration: -S9 (continuous treatment): 0, 0.30, 0.60, 1.2 mg/ml -S9 (short-term treatment): 0, 0.30, 0.60, 1.2 mg/ml +S9 (short-term treatment): 0, 0.30, 0.60, 1.2 mg/ml Metabolic activation: S9 from rat liver, induced with phenobarbital and 5,6-benzoflavone In comparison with historical solvent controls, polyploidy (1.25 and 1.00%) was increased significantly at 0.60 and 1.2 mg/ml on short-term treatment, with and without an exogenous metabolic activation system, respectively. However, a trend test showed no dose-dependence.
Reliability	:	(1) valid without restriction

09.12.2005 (30)

5.6 GENETIC TOXICITY 'IN VIVO'

5.7 CARCINOGENICITY

5.8.1 TOXICITY TO FERTILITY

Type	:	**Two generation study**
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation

Exposure period	:	see Remarks
Frequency of treatm.	:	6 hours/day - 7 days/week
Premating exposure period		
Male	:	70 days
Female	:	70 days
Duration of test	:	70 days prebreed through weaning of F2 offspring
No. of generation studies	:	2
Doses	:	0, 500, 1000 or 2000 ppm (2.05, 4.09, 8.18 mg/l)
Control group	:	yes, concurrent vehicle
NOAEL parental	:	= 1000 ppm
NOAEL F1 offspring	:	= 1000 ppm
NOAEL F2 offspring	:	= 1000 ppm
other: NOAEL reproductive toxicity	:	= 2000 ppm
Method	:	EPA OPPTS 870.3800
Year	:	1998
GLP	:	yes
Test substance	:	other TS: Methyl Isobutyl Ketone (CAS RN 108-10-1; 99.79 - 99.93%)

Method : Four groups of animals (30/sex/group) were exposed 6 hours/day, 7 days/week, to MIBK at concentrations of 500, 1000, and 2000 ppm. The control group was exposed to air. Each group of animals was exposed in a 2.0-m^3 stainless steel and glass whole-body inhalation chamber operated under dynamic conditions. Exposure concentrations within each chamber were measured during each daily exposure. During the mating period, each female was housed overnight in the home cage of the male. The observation of a copulatory plug in the vagina or the presence of sperm in a vaginal smear confirmed positive evidence of mating and that day was termed gestation day (GD) 0. Exposure of the F0 and F1 females was suspended for 5 days following parturition, to avoid excessively stressing the dams during early lactation; exposure resumed on lactation day (LD) 5. Male and female F1 pups (30/sex/group) were randomly selected prior to weaning (PND 21) to comprise the F1 generation.

Detailed physical examinations were recorded weekly for all parental animals (F0 and F1) and observations during and post-exposure were made.

Individual F0 and F1 male body weights were recorded weekly throughout the study and prior to the scheduled necropsy. Individual F0 and F1 female body weights were recorded weekly until evidence of copulation was observed and on GD 0, 4, 7, 11, 14, and 20 and LD 1, 4, 7, 14, and 21. Parental food consumption was determined at the same time as the body weight measurements, except during the mating period when food consumption was suspended due to cohabitation.

To assess estrous cyclicity, vaginal smears from each F0 and F1 female were evaluated daily beginning 3 weeks prior to mating and continuing until mating was observed. Females were allowed to deliver naturally and nurture their young to weaning (PND 21). On the day parturition was judged complete (PND 0), pups were sexed and examined for external malformations, and the numbers of stillborn and live pups were recorded. Intact offspring dying from PND 0 to 4 were necropsied.

Litters were culled to eight pups/litter (four/sex when possible) on PND 4. Litters were examined daily for survival and any adverse changes in appearance or behavior. Each pup was individually weighed and received a detailed physical examination on PND 1, 4, 7, 14, and 21. Pups were also individually sexed on PND 0, 4, 7, 14, and 21.

Each male pup was examined for balanopreputial separation beginning on PND 35 and each female for vaginal perforation beginning on PND 25. Pup body weights were recorded on the day of acquisition of these landmarks.

Samples of sperm from the right epididymis were collected from each adult F0 and F1 male and evaluated for the percentage of progressively motile sperm. Sperm morphology was evaluated by light microscopy. The left testis and epididymis from all F0 and F1 males in all dose groups were evaluated for homogenization-resistant spermatid counts and sperm production rate.

Surviving F0 and F1 adults were necropsied. The following list of tissues and organs were fixed in 10% neutral buffered formalin: adrenals, lymph node (mesenteric), aorta, ovaries (on section of each ovary from the F0 was examined) and oviducts, bone with marrow (sternebrae), pancreas, brain (forebrain, midbrain, hindbrain), peripheral nerve (sciatic), coagulating gland, pituitary, eyes with optic nerve, prostate, gastrointestinal tract, salivary gland (submaxillary), esophagus, seminal vesicles, stomach, skeletal muscle (vastus medialis), duodenum, skin with mammary gland, jejunum, spinal cord (cervical), ileum, spleen, cecum, colon, testes with epididymides (the right testis and epididymis were fixed in Bouin's solution), vas deferens, rectum, thymus, heart, kidneys(paired), thyroids (with parathyroids, if present), liver (section of two lobes), trachea, lungs (including bronchi, fixed by inflation with fixative), urinary bladder, uterus with vagina and all gross lesions.

Microscopic evaluations were performed on the following tissues for F0 and F1 parental animals (10/sex/group) from the control and high dose groups and for all adult animals found dead or euthanized in extremis: adrenal glands, prostate, brain, spleen, thymus, liver (all F0 animals examined and all F1 males examined), kidneys (all F0 animals examined and all F1 males examined), lung, pituitary, seminal vesicles, the right epididymis (caput, corpus and cauda), the right testis, vas deferens, vagina, cervix, coagulating gland, uterus, oviducts, ovaries (one section from each ovary from F0 females was examined). Quantitative histopathologic evaluation of 10 sections of the inner third of the ovary (including enumeration of primordial follicles) was conducted on 10 F1 females from the 0- and 2000-PPM groups. In addition, a qualitative assessment of the presence or absence of growing follicles, antral follicles and corpora lutea was performed.

Organs weighed from all F0 and F1 parental animals included adrenals, prostate, brain, seminal vesicles with coagulating glands (with accessory fluids), epididymides (weighed separately: total and cauda), kidneys, spleen, liver and testes (weighed separately), ovaries, thymus, pituitary, and

uterus with oviducts and cervix.

On PND 21, a complete necropsy, similar to that performed on parental animals, was conducted on F1 pups not selected for MIBK exposure and on F2 pups. Brain, spleen, and thymus gland weights were also recorded from these pups.

All statistical analyses were conducted using two-tailed tests (except as noted below) for a minimum significance level of 5% comparing each treated group to the control group. Data obtained from nongravid animals were excluded from statistical analyses following the mating period. Parental mating and fertility indices were evaluated by the chi-squared test with Yates' correction factor. Parental weekly body weights and weight changes, gestation and lactation body weights and body weight changes, parental food consumption, food efficiency, mean gestation length, precoital interval, implantation sites, unaccounted implantation sites, pup body weights, mean litter weights, absolute and relative organ weights, live litter size, sperm production rate, sperm numbers, ovarian primordial follicle counts, number of pups born, balanopreputial separation (mean day of acquisition and body weight), vaginal patency (mean day of acquisition and body weight) were subjected to a one-way analysis of variance ANOVA. If the ANOVA was significant, Dunnett's test was used to determine which treated groups differed from the control. Sperm motility and morphology, and proportional postnatal offspring survival were analyzed by the Kruskal-Wallis test to assess differences in group means. The Mann-Whitney U test was used to determine which treatment groups differed significantly from control. Histopathologic findings were evaluated using a one-tailed Kolmogorov-Smirnov test Pup organ weights by litter were analyzed by using an Analysis of Covariance (with the litter size as the covariant) and Student's T-test.

Result : F0 adults:
There were no MIBK-related mortalities or clinical signs of toxicity noted during the study. However, absent or reduced reaction to an auditory startle stimulus was observed during exposures in the Fo and F1 adults at 1000 and 2000 ppm groups. The effect ameliorated one hour after completion of exposure. No other MIBK-related clinical findings were observed at any exposure level evaluated.

Weekly body weights and body weight gains were unaffected by MIBK exposure in the F0 female rats in the 500 and 1000 ppm groups and in F0 male rats at all exposure levels evaluated. Statistically significant reductions in body weight gains in the 2000 ppm group F0 females were observed. Female body weights and body weight gains in the 500, 1000, and 2000 ppm groups were comparable to the control group throughout gestation and lactation. No clear treament-related effects on food consumption were noted.

The regularity and duration of estrus were not affected by exposure. Furthermore, no adverse exposure-related effects were observed on fertility and mating indices or on F0 spermatogenic endpoints.

Exposure-related increases in liver weights (absolute and relative to final body weights) occurred in the 2000 ppm

group males and females. Also, MIBK-related centrilobular hepatocellular hypertrophy was noted in 0, 3, 15, and 26 F0 males in the 0, 500, 1000, and 2000 ppm groups, respectively. This male-specific hepatic hypertrophy was characterized by centrilobular random disruption of normal plate structure/architecture by enlarged, rounded hepatocytes with variable increases in acidophilic cytoplasm containing basophilic clumping of organelles. Increased male absolute and relative kidney weights occurred in all exposure groups and correlated with an increased occurrence of nephropathy characterized by basophilic tubules with variable inflammation and thickening of the tubular basement membrane in the 1000 and 2000 ppm groups. Kidney weights in the females were unaffected by exposure at all MIBK concentrations. No other changes were considered related to MIBK toxicity.

F1 offspring:
The number of pups born, live litter size, sex ratio at birth, pup survival at various intervals and pup body weights were unaffected by parental exposure. The day of acquisition of balanopreputial separation and vaginal patency was also unaffected by parental MIBK exposure. No internal findings that could be attributed to parental MIBK exposure were noted at the necropsies of pups that were found dead or euthanized in extremis.

F1 adults:
One 2000 ppm F1 male was found dead on its first day of exposure (PND 22). This male was replaced and all remaining F1 animals survived to the scheduled necropsy. In addition, approximately 1 hour post-exposure on PND 22, males and females in the 2000-ppm group exhibited clinical signs of neuro- or neuromuscular toxicity i.e., rocking, lurching, or swaying while ambulating; prostration, half-closed eyelids and/or bilateral lacrimation. Because of the single mortality and the CNS depression or narcosis noted in these animals, exposures for all groups of F1 weanlings were suspended through PND 27. After exposures were reinitiated on PND 28, only six males (out of 30) in the 2000 ppm group exhibited previously observed clinical signs of neurotoxicity 1 hour post-exposure. These CNS effects proved to be transient as they were not observed on subsequent days. Furthermore, no recurrence was observed in females upon resumption of exposure. Similar to the F0 rats, during the exposure period an increased number of observations of rats having absent or diminished reaction to an auditory startle was observed in the 1000 ppm group males and the 2000 ppm group males and females.

Weekly body weights were slightly reduced throughout the study in the 2000-ppm group males and throughout the pre-breeding and post-lactational phases in the 2000-ppm group females. While these body weight differences from the control group were statistically significant throughout the study, weekly body weight gains were comparable among all exposure groups after week 17-18 for F1 males and week 18-19 for F1 females. The differences in body weight noted throughout the remainder of the F1 generation exposures were due primarily to these initial reductions in weight gain, and not to any differences in weight gain induced by exposure to the test substance. No other changes were

considered related to MIBK toxicity.
The regularity and duration of estrus were not affected by exposure. Furthermore, no adverse exposure-related effects were observed on the number of days between pairing and coitus, gestation lengths nor reproductive performance e.g., fertility and mating indices. Exposure to MIBK also had no effects on F1 spermatogenic endpoints e.g., mean testicular and epididymal sperm numbers, sperm production rate, and sperm motility and morphology.

There were no MIBK-related post mortem findings noted at necropsy. Absolute and relative (to final body weight) liver weights were significantly increased for males and females in the 2000 ppm group. As with the F0 animals, exposure-related increases in centrilobular hepatocellular hypertrophy was noted in F1 males in the 1000 and 2000 ppm group, with increased severity in the 2000 ppm group males.

Kidney changes consistent with the alpha-2u-globulin associated nephropathy previously seen for MIBK were observed in male rats in this study.

F2 offspring:
The number of pups born, live litter size, sex ratio at birth, pup survival at various intervals and pup body weights were unaffected by parental exposure to MIBK. There were no post mortem observations that were considered to be exposure-related.

Conclusion : MIBK, at all exposure levels, did not affect any reproductive parameters nor offspring growth, development or behavior. The NOAEC for parental systemic toxicity (apart from male nephropathy) was considered to be 1000 ppm, based on transient reduced body weight gain and food consumption. The NOAEC for neonatal toxicity (based on acute CNS depressive effects seen on PND 22 and 28) was considered to be 1000 ppm. The NOAEC for reproductive toxicity was considered to be 2000 ppm, the highest concentration tested.

Remark : Exposure period:
F0 and F1 prebreed exposure period = 70 days
F0 and F1 adult/parental males throughout mating to one day prior to scheduled termination
F0 and F1 adult/parental females - throughout mating and gestation (through gestation day 20) and re-initiating on lactation day 5
F1 weanling exposures began on PND 22 (one day after weaning); however, due to signs of toxicity, including the death of one male on PND 22, all exposures were suspended through PND 27. Exposures were reinitiated on PND 28.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
08.12.2005 (31)

Type : **other: OECD Combined Repeat Dose and Reproductive/Developmental Toxicity Screening Test**
Species : rat
Sex :
Strain : Crj: CD(SD)
Route of admin. : gavage
Exposure period :
Frequency of treatm. : daily
Premating exposure period

Male	:	
Female	:	
Duration of test	:	45 days
No. of generation studies	:	
Doses	:	30, 100, 300, 1000 mg/kg/day (in distilled water)
Control group	:	yes, concurrent vehicle
Method	:	OECD Guide-line 422
Year	:	1997
GLP	:	yes
Test substance	:	other TS
Test substance	:	4-Hydroxy-4-Methylpentan-2-one (HMP): CAS RN 123-42-2 Diacetone alcohol Produced by Mitsubishi Chemical, Lot No. 50831, Purity: 99.8%, Kept at 4C until use
Test condition	:	Age at study initiation was 9 weeks old (338-385 g) for males and 8 weeks old (198 - 225 g) for females. Number of parents per sex per dose was 10. Distilled water was used as a vehicle. Male/female per cage was 1/1, length of cohabitation was 4 days, and proof of pregnancy was judged by formation of vaginal closing. Functional observation, estrous cycle length and pattern, sperm examination, measurement of anogenital distance and so on were not performed because the test was conducted by the TG adopted in 1990.
Result	:	Age at study initiation was 9 weeks old (338-385 g) for males and 8 weeks old (198 - 225 g) for females. Number of parents per sex per dose was 10. Distilled water was used as a vehicle. Male/female per cage was 1/1, length of cohabitation was 4 days, and proof of pregnancy was judged by formation of vaginal closing. Functional observation, estrous cycle length and pattern, sperm examination, measurement of anogenital distance and so on were not performed because the test was conducted by the TG adopted in 1990. and viability index on day 4 of lactation, etc. at the highest dose.
Conclusion	:	There is suggestive evidence that there was reproductive/developmental toxicity in rats that received 1,000 mg/kg by oral gavage doses of diacetone alcohol. A clear NOAEL was established at 300 mg/kg bw/day.
Remark	:	Premating exposure period for males and females: 14 days Statistical analysis: Dunnett's or Scheffe's test for continuous data and Chi square test for quantal data
Reliability	:	(1) valid without restriction

09.12.2005 (30)

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	**rat**
Sex	:	female
Strain	:	Fischer 344
Route of admin.	:	inhalation
Exposure period	:	Gestation days 6-15
Frequency of treatm.	:	6 hr/day
Duration of test	:	21 days

Doses	:	0, 300, 1000, 3000 ppm (1.23, 4.09, 12.3 mg/l)
Control group	:	yes
NOAEL maternal tox.	:	= 1000 ppm
NOAEL teratogen.	:	= 3000 ppm
NOAEL Fetotoxicity	:	= 1000 ppm
Method	:	other: Equivalent to OECD 414
Year	:	1987
GLP	:	yes
Test substance	:	other TS: Methyl Isobutyl Ketone (CAS RN 108-10-1; 99.5%)

Method : Pregnant Fischer 344 rats (35/group) were exposed to atmospheres containing MIBK vapor at 0, 300, 1000, or 3000 ppm, 6 hrs/day on gestation days (gd) 6-15. The control group was exposed to air. The animals were observed daily for clinical signs throughout the study (gd 0 through 21). Food consumption was measured for 3-day intervals starting on gd 0. Maternal body weights were taken on gd 0, 6, 9, 12, 15, 18 and 21. Where appropriate, 25 females were randomly selected from each group and sacrificed on gd 21. Maternal and fetal examinations were made consistent with OECD Guideline 414.

Whole-body exposures were made in glass and stainless steel chambers with a total volume of approximately 4320 l (a developmental toxicity study in mice was conducted simultaneously in the same chambers). Temperature, relative humidity, and airflow were recorded at least four times during each 6-hr exposure. Chamber distribution of MIBK vapor was determined as part of the subchronic studies with MIBK. All chambers were analyzed for MIBK concentration once an hour.

The unit for statistical comparison was the pregnant female or the litter. Statistical analyses for continuous variable data were intercompared for the four groups by use of Levene's test for equal variances, analysis of variance (ANOVA) and tests with Bonferroni probabilities. When Levene's test indicated homogeneous variances and the ANOVA was significant, the pooled t test was used for pairwise comparisons. Otherwise an ANOVA for unequal variances followed, when necessary, by the separate variance t test was employed. Nonparametric data were analyzed by the Kruskal-Wallis. Following identification of significance, the Mann-Whitney U test was employed. Incidence data were compared using Fisher's exact test

Result : No female rats died, delivered early or aborted. Maternal body weight and body weight gain was significantly reduced in the 3000 ppm dose group at gd 9, 12, 15 and 18 and gd 6-9, 6-12, 6-15 and 6-18, respectively. Food consumption (g/dam/day) was significantly reduced in the 3000 ppm dose group at gd 6-9, 9-12, 12-15 and 6-15, which corresponds with the reduced body weight and body weight gains.

The pregnancy rate was slightly reduced at 3000 ppm (65.7%), but the difference was not statistically significant as compared to the controls 86.2%). The number of litters evaluated were 25, 26, 25 and 23 for the 0, 300, 1000 and 3000 ppm groups, respectively.

Treatment related clinical signs were observed only during the exposure period at 3000 ppm. They includedclinical

signs, such as loss of coordination, negative tail and/or toe pinch, paresis, muscular weakness in hindlimbs, piloerection, lacrimation, and red perioral encrustation.

At scheduled sacrifice, maternal relative kidney weight was significantly elevated (104% of controls) at 3000 ppm. No other absolute or relative organ weights were affected by treatment. There were no treatment related findings present at gross necropsy.

There were no treatment related effects on the following gestational parameters: number of corpora lutea, total implantations, viable or nonviable implantations per litter or percentage preimplatntation loss, live fetuses or sex ratio.

Fetal body weight per litter was significantly reduced at the highest dose level (~93-94% of controls) and slightly reduced at 300 ppm (~97% of controls), but no difference was seen at 1000 ppm.

Fetal Body Weights/litter (+/- SD) (g)	Dose (ppm) 0	300	1000	3000
All fetuses	4.46 (0.22)	4.33 (0.12)*	4.39 (0.14)	4.18 (0.13)***
Male	4.59 (0.21)	4.46 (0.13)*	4.54 (0.14)	4.32 (0.14)***
Female	4.34 (0.23)	4.20 (0.13)*	4.25 (0.15)	4.04 (0.15)***

* p< 0.05 vs. control
*** p < 0.001 vs. control
SD = Standard Deviation

There were no treatment related effects on the incidence of external, visceral, skeletal or total malformations in rat fetuses. There were also no significant changes in the incidence of any external or visceral variations across exposure groups. There was an increased incidence of 5 skeletal variations observed at 3000 ppm that involved the vertebrae, sternbrae and distal limbs. Almost all of the fetuses in the 3000 ppm treatment group displayed an increase in the incidence of reduced skeletal ossification. Also significantly increased was the incidence of unilateral rudimentary rib at the first lumbar arch at 3000 ppm relative to controls. No effects were observed at the other concentrations and no teratogenic effects were noted at any concentration.

Reliability : (1) valid without restriction
Flag : Critical study for SIDS endpoint
08.12.2005 (47)

Species : **mouse**
Sex : female
Strain : CD-1
Route of admin. : inhalation
Exposure period : Gestation day 6-15
Frequency of treatm. : 6 hr/day
Duration of test : 18 days
Doses : 0, 300, 1000, 3000 ppm (1.23, 4.09, 12.3 mg/l)
Control group : yes

NOAEL maternal tox.	:	= 1000 ppm
NOAEL teratogen.	:	= 3000 ppm
NOAEL Fetotoxicity	:	= 1000 ppm
Method	:	other: Equivalent to OECD 414
Year	:	1987
GLP	:	yes
Test substance	:	other TS: Methyl Isobutyl Ketone (CAS RN 108-10-1)

Method : Pregnant CD-1 mice (30/group) were exposed to atmospheres containing MIBK vapor at 0, 300, 1000, or 3000 ppm, 6 hrs/day on gestation days (gd) 6-15. The control group was exposed to air. The animals were observed daily for clinical signs throughout the study (gd 0 through 21). Maternal body weights were taken on gd 0, 6, 9, 12, 15, and 18. Where appropriate, 25 females were randomly selected from each group and sacrificed on gd 18. Maternal and fetal examinations were made consistent with OECD Guideline 414.

Whole-body exposures were made in glass and stainless steel chambers with a total volume of approximately 4320 l (a developmental toxicity study in rats was conducted simultaneously in the same chambers). Temperature, relative humidity, and airflow were recorded at least four times during each 6-hr exposure. Chamber distribution of MIBK vapor was determined as part of the subchronic studies with MIBK. All chambers were analyzed for MIBK concentration once an hour.

The unit for statistical comparison was the pregnant female or the litter. Statistical analyses for continuous variable data were intercompared for the four groups by use of Levene's test for equal variances, analysis of variance (ANOVA) and tests with Bonferroni probabilities. When Levene's test indicated homogeneous variances and the ANOVA was significant, the pooled t test was used for pairwise comparisons. Otherwise an ANOVA for unequal variances followed, when necessary, by the separate variance t test was employed. Nonparametric data were analyzed by the Kruskal-Wallis. Following identification of significance, the Mann-Whitney U test was employed. Incidence data were compared using Fisher's exact test

Result : Three pregnant females (3/25) died at 3000 ppm on gd 6 after the first exposure. Two dams at 300 ppm and three at 1000 pppm delivered early. The pregnancay rate at scheduled sacrifice was equivalent across the treatment groups. One litter each at 0 and 1000 ppm were completely absorbed.

There were no treatment-related changes in maternal body weight at any time point evaluated. Maternal body weight gain was significantly elevated at 3000 ppm at gd 6-9.

Clinical signs of toxicity were only present in the 3000 ppm group during the exposure period. These signs included: irregular gait, paresis, hypoactivity, ataxia, negative toe pinch, unkempt fur and lacrimation.

There were no treatment-related differences in relative and absolute organ weights with the exception of increases in the absolute (117.8% of controls) and relative (104.5%) weight of the livers at 3000 ppm. There were no treatment related findings present at gross necropsy.

There was no treatment-related effect on gestational parameters. There was a significant increase in the number of dead fetuses, but not early or late resorptions, in the 3000 ppm group as compared to control.

Total, female and male fetal body weights per litter were significantly reduced at 3000 ppm as compared to controls.

Fetal Body Weights/litter (+/- SD) (g)	Dose (ppm) 0	300	1000	3000
All fetuses	1.333 (0.169)	1.336 (0.153)	1.315 (0.155)	1.154 (0.098)***
Male	1.313 (0.110)	1.333 (0.111)	1.315 (0.129)	1.179 (0.100)***
Female	1.314 (0.172)	1.311 (0.158)	1.319 (0.242)	1.131 (0.099)**

** p< 0.01 vs. control
*** p < 0.001 vs. control
SD = Standard Deviation

There were no treatment related effects on the number of fetuses or of litters with one or more affected fetuses with individual malformations, pooled external, visceral, skeletal or total malformations in any treatment group as compared to controls. There were no significant changes in the incidence of any external variations across exposure groups. Incidences of visceral variations significantly increased at 3000 ppm were dilated lateral ventricles of the cerebrum and dilated renal blood vessels. There was an increased incidence of skeletal variations observed at 3000 ppm that involved the vertebrae, sternbrae and distal limbs with an increased incidence of reduced skeletal ossification.

Reliability : (1) valid without restriction
08.12.2005 (47)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

Test substance : Methyl isobutyl carbinol was technical grade solvent supplied by Shell Development Company, Emeryville, California.

Remark : A 15-min exposure to 50 ppm (approximately 200 mg/m3) caused eye irritation in most of the 12 male and 12 female volunteers. Nose and throat irritation were reported at higher, unspecified concentrations. The maximum concentration which the volunteers considered satisfactory for an 8-hr exposure was 25 ppm (approximately 100 mg/m3). Sensory irritation

Reliability : (2) valid with restrictions

08.12.2005 (42)

5.11 ADDITIONAL REMARKS

Type : **Biochemical or cellular interactions**

Remark : It has been reported that methyl isobutyl carbinol potentiates haloalkane hepatotoxicity. In one study, 3.75, 5.60 or 7.5 mmol/kg bw (approximately 380, 570 and 765 mg/kg bw respectively), in corn oil, was administered to male Sprague-Dawley rats 24 hr before an intraperitoneal injection of chloroform. Methyl isobutyl carbinol potentiated the hepatotoxic effect of chloroform when assessed 24 hr after challenge; the minimal effective dose being 570 mg/kg bw.

08.12.2005 (35) (54)

Type : **Biochemical or cellular interactions**

Remark : Single or repeated (daily for 3 days) gavage doses of 1.88-15 mmol/kg (approximately 190-1530 mg/kg bw) methyl isobutyl carbinol (Aldrich Chemical Co.; >99% purity) in corn oil to male Sprague-Dawley rats, potentiated the cholestasis induced by an intravenous injection of monohydrate manganese sulphate, with or without bilirubin, administered 18 hr after the final methyl isobutyl carbinol dose. Methyl isobutyl carbinol was not a cholestatic agent on its own.

23.11.2004 (54)

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