

FOREWORD

INTRODUCTION

ISOBUTYLENE
CAS N°: 115-11-7

SIDS Initial Assessment Report

For

SIAM 17

11-14 November 2003, Arona, Italy

1. **Chemical Name:** Isobutylene
2. **CAS Number:** 115-11-7
3. **Sponsor Country:** France
4. **Shared Partnership with:** CEFIC Lower Olefins Sector Group
5. **Roles/Responsibilities of the Partners:**
 - Name of industry sponsor /consortium CEFIC Lower Olefins Sector Group/ Christian Gilliard
 - Process used Documents drafted by ExxonMobil Biomedical Sciences, Inc. P.O. Box 971, 1545 Route 22 East Annandale, NJ 08801-0971, USA. Reviewed by LOSG industry toxicologists and by French Competent Authority by reference to published data sources.
6. **Sponsorship History**
 - How was the chemical or category brought into the OECD HPV Chemicals Programme ? Industry prepared documents intended for consideration at SIAM 17, initial drafts were submitted February 2003. Data searches were conducted of available literature, databases, and internal consortia files.
7. **Review Process Prior to the SIAM:** The SIDS documents were posted on the Pre-SIAM CDG for comments by the other OECD Member countries. Responses to these comments were also posted to the Pre-SIAM CDG.
8. **Quality check process:** **Industry Consortium:**

Critical biological studies discussed in the SIAR were reviewed for quality by industry and assigned a reliability code, based on the review process guidance of Klimisch *et al.* (1999). Robust summaries of critical data were added to a SIDS dossier for isobutylene and flagged as "critical", the summary formats for selected endpoints were based on descriptions in the OECD Form and Guidance for preparing and submitting the SIDS DOSSIER (INCLUDING ROBUST STUDY SUMMARIES), which is from the Manual for Investigation of HPV Chemicals. Selected physicochemical data from published journals or peer-reviewed databases were added to the dossier in robust summary format. Peer-reviewed databases were not rereviewed. Additional non-SIDS data in IUCLID that contributed to a more complete understanding of isobutylene hazard were discussed in the SIAR,

but may not have been reviewed for quality.

French Government:

French Competent Authority peer-reviewed the SIDS documents and audited selected key studies to check the robust study summaries.

9. Date of Submission: 31st October 2003

10. Date of last Update: 31st October 2003

11. Comments:

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	115-11-7
Chemical Name	Isobutylene
Structural Formula	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2=\text{C}-\text{CH}_3 \end{array}$

SUMMARY CONCLUSIONS OF THE SIAR**Human Health**

Isobutylene has a low order of acute toxicity. As isobutylene is a gas at normal temperature and pressure, ingestion or dermal absorption of this material is unlikely. The 2-hour LC50 of isobutylene in mice was 180,000 ppm (415 mg/L) and the 4-hour LC50 in rats was 270,000 ppm (620 mg/L). Inhalation of isobutylene can produce central nervous system depression, anesthesia and/or asphyxiation. However, these effects are only seen at very high concentrations, i.e., approximately 20% or higher. Isobutylene is predicted to produce narcosis in humans at concentrations exceeding the lower explosive limit (LEL) of 18,000 ppm.

There are no data to evaluate the dermal or ocular irritation potential of isobutylene. However, should skin or eye contact occur to this chemical in its liquid state, tissue freezing, severe cold burn, and/or frostbite may result.

Repeated dose toxicity clearly demonstrated that isobutylene is not toxic to rodents at concentrations up to 8,000 ppm (18.4 mg/L) for 14 weeks. There was a minimal increase in right kidney weights of 4,000 and 8,000 ppm (9.18 and 18.4 mg/L, respectively) male rats and 8,000 ppm (18.4 mg/L) male mice and the relative (to body weight) right kidney weights of all exposed groups of male rats and 8,000 ppm (18.4 mg/L) male mice were greater than those of the chamber controls. The absolute liver weights of female rats exposed to 1,000 ppm and above, and the relative (to body weight) liver weights of all exposed groups of female rats were greater (up to 20%) than those of the chamber controls. However, the increases in absolute and relative (to body weight) liver weights did not occur in a concentration-related manner. The absolute and relative (to body weight) right kidney weights of all groups of exposed female mice were greater (up to 18%) than those of the chamber controls, but in general, were not exposure concentration related. There were no histopathologic effects associated with increased kidney or liver weights as a result of isobutylene exposure. There were no exposure-related gross lesions in the rats. Some minimal hypertrophy of goblet cells lining the nasopharyngeal duct in the most caudal section of the nasal cavity was observed in all groups of exposed male and female rats but not mice. There were no clinical findings or biologically significant effects on male or female reproductive organs attributed to isobutylene exposure in rats or mice. The NOAEL was 8,000 ppm (18.4 mg/L).

Although isobutylene produced an increase in follicular cell carcinomas of the thyroid in male rats exposed for 105 weeks, this was observed only at the highest exposure concentration (i.e., 8000 ppm) and did not occur in female rats nor male or female mice. Overall, the data suggest that isobutylene has a low carcinogenic potential. In addition, the follicular cell carcinomas in the thyroid were reported to be morphologically similar to spontaneously developing follicular cell carcinomas and there was no concurrent increase in the incidence of follicular cell hyperplasia or adenoma in male rats. It should also be noted that there was no evidence of any carcinogenic activity in female rats or mice up to 8000 ppm. Taken in concert, these data suggest that isobutylene has a low carcinogenic potential. The NOAEL was 2,000 ppm (4.5 mg/L).

Test data clearly demonstrate that isobutylene is not mutagenic in a battery of *in vitro* and *in vivo* mutagenicity studies. Isobutylene was not mutagenic when tested in reverse mutation assays conducted in *Salmonella typhimurium* and *Escherichia coli* either in the presence or absence of metabolic activation. Isobutylene did not increase the number of transformed foci in C3H/10T1/2 clone 8 mouse embryo fibroblast cells. There was no evidence of mutagenic activity in mouse lymphoma L5178Y cells either in the presence or absence of metabolic activation. In addition, isobutylene did not induce an increase in micronuclei formation in mouse bone marrow cells

from animals exposed up to 10,000 ppm.

In a prenatal developmental toxicity study, inhalation exposure of pregnant Wistar rats to isobutylene on days 5 to 21 (inclusive) of gestation elicited no maternal toxicity at all tested concentrations up to 8,000 ppm. There was no effect of isobutylene on the number, growth or survival of the fetuses *in utero* and no adverse effects on fetal development. These findings, along with the with findings of no biologically significant effects on male or female reproductive organs attributed to isobutylene exposure in 14-week repeat dose inhalation studies in two rodent species, leads to a conclusion of low concern for reproductive toxicity.

Environment

Isobutylene is a flammable gas with a reported vapour pressure of 2,9732 hPa (25 °C); a water solubility of 263 mg/l (25 °C), a log K_{ow} of 2.34, a melting point of -140.4°C, a boiling point of -6.9°C and a density of 0.588 g/cm³ (25°C).

Results of distribution modelling show that isobutylene will partition primarily to the air compartment (99.99%), with a negligible amount partitioning to water (0.01%). In spite of its water solubility, wet deposition of isobutylene is not likely to play a significant role in its atmospheric fate because of rapid photodegradation. Volatilisation to the air will contribute to the rapid loss of isobutylene from aqueous and terrestrial habitats. In the air, isobutylene has the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals and ozone with calculated degradation half-lives ranging from approximately 2 to 8 and 25 hours, respectively, depending on hydroxyl radical and ozone concentrations. Aqueous photolysis and hydrolysis will not contribute to the transformation of isobutylene in aquatic environments because it is either poorly or not susceptible to these reactions.

The photochemical ozone creation potential index for isobutylene has been reported to range from 62.7 to 70.3. Because of the relatively short half-life of isobutylene in the atmosphere and the low environmental concentrations typically found, its contribution to potential global warming can be considered minor. The ozone depletion potential of this substance is negligible.

Isobutylene concentrations have been reported to range in urban air samples ranging from 1 to 10 ppb.

Although the biodegradability of isobutylene has not been evaluated, studies have demonstrated that 1-butene can be degraded by bacteria isolated from soil and surface water samples. The results from these studies suggest that isobutylene may also be subject to microbial degradation because of the similarity between these two aliphatic alkenes. However, biodegradation is unlikely to contribute to the overall degradation of isobutylene in the environment because it is a gas. Isobutylene is not expected to sorb significantly to organic matter in soil, sediment, and wastewater solids based on a log K_{oc} of 1.55.

Due to the fact that isobutylene is a gas at ambient temperature and pressure and is expected to partition predominantly to the atmosphere, no aquatic toxicity testing has been conducted. The ECOSAR model was used to predict aquatic toxicity using the equation for neutral organics, a reliable estimation method for this class of substance. Calculated acute toxicity values for fish and invertebrates are 19.9 and 21.9 mg/L, respectively. For algae, the calculated 96-hr EC50 is 13.9 mg/L. Chronic toxicity values of 2.7, 1.3, and 1.7 mg/L are calculated for fish (based on survival/growth), invertebrates (based on survival/reproduction), and algae (based on growth), respectively. Isobutylene has a low potential to bioaccumulate in aquatic species based on a calculated bioconcentration factor of 12.6.

A calculated 14-day LC₅₀ value of 271.2 mg/kg soil has been calculated for an earthworm.

Exposure

Worldwide isobutylene production from all sources exceeds 10,000 kilotonnes/year. Approximate production volumes are reported for Japan, 1,000 kilotonnes/year, Western Europe, 995 kilotonnes/year, and the United States, 8,300 kilotonnes/year.

Isobutylene is a component of natural gas and crude oil and is used as a chemical intermediate. Although isobutylene has been identified in natural environments, this has traditionally been associated with losses from petrogenic sources resulting from offgassing or venting. Anthropogenic sources of isobutylene can result from combustion of fossil fuels and losses from gas plants and refineries.

Exposure to isobutylene may occur at workplaces where it is manufactured. Based on physical properties, the primary workplace exposure would be by inhalation. No consumer exposure is foreseen because there are no direct sales to consumers.

RECOMMENDATION

The chemical is currently of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health:

The chemical may possess properties indicating a hazard for human health (carcinogenicity, although it is unknown if the findings related to carcinogenicity are of relevance to humans). Based on data presented by the sponsor country, exposure to human is anticipated to be low, and therefore, this chemical is currently of low priority for further work.

Countries may desire to investigate any exposure scenarios that were not presented by Sponsor Countries.

Environment:

The chemical possesses properties suggesting a hazard for the environment. Although this does not warrant further work (as it is related to acute aquatic toxicity which may become evident only at very high exposure levels), it should nevertheless be noted by chemical safety professionals and other users.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number:	115-11-7
IUPAC Name:	2-Methylpropene
Molecular Formula:	C ₄ H ₈
Structural Formula:	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2=\text{C}-\text{CH}_3 \end{array}$
Molecular Weight:	56.11
Synonyms:	Isobutene; 2-Methyl-1-propene; 2-Methylpropene; 1,1-Dimethylethene; 1,1-Dimethylethylene; Propene, 2-methyl; Isopropylidenemethylene; γ -Butylene

1.2 Purity/Impurities/Additives

Commercial isobutylene, CAS No. 115-11-7, is a colorless gas with a typical purity of >99%, containing no additives. Common impurities include n-butylenes, <1%, and n-butanes, <1%. Studies with isobutylene in this SIAR that did not define isobutylene purity are assumed to have used a commercial grade with a purity of approximately 99%.

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Property	Value	Reference or Comment
Physical state	Gaseous	Gas at ambient temperatures
Melting point (°C)	-140.4	Lide <i>et al.</i> , 1997
Boiling point (°C, @ 1,013 hPa)	-6.9	Lide <i>et al.</i> , 1997
Relative density (g/cm ³ , @25 °C)	0.588	O'Neil <i>et al.</i> , 2001
Vapor pressure (hPa, @25 °C)	2,973	EPIWIN, 1999
Water solubility (mg/L, @25 °C)	263	McAuliffe, 1966
Partition coefficient n-octanol/water (log K _{ow} value)	2.34	Hansch <i>et al.</i> , 1995
Henry's Law constant (HLC) (Pa-m ³ /mole @25 °C)	63,400	HLC calculated using 263 mg/L water solubility, 2,973 hPa vapor pressure, and 56.11 molecular weight.
Upper Flammability Limit (@25 °C)	9.6% (by volume)*	Exxon, 1991
Lower Flammability Limit (@25 °C)	1.8% (by volume)*	Exxon, 1991

* Data are from a safety data sheet and were not reviewed for quality.

Isobutylene is a flammable gas.

2 GENERAL INFORMATION ON EXPOSURE

Exposure to isobutylene may occur at workplaces where it is manufactured. Based on physical properties, the primary workplace exposure would be by inhalation. No consumer exposure is foreseen because there are no direct sales to consumers. Exposure to isobutylene in the environment may occur from motor vehicle exhaust.

2.1 Production Volumes and Use Pattern

Isobutylene is produced commercially by catalytic or thermal cracking of high boiling petroleum fractions or steam cracking of a mixture of saturated hydrocarbons. Isobutylene (13 to 28% of the product stream of C4 hydrocarbons) is separated from the resultant product mixture of C4 hydrocarbons either by extraction into 45 to 65% sulfuric acid with subsequent regeneration of the isobutylene by steam tripping or by the removal of normal butenes by adsorption on molecular sieves. Other processes that may be used to produce isobutylene include the dehydration of ter-butyl alcohol and the thermal dehydrogenation of isobutane.

World-wide, isobutylene production from all sources exceeds 10,000 kilotonnes/year (Lacson et al., 2002). For the year 2000, production in Japan was estimated at 1,000 kilotonnes. In 2001, Western Europe produced 995 kilotonnes and the United States 8,300 kilotonnes (Lacson et al., 2002).

Isobutylene is only used as a chemical intermediate. It is mainly used as a monomer or copolymer for the production of synthetic rubber and various plastics. Approximately 72% of available isobutylene is used for the production of butyl rubber. Approximately 17% is used for the production of antioxidants for food, food packaging, supplements and for plastics. Approximately 9% is used for the production of (polymer) fuel oil or lube oil additives. Approximately 2% is used for various other intermediate applications.

2.2 Environmental Exposure and Fate

Isobutylene concentrations have been reported in air samples, although there is insufficient information to assess quality. Isobutylene concentrations in urban air have been reported to range from 1 to 10 ppb (Manufacturing Chemists Association, Inc., 1974).

2.2.1 Sources of Environmental Exposure

Isobutylene has been reported as a component of natural gas and crude oil. Although isobutylene has been identified in natural environments, this has traditionally been associated with losses from petrogenic sources resulting from off gassing or venting (e.g. underwater or near-shore oil seepage). Trace levels of isobutylene can be identified in urban and sub-urban air arising from combustion of fossil fuels and losses from gas plants and refineries.

2.2.2 Photodegradation

The environmental fate of isobutylene will largely occur in the atmosphere because it is a gas. Results from the Mackay Level I distribution model (Mackay, 1998) show that isobutylene will partition predominantly to the air compartment. Isobutylene has the potential to degrade to a significant extent in the atmosphere through indirect photolytic process mediated primarily by hydroxyl radicals (OH). In spite of its water solubility, wet deposition of isobutylene is not likely to play a significant role in its atmospheric fate. In comparison, direct photolysis is not expected to contribute to the fate of isobutylene in the aqueous environment.

Indirect Photolysis

In air, a chemical can react with photosensitised oxygen in the form of OH⁻ or ozone (O₃). These reactions can result in a degradative change in the parent chemical that can ultimately lead to its complete degradation.

Isobutylene can rapidly react with OH⁻ in air, which can be a predominant daylight atmospheric degradation process for this chemical. It can also react with O₃. Isobutylene air half-lives of 7.5 and 22.73 hours have been reported based on reactions with OH⁻ (Atkinson, 1985) and O₃ (Atkinson and Carter, 1984), respectively. The OH⁻ reaction half life was calculated using a rate constant of $5.14 \times 10^{-11} \text{ cm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ and an OH⁻ concentration of $5 \times 10^5 \text{ OH}^-/\text{cm}^3$, while the O₃ reaction half life was calculated using a rate constant of $1.1 \times 10^{-17} \text{ cm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ and an O₃ concentration of $7.0 \times 10^{11} \text{ O}_3/\text{cm}^3$.

Potential OH⁻ reaction rate and atmospheric chemical half-life is calculated based on an average OH⁻ radical concentration. The atmospheric oxidation potential model (Meylan and Howard, 1993) calculates a rate constant of $51.67 \times 10^{-12} \text{ cm}^3 \text{ mol}^{-1} \text{ s}^{-1}$ and an average isobutylene atmospheric half-life (t_{1/2}) of 2.48 hours or 0.21 days based on a 12-hour day (the 12-hour day half-life value normalizes degradation to a standard day light period during which hydroxyl radicals needed for degradation are generated). The rate constant was calculated using an average global OH⁻ concentration of $1.5 \times 10^6 \text{ OH}^-/\text{cm}^3$ (EPIWIN, 1999).

These data indicate that indirect photodegradation can contribute significantly to the rapid degradation of isobutylene in the environment.

Direct Photolysis

Direct photochemical degradation in aqueous solution occurs through the absorbance of solar radiation by a chemical substance. If the absorbed energy is high enough, then the resultant excited state of the chemical may undergo a transformation. A prerequisite for direct photodegradation is the ability of one or more bonds within a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range. Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds, and wavelengths below 290 nm are shielded from the earth by the stratospheric ozone layer.

An approach to assessing the potential for a substance to undergo photochemical degradation is to assume that degradation will occur in proportion to the amount of light wavelengths >290 nm absorbed by constituent molecules (Zepp and Cline, 1977). Isobutylene does not absorb light within a range of 290 to 750 nm. These data indicate that photolysis will not significantly contribute to the degradation of isobutylene in the aquatic environment.

2.2.3 Stability in Water

Results from the distribution model (Mackay Level I) show that isobutylene will partition negligibly to the water compartment. However, the low levels of isobutylene that may occur in aquatic environments are unlikely to degrade by hydrolysis because this process requires specific chemical structures not present in isobutylene. The lack of a suitable leaving group renders a compound resistant to hydrolysis. Simple hydrocarbons such as isobutylene are resistant to hydrolysis because they lack a functional group that is hydrolytically reactive (Harris, 1982). Therefore, hydrolysis will not contribute to its removal from the environment.

2.2.4 Transport between Environmental Compartments

Fugacity-based multimedia modeling provides basic information on the relative distribution of a chemical between selected environmental compartments (i.e., air, soil, water, sediment, suspended sediment, and biota). A widely used fugacity model is the EQC (Equilibrium Criterion) Level I model (Mackay, 1996; Mackay, 1998). This model requires the input of basic physicochemical parameters (i.e., molecular weight, water solubility, K_{ow}, melting point).

Results of the Mackay Level I environmental distribution model (Table 2) suggest that isobutylene will partition primarily to air. These results can be explained by isobutylene's high vapor pressure, 2,973 hPa at 25°C (EPIWIN, 1999).

Table 2. Environmental distribution as calculated by the Mackay (1998) Level I fugacity model.

Environmental Compartment	Percent Distribution*
Air	99.99
Water	0.01
Soil	0.00
Sediment	0.00
Suspended Sediment	0.00
Biota	0.00

*Distribution is based on the following model input parameters:

Molecular Weight	56.11
Temperature	25 °C
Log K _{ow}	2.34
Water Solubility	263 g/m ³
Vapor Pressure	2,973 hPa
Melting Point	-140.4 °C

Isobutylene has the potential to rapidly volatilize from surface waters, based on a Henry's Law constant (HLC) representing volatility of 63,400 Pa·m³/mole. The HLC was calculated using a water solubility of 263 mg/L, a vapor pressure of 2,973 hPa, and a molecular weight of 56.11. The volatilization half-life of isobutylene from a model river and lake is estimated to be approximately 46 minutes and 2.97 days, respectively (EPIWIN, 1999). Isobutylene is not expected to sorb significantly to organic matter in soil, sediment, and wastewater solids based on a log K_{oc} of 1.55 (EPIWIN, 1999).

2.2.5 Biodegradation

Results from standard aerobic, aquatic biodegradation tests are not available for isobutylene. As a gas, isobutylene is not amenable to standard testing procedures and would present severe technical challenges to achieving aqueous concentrations because of its potential to rapidly partition from water to air. There are no data to assess the inherent or ready biodegradability of isobutylene. However, there is information in the literature to suggest that there is a potential for isobutylene to be metabolised by selected bacteria in the environment, although there is no information available on degradation rates. Additionally, isobutylene is predicted by BIOWIN v 3.67 to biodegrade

rapidly (EPIWIN, 1999), although this assessment has not been confirmed with standardized testing.

The microbial metabolism of aliphatic alkenes can be initiated by attack at the double bond (Watkinson and Morgan, 1990). Four degradative processes have been identified:

- oxygenase attack upon a terminal methyl group to the corresponding unsaturated alcohol and acid,
- subterminal oxygenase attack to the corresponding alcohol and acid,
- oxidation across the double bond to the corresponding epoxide, and
- oxidation across the double bond to the corresponding diol.

Although, isobutylene has not been reported as a growth substrate for bacteria, isolated bacterial strains have been evaluated for their potential to biodegrade 1-butene under aerobic conditions. Bacteria from two genus, *Mycobacterium* spp. and *Xanthobacter* spp., isolated from environmental samples have demonstrated the ability to degrade 1-butene (van Ginkel and de Bont, 1986; Habets-Crützen *et al.*, 1984; Hou *et al.*, 1983; Weijers *et al.*, 1995). Weijers *et al.* (1995) showed that epoxybutane can be converted to the corresponding ketone using a cell extract from a *Xanthobacter* spp. In the same study, 2-methyl-1,2-epoxypropane was not converted suggesting that isobutylene metabolism is not mediated in a manner similar to 1-butene by this organism. However, because of the structural similarity between 1-butene and isobutylene, these studies suggest that isobutylene biodegradation may occur through a process not yet evaluated.

2.2.6 Bioaccumulation

A log bioconcentration factor of 1.10 for isobutylene is calculated using a log Kow value of 2.34 (Hansch *et al.*, 1995). This suggests that isobutylene has a low potential for bioconcentration in aquatic species and is not expected to bioaccumulate.

2.2.7 Other Information on Environmental Fate

Isobutylene is highly volatile and will rapidly partition to the air from terrestrial environments.

The photochemical ozone creation potential (POCP) index for a chemical provides a relative measure of its reactivity or ozone forming potential. The POCP index can also provide a means of ranking volatile organic compounds (VOCs) by their ability to form ozone in the troposphere. Reported POCP indices for isobutylene in northwestern Europe range from 62.7 to 70.3 (Derwent *et al.*, 1996; Derwent *et al.*, 1998), in comparison with an POCP index of 100 for ethylene, the reference substance.

Based on data presented in this SIAR, it can be concluded that isobutylene can react easily with hydroxyl radicals and ozone. The atmospheric life-time is approximately 1 day or less. Isobutylene does not have Cl- or Br-atoms. Therefore, reactive Cl- or Br-substances, which can have an adverse impact on stratospheric ozone concentration, are not formed following photochemical degradation. The ozone depletion potential of this substance is negligible. When considered with isobutylene's relatively short atmospheric half-life, its contribution to global warming can be considered minor.

2.3 Human Exposure

Isobutylene is a normal component of human breath and has been measured at a concentration of 0.43 ± 0.09 nmol/L (Hempel *et al.*, 1980).

2.3.1 Occupational Exposure

There are neither National exposure limits nor an ACGIH TLV for isobutylene. Isobutylene is listed in EU Council Directive 98/24/EC on the protection of workers from the risks related to chemical agents at work, "Hazardous chemical agent" [art. 2(b)(i)]. 1998 O.J. (L 131) 11.

Based on physical properties, the primary workplace exposure would be by inhalation. Workplace industrial exposure by inhalation to isobutylene may occur in a number of ways (Personal Communication, 2003). These include :

(i) Exposure linked to handling, transfer, loading and unloading of either (a) LPGs containing isobutylene or (b) pure isobutylene between vessels (e.g. pipe to sphere transfer). These types of exposure can occur due to losses of very volatile organic compounds (VVOCs) in plant equipment. Types of losses vary but historically these are known to occur through hose connections, within valves or seals in the loading/unloading system and through pressure relief valves. To some extent, replacement of hoses (and in particular flexible hoses) by hard piping has ameliorated these types of losses. Employees affected routinely tend to be supply, distribution or transport process technicians (i.e. including shipping, marine terminal and road car operating personnel). Maintenance technicians may also be affected although this would not be anticipated to be routine in nature.

(ii) Exposure due to fugitive emissions from fixed plant. Here, loss of LPGs containing isobutylene or pure isobutylene may occur from leaking valves, seals and sampling points. Key areas which have been historically associated with isobutylene loss include leaks in the storage and compressor systems (where relevant), and leaks associated with high service pumps with simple (i.e. single) mechanical seals. Leaks (as fugitive emissions) have also been identified in piping systems between vessels or fractionating towers (e.g. C3 / C4# separation). Both process and maintenance technicians, as well as non-affiliated plant workers, are potentially exposed.

(iii) Isobutylene is encountered in cat-cracked LPG streams and as a component in Rich and Spent C4#s streams at varying concentrations. Isobutylene is commercially separated from other C4 butenes by catalytic conversion to methyl tertiary butyl ether, MTBE, (98% conversion), followed by further catalytically-controlled reaction back to isobutylene and methanol. Here, isobutylene is obtained at 99% purity for storage and subsequent use. Some exposure to isobutylene may be encountered in process sampling steps and in vessel maintenance tasks. However, exposure risk to isobutylene may be more pronounced in catalyst changeout activities as the catalyst is present as layers of "catalyst packs", sometimes referred to as "teabags" which require stepwise manual removal. Traces of isobutylene are found in catalyst even after thorough purging and preparation. Maintenance or contract workers normally carry out this task.

Isobutylene is the primary feed to several chemical manufacturing processes (e.g. Synthetic Rubber) where it is reacted with isoprene in a catalytically-mediated reaction to produce butyl rubber. Exposure may occur at various stages in the process, including fugitive emission, and where rubber mixtures (e.g. rubber cement) is sampled for process quality testing. Sampling takes place into bombs (300 ml) used in closed-loop mode for pure isobutylene and into containers or special bags for "rubber slurry" or "rubber cement" sampling. Volatilisation losses can give rise to a pathway for exposure by inhalation.

(iv) Exposure during sampling tasks for (a) any LPG streams containing isobutylene and (b) pure isobutylene. Historically, sampling bombs for LPGs, including isobutylene, were required to be "open-atmosphere vented" to remove contaminants from the bomb and the sampling "deadleg" within the sampled line. However, despite improvements in exposure reduction with the advent of closed-loop sampling systems (where fitted), any wear or leakage in the joints within closed-loop systems have been known to result in employee exposure. Process technicians are primarily at risk of exposure although lab technicians who take samples are also possible affected. Similarly, persons

carrying out lab testing of isobutylene by gas-chromatography are also at risk where the GC is not within a fumehood. For example, isobutylene streams are either direct-injected by bomb which is purged through an open vent in the gas-sample valve, or transferred via a bladder which is also prone to low-level leakage.

2.3.2 Consumer Exposure

There are no direct sales to consumers. Isobutylene is used as a chemical intermediate primarily in the manufacture of polymers. Although a potential component of natural gas, recent analyses reported on the internet by commercial gas companies and energy institutions, do not list it as a significant component, Internet Search (2003). Consequently, potential consumer exposure will be negligible.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Studies in Animals

In vivo Studies

Pharmacokinetic studies have been conducted in rats with isobutylene (Henderson *et al.*, 1993; Sabourin *et al.*, 1992). In male F344/N rats, inhaled isobutylene is rapidly metabolized to oxidized products excreted mainly in the urine. Blood levels of isobutylene were linearly related to exposure concentrations between 40 and 400 ppm but increased to supralinear at 4000 ppm, suggesting saturation of metabolism. Absorption of inhaled isobutylene was approximately 8% up to 40 ppm but decreased slightly at higher concentrations (e.g., only 5% was absorbed at 400 ppm). The amount of isobutylene metabolized per ppm-hr of exposure was also linear up to 40 ppm but decreased at higher concentrations. Over 90% of the absorbed isobutylene was metabolized at exposure concentrations up to 400 ppm, but exposure to 4000 ppm resulted in approximately 20% of the absorbed dose to be exhaled as unmetabolised isobutylene.

Isobutylene appears to be metabolized via cytochrome P450 to an epoxide, 2-methyl-1,2-epoxypropane (MEP) followed by hydrolysis via epoxide hydrolase to the diol, which is oxidized to 2-hydroxyisobutyric acid (HIBA). MEP has been identified as the primary metabolite of isobutylene in liver tissue of various species, including man (Cornet *et al.*, 1995). In vitro studies indicate that mouse liver enzymes oxidize isobutylene to the epoxide in a reaction that is cytochrome P450-dependent and which is inducible by phenobarbital treatment (Cornet *et al.*, 1991). Also, the formation of isobutylene epoxide was enhanced by inhibition of epoxide hydrolase or glutathione S-transferase, suggesting that the epoxide is further metabolized via these pathways.

Metabolism of isobutylene is saturable in both rats and mice, and can be blocked with inhibitors of cytochrome P-450 enzymes in vivo and in vitro (Csanady *et al.*, 1991). At concentrations up to 500 ppm, the metabolic elimination in rats and mice can be described by a first order process.

Inhalation uptake as well as exhalation of isobutylene is expected to be higher in mice than rats because of the higher respiratory frequency in mice. In addition, mice metabolise isobutylene faster than rats, which can be explained by the higher activity of microsomal monooxygenases in mice compared with rats (Csanady *et al.*, 1991).

Studies in Humans

There are no studies in humans.

3.1.2 Acute Toxicity

There are several acute toxicity studies referenced in the dossier. One study was conducted by the oral route and the others were conducted by inhalation route of exposure. There are no acute dermal toxicity data on isobutylene.

Studies in Animals

Inhalation

Mice and rats were exposed to varying concentrations of isobutylene vapours in order to determine the LC50 for each species. In these studies, the 2-hour LC50 of isobutylene in mice was 180,000 ppm (415 mg/L) and the 4-hour LC50 in rats was 270,000 ppm (620 mg/L) (Shugaev, 1969). Shugaev (1969) reported rats inhaling isobutylene for 1-hour at the LC50 were in a state of deep "narcosis" that was likely anesthesia, since isobutylene concentrations of 198,000 ppm (19.8%) induced anesthesia in mice within 10 minutes and a concentration of 320,000 ppm (32%) produced respiratory arrest (Virtue, 1950). Isobutylene is predicted to produce narcosis in man at concentrations exceeding the lower explosive limit (LEL) of 18,000 ppm based on anaesthetic potency data of Virtue (1950) and the structure-activity relationship derived by Drummond (1993) for similar light hydrocarbon gases.

Oral

A nominal weight of 29.7 mg isobutylene was administered (in corn oil) at a constant volume of approximately 1 mL (5 mL/kg body weight) by oral gavage at a single dose of 5.0% (or 150 mg/kg/day) to 6 male and 6 female Sprague Dawley rats. Pairs (one male, one female) were sacrificed at different timepoints within 6 hours post dosing. Blood and urine samples were taken during necropsy from all animals. There were no ketone bodies noted in urine analyses performed in this study. No adverse clinical effects nor mortality occurred as a result of the exposure. The only treatment-related effects at necropsy was slight distension of the ileum and jejunum with some mucoid secretions noted in 7 of 8 animals killed up to 4 hours after dosing. (Hazelton, 1986a).

Studies in Humans

There are no acute toxicity studies in humans.

Conclusion

Isobutylene has a low order of acute toxicity by the oral and inhalation routes of exposure. The 2-hour LC50 of isobutylene in mice was 180,000 ppm (415 mg/L) and the 4-hour LC50 in rats was 270,000 ppm (620 mg/L). At concentrations exceeding the LEL, isobutylene has the potential to produce narcosis or cause asphyxia by reducing the available concentration of oxygen.

3.1.3 Irritation

Studies in Animals

There are no irritation studies in animals.

Studies in Humans

There are no irritation studies in humans.

3.1.4 Sensitisation

Studies in Animals

There are no sensitisation studies in animals.

Studies in Humans

There are no sensitisation studies in humans.

3.1.5 Repeated Dose Toxicity

There are several reliable repeated dose studies referenced in the dossier. These studies are summarised in Table 3. The inhalation and oral studies conducted in rats by Hazleton (1982, 1986a,b) and the rat and mouse inhalation studies conducted under the US National Toxicology Program (NTP, 1998) were selected as the critical studies.

Table 3. Summary of repeated dose toxicity studies for isobutylene.

Route	Species	Period	Doses	NOAEL	Observed effects	Reference
Oral	Rat	28-d	1.5, 15, 150 mg/kg	150 mg/kg/d	↓WBC count in high dose (Males & Females)	Hazleton (1986b)
Inhalation	Rat	13-wk	250, 1000, 8000 ppm (0.57, 2.29, 18.4 mg/L, respectively)	8000 ppm (18.4 mg/L)	↑ Urinary ketone bodies (of unknown significance)	Hazleton (1982)
Inhalation	Rat	14-wk	500, 1000, 2000, 4000, 8000 ppm (1.14, 2.29, 4.59, 9.18, 18.4 mg/L, respectively)	8000 ppm (18.4 mg/L)	↑ Kidney wt (Males, ≥4000 ppm) ↑ Liver wt (Females, ≥1000 ppm) Minimal nasal effects (both sexes, ≥500 ppm)	NTP (1998)
Inhalation	Mouse	14-wk	500, 1000, 2000, 4000, 8000 ppm (1.14, 2.29, 4.59, 9.18, 18.4 mg/L, respectively)	8000 ppm (18.4 mg/L)	↑ Kidney wt (Males, 8000 ppm) ↑ Kidney wt (Females, ≥500 ppm)	NTP (1998)
Inhalation	Rat	105-wk	500, 2000, 8000 ppm (1.14, 4.59, 18.4 mg/L, respectively)	2000 ppm (4.59 mg/L)	↑ Kidney wt (Males, 8000 ppm) ↑ Kidney wt (Females, ≥500 ppm) Minimal nasal effects (both sexes, ≥500 ppm)	NTP (1998)
Inhalation	Mouse	105-wk	500, 2000, 8000 ppm (1.14, 4.59, 18.4 mg/L, respectively)	8000 ppm (18.4 mg/L)	↑ Kidney wt (Males, 8000 ppm) ↑ Kidney wt (Females, ≥500 ppm) Minimal nasal effects (both sexes, ≥500 ppm) ↓ Body wt (Females, ≥2,000 ppm)	NTP (1998)

Studies in Animals

Inhalation

Sprague-Dawley rats (10/sex/group) were exposed by inhalation to 250, 1000, or 8000 ppm of isobutylene for 6 hr/day, 5 day/week for 13 weeks (Hazleton, 1982). No significant toxicological effects were observed at any concentration. The only significant clinical change was an elevation in ketone bodies detected in urine by a semi-quantitative method (e.g., Multistix) at 1000 ppm (males and females) and 8000 ppm (males). Toxicological significance of elevated ketones is unknown but the finding indicates absorption; possibly the urine ketone bodies were derived from metabolism of the 4-carbon isobutylene. It was likely that internal organ exposure was higher in this inhalation study than in the oral studies where ketone bodies were not found (Hazleton, 1986a). However, blood and organ levels were not measured after inhalation. Histopathological examination did not reveal any treatment-related changes. The NOAEL was 8000 ppm.

The NTP conducted subchronic inhalation studies on isobutylene in F344/N rats and B6C3F1 mice. Groups of 10 male and 10 female rats or mice were exposed to isobutylene at concentrations of 500, 1000, 2000, 4000, or 8000 ppm for 6 hours/day, 5 days/week for 14 weeks. Concentrations greater than 8,000 ppm isobutylene were not used because of the danger of explosion.

All rats survived to the end of the study. There were no exposure-related body weight changes, clinical findings or effects on hematologic or clinical chemistry indices. Furthermore, there were no biologically significant effects on male or female reproductive organs (discussed further in Section 3.1.8). The right kidney weights of 4,000 and 8,000 ppm males and the relative (to body weight) right kidney weights of all exposed groups of males were greater than those of the chamber controls; however, the differences were no greater than 10% and 8%, respectively. No effects were observed on either the kidney weights or relative (to body weight) kidney weights of female rats. The absolute liver weights of females exposed to 1,000 ppm and above, and the relative (to body weight) liver weights of all exposed groups of female rats were greater (up to 20%) than those of the chamber controls. However, the increases in absolute and relative (to body weight) liver weights did not occur in a concentration-related manner. There were no histopathologic effects associated with increased kidney or liver weights as a result of isobutylene exposure. There were no exposure-related gross lesions in the rats. Some minimal hypertrophy of goblet cells lining the nasopharyngeal duct in the most caudal section of the nasal cavity was observed in all groups of exposed male and female rats (males: 0/10 in 0 ppm controls, 4/10 in 500 ppm, 7/10 in 1,000 ppm, 9/10 in 2,000 ppm, 8/10 in 4,000 ppm, 9/10 in 8,000 ppm; females: 0/10, 4/10, 8/10, 8/10, 7/10, 10/10, respective exposure groups). This finding was also observed in the 2-year inhalation carcinogenesis studies described below.

All mice survived to the end of the study. The final mean body weights and body weight gains of all exposed groups of males and females were similar to those of the chamber controls. There were no clinical findings or biologically significant effects on male or female reproductive organs attributed to isobutylene exposure (discussed further in Section 3.6). The absolute and relative (to body weight) right kidney weights of 8,000 ppm males were greater (approximately 11%) than those of the chamber controls. The absolute and relative (to body weight) right kidney weights of all groups of exposed females were greater (up to 18%) than those of the chamber controls, but in general, were not exposure concentration related. There were no lesions detected grossly at necropsy or microscopically that supported these weight increases. No effects on the nasal cavity were observed.

The two studies described above were used to set the exposure concentrations for 2-year carcinogenicity studies, which are also key to the discussions about repeated dose toxicity. Rats or

mice (50 males and 50 females/group, 6 weeks of age) were exposed by inhalation for 6 hours/day, 5 days/week, for 105 weeks to 0, 500, 2,000 or 8,000 ppm, isobutylene.

The survival of exposed male and female rats was similar to that of the chamber controls. Mean body weights of exposed groups were generally similar to those of the chamber controls throughout the study. There were no exposure-related clinical findings. Isobutylene exposure caused an increased incidence of thyroid gland follicular cell carcinoma in the 8,000 ppm group male rats. However, there were no concurrent increases in the incidences of thyroid gland follicular cell hyperplasia or adenoma in male rats, nor were there increased incidences of proliferative lesions of the thyroid gland in exposed female rats compared to the chamber controls.

Exposure of rats to isobutylene caused an increase, although marginal, in the incidences of hyaline degeneration of the olfactory epithelium of the nose in males and females (males: 43/49 in 0 ppm controls, 45/49 in 500 ppm, 46/50 in 2,000 ppm, 49/49 in 8,000 ppm; females: 44/50, 47/50, 48/50, 47/49, respectively). More importantly, the severities of this lesion (mild to moderate) were increased in exposed male and females in a concentration-related fashion (males: 1.3, 1.4, 2.2, 2.6; females: 1.5, 2.4, 2.8, 2.8, respectively, on a severity scale of 0 to 4). In inhalation studies, hyaline degeneration is a commonly observed change in the epithelium of the nasal cavity, the incidence and severity of which may increase with increasing exposure concentration. The accumulation of these protein globules is considered a nonspecific adaptive response to prolonged inhalation of irritant material and has no adverse effect on affected animals (NTP, 1998). This finding was also noted in studies with propylene, another light olefinic gas (NTP, 1985). Some minimal hypertrophy of goblet cells lining the nasopharyngeal duct in the most caudal section of the nasal cavity was observed in all groups of exposed male and female rats (males: 43/49 in 0 ppm controls, 45/49 in 500 ppm, 46/50 in 2,000 ppm, 49/49 in 8,000 ppm; females: 44/50, 47/50, 48/50, 47/49, respective exposure groups). However, no nasal neoplasms were observed in male or female rats exposed to isobutylene.

In the mouse study, neither survival rates nor body weight gains of males were significantly affected by isobutylene exposure. Although survival rates for female mice were not affected by exposure, female mice exposed to 2,000 or 8,000 ppm weighed slightly less than the chamber controls in the second year of the study. There were no treatment-related clinical findings in mice. The only lesions associated with exposure in mice were nonneoplastic nasal lesions that were minimal to mild in severity; however, the incidences increased with increasing exposure concentration. Hyaline degeneration of the respiratory epithelium occurred in all exposed groups of males and females, was significantly greater than that in control groups (males: 6/50 in 0 ppm controls, 19/49 in 500 ppm, 29/50 in 2,000 ppm, 39/48 in 8,000 ppm; females: 21/47, 39/50/ 41/49, 48/50, respectively), and occurred with positive trends. The severities of this lesion (minimal to mild) were less than that observed in rats but increased in exposed males in a concentration-related fashion and in females only at 8,000 ppm (males: 1.0, 1.2, 1.5, 1.8; females: 1.8, 1.5, 1.6, 2.3, respectively). The incidence of hyaline degeneration of the olfactory epithelium in males occurred with a positive trend and was significantly greater in 2,000 and 8,000 ppm males than in controls (6/50, 7/50, 16/50, 17/48, respectively, with severity of 1.0, 1.1, 1.6, 1.4). The incidence of hyaline degeneration of the olfactory epithelium in females also occurred with a positive trend; however, the incidences were not statistically different from controls (17/47, 19/50, 24/49, 27/50, respectively with severity of 1.5, 1.2, 1.1, 1.2). Although they were not observed in the 14-week mouse study, these lesions are fairly common in long-term inhalation studies, and as discussed above, have no adverse effect on affected animals (NTP, 1998). No nasal neoplasms were observed in male or female mice.

The cancer findings from the rat and mouse 2-year studies are discussed in detail below.

Oral

Groups of 5 male and 5 female Sprague-Dawley rats were administered 1.5, 15, or 150 mg/kg/day isobutylene by oral gavage for 28 consecutive days (Hazleton, 1986b). There were no deaths. There were no changes in body weight or food consumption. The only statistically significant treatment-related effect was a decrease in total white blood cell count of 44% in female rats and 11% in male rats in the 150 mg/kg/day group, predominantly in leucocytes and monocytes. However, these values were within the historical background range of the laboratory. Differential counts of WBC cell types were performed but not analysed statistically. Slight, non-significant increases in BUN (male) and blood glucose (female) were also observed in this group; however, the maximum changes observed in these clinical chemistry parameters were within the normal range experienced in this strain of rat at the laboratory. The range finding study (Hazleton, 1986a) showed very low levels of isobutylene in blood after dosing with 29.7 mg/kg (nominal) reaching a maximum of 1.2 µg/ml 20 min after dosing, and a maximum of 17% of the dose in the GI tract 20 min after dosing. No toxicologically significant changes were observed at dose levels up to 150 mg/kg/day administered over 28 days. A reasonable explanation for the low recovery of isobutylene might be that a considerable amount was lost back to the atmosphere via volatilisation after instillation as a bolus dose in the warm stomach. Histopathological examination did not reveal any treatment-related changes. The laboratory concluded no toxicologically significant changes were observed at dose levels up to 150 mg/kg/day of isobutylene dosed continually over a 4 week period. Thus, the NOAEL was 150 mg/kg/day.

Studies in Humans

There are no repeated dose toxicity studies in humans.

Conclusion

These studies demonstrate that isobutylene is not toxic to rats or mice exposed to concentrations up to 2,000 ppm for 105 weeks, but induces a mild adaptive response in the nose of chronically exposed animals.

3.1.6 Mutagenicity

Isobutylene has been tested for mutagenic activity in both in vitro and in vivo test systems. The critical studies are discussed below.

Studies in Animals

In vitro Studies

Isobutylene was tested in an Ames assay in 5 strains of *Salmonella typhimurium* (i.e., TA1535, TA1537, TA1538, TA100 and TA98) with and without metabolic activation and in *Escherichia coli* WP2uvrA(pKM101) (Inveresk, 1981a). In the first test, isobutylene was tested at concentrations of 5, 10, 20, 30, 40 and 50%. In the second test, isobutylene was tested at concentrations of 10, 20, 40, 60, 80 and 100%. No mutagenic activity was induced by isobutylene in any strain at any concentration in the first or second tests. Reduction in the number of colonies in all strains indicative of toxicity and growth inhibition was observed with and without metabolic activation at 80% and 100% isobutylene. Positive controls responded appropriately, inducing from 3-fold to 30-fold increases above negative controls in both the presence and absence of S9. In summary, isobutylene was adequately tested at sufficiently high doses to induce toxicity, and is not mutagenic to bacteria in this test system.

Isobutylene was tested in an *in vitro* cell transformation assay using a mouse embryo fibroblast derived cell line, i.e., C3H/10T1/2 clone 8 mouse cell line (Inveresk, 1981b). The concentrations of isobutylene tested in this transformation assay were 100%, 50%, and 25% in 5% CO₂/air. The assay was performed both in the presence and absence of metabolic activation. No transformed colonies were observed at any exposure level. Positive control compounds, known carcinogens *in vivo*, induced clear evidence of morphological transformation. Thus, under the conditions of this assay, isobutylene had no transforming effect in C3H/10T1/2 cells in the presence or absence of liver metabolic activation.

Isobutylene was tested in a mouse lymphoma specific locus mutation assay (Inveresk, 1981c). In this assay, exponentially growing L5178Y cells were exposed to isobutylene at concentrations ranging from 100% to 6.25% with and without metabolic activation. All cultures were incubated with shaking at 37 °C for 24 hours. Positive control compound without S-9 was ethyl methane sulfonate; with S-9, 2-acetylaminofluorene; cultures were treated for 3 hours. After incubation, cells were harvested by centrifugation, resuspended in fresh medium, and samples from each suspension plated on soft agar for varying times to determine survival or to look for the expression of genetic damage. In both the presence and absence of S-9 mix, isobutylene showed no evidence of mutagenic activity in the mouse lymphoma assay.

In vivo Studies

Isobutylene was evaluated *in vivo* for its ability to induce micronuclei in bone marrow polychromatic erythrocytes (PCEs) in male B6C3F1 mice (EBSI, 1990). Male mice (10/group) were exposed to isobutylene, 6 hours a day for two days at 0, 1000, 3260 or 10,000 ppm. Actual exposure concentrations were determined by on-line gas chromatography reported hourly. Nominal concentrations were calculated. All mice were killed 24 hours after the second exposure. The bone marrow was removed from both femurs, and slides were prepared and stained with acridine orange for fluorescence. 1000 polychromatic erythrocytes (PCEs) were examined for micronuclei. Ratio of PCEs to normochromatic erythrocytes (NCEs) was determined by counting 1000 erythrocytes (PCE + NCE). Isobutylene did not induce a statistically significant positive response nor a dose-related increase in the number of micronuclei in PCEs of mouse bone marrow at any dose level. A significant regression coefficient ($p < 0.05$) for increased percentage of PCEs was observed. However, this event was within historical control values and is not considered biologically significant. The positive control (1,3-butadiene) induced statistically significant increases in micronuclei and a reduced %PCE indicative of toxicity. Negative control values were within normal range. Thus, isobutylene was not clastogenic in mouse bone marrow under the conditions of this test system.

Studies in Humans

There are no mutagenicity studies in humans.

Conclusion

Isobutylene is not mutagenic. It did not induce gene mutations in reverse mutation assays conducted in *S. typhimurium* and *E. coli* either in the presence or absence of metabolic activation. Isobutylene did not increase the number of transformed foci in C3H/10T1/2 clone 8 mouse embryo fibroblast cells. In the mouse lymphoma assay, there was no evidence of mutagenic activity in mouse lymphoma L5178Y cells either in the presence or absence of metabolic activation. In addition, isobutylene at concentrations up to 10,000 ppm did not induce an increase in micronuclei formation in mouse bone marrow cells.

3.1.7 Carcinogenicity

Two-year carcinogenicity studies were conducted by the National Toxicology Program (NTP, 1998) in F344/N rats and B6C3F1 mice. These studies, conducted under GLP conditions, were selected as critical studies.

In vivo Studies in Animals

Rats or mice (50 males and 50 females/group, 6 weeks of age) were exposed by inhalation for 6 hours/day, 5 days/week, 105 weeks to 0, 500, 2,000 or 8,000 ppm, isobutylene. Major findings are summarized in Table 4.

Table 4. Findings from NTP carcinogenicity studies of isobutylene.

	Species	Doses (ppm)	NOAEL (ppm)	Observed effects
Neoplastic	Rat	500, 2000, 8000 (1.14, 4.59, 18.4 mg/L, respectively)	2000 ppm see discussion of relevance in text below	↑ Thyroid tumors (follicular cell carcinoma) (Males, 8000 ppm)
	Mouse	500, 2000, 8000 (1.14, 4.59, 18.4 mg/L, respectively)	8000 ppm	none
Nonneoplastic	Rat	500, 2000, 8000 (1.14, 4.59, 18.4 mg/L, respectively)	2000 ppm	↑ Kidney wt (Males, 8000 ppm) ↑ Kidney wt (Females, ≥500 ppm) Minimal nasal effects (both sexes, ≥500 ppm)
	Mouse	500, 2000, 8000 (1.14, 4.59, 18.4 mg/L, respectively)	8000 ppm	↑ Kidney wt (Males, 8000 ppm) ↑ Kidney wt (Females, ≥500 ppm) Minimal nasal effects (both sexes, ≥500 ppm) ↓ Body wt (Females, ≥2,000 ppm)

The survival of exposed male and female rats was similar to that of the chamber controls. Mean body weights of exposed groups were generally similar to those of the chamber controls throughout the study. There were no exposure-related clinical findings or gross lesions in the rats. Exposure of rats to isobutene caused an increase, although marginal, in the incidences of hyaline degeneration of the olfactory epithelium of the nose in males and females; more importantly, the severities of this lesion (mild to moderate) were increased in exposed males and females in a concentration-related fashion. However, no nasal neoplasms were observed in male or female rats. Isobutylene exposure caused an increased incidence of thyroid gland follicular cell carcinoma in the 8,000 ppm group male rats compared to the chamber controls. The histomorphology of the carcinomas in this group was similar to the morphologic spectrum typical of spontaneously developing follicular cell carcinomas. The combined incidence of C-cell adenoma and carcinomas in male rats was 5/48 (controls), 4/48 (500 ppm), 7/48 (2000 ppm,) and 8/50 (8000 ppm). The incidence of follicular cell carcinoma in male rats was 1/48 (controls), 0/48 (500 ppm), 0/48 (2000 ppm) and 5/50 (8000 ppm). There were no concurrent increases in the incidences of thyroid gland follicular cell hyperplasia or

adenoma in male rats, nor were there increased incidences of proliferative lesions of the thyroid gland in exposed female rats compared to the chamber controls. The historical control range for follicular cell carcinoma in male rats in inhalation studies was reported as 0% to 4% (NTP, 1998; Haseman *et al.*, 1998). The highest historical control incidence of this neoplasm by any route for male rats was reported as 3/50 (6%) (in a dosed feed study) (NTP, 1998; Haseman *et al.*, 1998). Thus, the five carcinomas in the 8,000 ppm male group were considered treatment related by the NTP because of the significant increase over historical control rates for inhalation studies as well as all other routes of administration. The relevance of this finding to humans is unknown and discussed further below.

The NTP concluded that under the conditions of this study, there was some evidence of carcinogenic activity of isobutylene in male F344/N rats at the highest dose based on an increased incidence of follicular cell carcinoma of the thyroid gland. There was no evidence of carcinogenic activity in female F344/N rats exposed to isobutylene at concentrations of 500, 2,000 or 8,000 ppm. Although the NTP considered the thyroid tumors to be treatment related, the relevance of this finding is questionable for the following reasons: the tumors occurred only in one sex of one species, there were no precursor lesions, such as hyperplasia or adenoma, the tumor type occurs spontaneously, there was no dose-response relationship, the tumors were only singular and unilateral and did not form metastases, and there was no increase in liver weight giving indication of a secondary mechanism. Further, the thyroid was not a target organ of isobutylene toxicity in repeated dose studies. A review of the NTP inhalation study on propylene reveals a 7% incidence of thyroid follicular-cell carcinoma (3/45 animals) and a 2% incidence of follicular-cell adenoma (1/45) in male chamber control F344 rats (NTP, 1985). When the absolute numbers of follicular-cell carcinomas in the 8,000 ppm isobutylene exposed male rats are compared to the low incidence in the control rats in this study and further compared to the 7% incidence in control rats in the propylene study, the apparent significance of the finding is further diminished. Finally, subsequent to the publication of the study report, IARC published guidance for evaluating the relevance of rat thyroid follicular-cell tumors for human cancer risk (IARC, 1999).

In this guidance document, IARC notes that no non-radioactive chemical exposure is known to cause tumors of thyroid follicular epithelium in humans, although a small excess of thyroid cancer mortality has been recorded in one cohort of individuals exposed to polychlorinated-para-dibenzodioxins. In contrast, such tumors are readily induced in rodents by both genotoxic and non-genotoxic agents, including goitrogens. The Advisory Group concluded that agents that cause thyroid neoplasia through an adaptive hormonal mechanism belong to a different category from those acting through genotoxic effects or mechanisms involving pathological responses to tissue injury. To define an agent as causing thyroid follicular-cell neoplasia in rodents, solely through hormonal imbalance, the agent and its metabolites must lack genotoxic activity. This should be based on an overall evaluation of *in vivo* and *in vitro* data, and persistent hormonal imbalance must have been demonstrated under the conditions of the carcinogenicity assay. As persistent hormonal imbalance was not evaluated in the isobutylene bioassay, the relevance of this finding to humans is not known.

In the mouse study, neither survival rates nor body weight gains of males were significantly affected by isobutylene exposure. Although survival rates for female mice were not affected by exposure, female mice exposed to 2,000 or 8,000 ppm weighed slightly less than the chamber controls in the second year of the study. There were no treatment-related clinical findings in mice. The only lesions associated with exposure in mice were nonneoplastic nasal lesions in all exposed groups of males and females. No nasal neoplasms were observed in male or female mice.

The NTP concluded that under the conditions of this study, there was no evidence of carcinogenic activity of isobutylene in male or female B6C3F1 mice exposed to 500, 2,000 or 8,000 ppm.

Studies in Humans

There are no carcinogenicity studies in humans.

Conclusion

Based on the results of the NTP studies, isobutylene has a low potential for carcinogenicity. Although isobutylene produced an increase in follicular cell carcinomas of the thyroid, this effect occurred only in male rats at the highest dose, i.e., 8000 ppm. Thyroid tumors did not occur in female rats nor did they occur in male or female mice. As isobutylene is not genotoxic and as the thyroid tumors only occurred in male rats at the highest dose, i.e., 8000 ppm, the mechanism for the formation of the thyroid tumors most likely has a threshold. Overall, this data suggests that isobutylene has a low potential for carcinogenicity.

3.1.8 Toxicity for Reproduction

A prenatal developmental inhalation toxicity study conducted to OECD TG 414 under GLP conditions by the Central Toxicology Laboratory (CTL, 2002) was selected as the critical study.

Studies in Animals

Developmental Toxicity

A prenatal developmental inhalation toxicity study conducted to OECD TG 414 under GLP conditions by the Central Toxicology Laboratory (CTL, 2002) was selected as the critical study.

Twenty-four mated female Wistar rats per test group were whole-body exposed to dynamically generated atmospheres of isobutylene for 6 hours per day on days 5 through 21 (inclusive) of gestation. The target concentrations were 500, 2000 and 8000 ppm. A concurrent control group was exposed to clean air. Chamber concentrations were determined analytically using a gas chromatographic method. The general state of health was examined each day. On exposure days, clinical observation was performed before, during and after exposure. During the preflow period and on post exposure days clinical findings were recorded once each working day. Food consumption, water consumption and body weight of the animals were frequently determined.

On day 22 of gestation, all animals were sacrificed and assessed by gross pathology (including weight determinations of the unopened uterus and the placentae). For each dam, corpora lutea were counted and number and distribution of implantation sites (differentiated as resorptions, live and dead fetuses) was determined. The fetuses were removed from the uterus, sexed, weighed and further investigated for any external findings. Thereafter, all fetuses were examined internally for visceral variation and abnormality, sexed and eviscerated. The fetuses were then fixed in 70% industrial methylated spirits. After approximately 24 hours, the head of each fetus was cut along the fronto-parietal suture line and the brain was examined for macroscopic abnormalities. The fetuses were then returned to the 70% methylated spirits, processed and stained with Alizarin Red S and Alcian Blue and then examined for variation and abnormality of bone and cartilage and the degree of ossification of the *manus* and *pes* was assessed.

Exposure to isobutylene on days 5 to 21 (inclusive) of gestation did not elicit any maternal effects, i.e., there were no treatment-related changes in clinical condition, no effects on maternal body weight or food consumption and no macroscopic findings in tissues examined post mortem.

There was no effect of isobutylene on the number, growth or survival of the fetuses *in utero*. There was no effect of isobutylene on fetal development. A comparison of foetal skeletal defects and variants is presented in Table 5, below. The number of foetuses (litters) with major defects was 3 (2), 5 (5), 5 (3), and 3 (3) in the control, 500, 2000, and 8000 ppm groups, respectively.

Consideration of the specific major skeletal defects showed that the incidence of fetuses with cleft sternbrae, including cleft sternal cartilage and xiphoid cartilage, was 0, 3, 2, and 3 in the control, 500, 2,000 ppm, and 8,000 ppm groups, respectively. Although cleft sternbrae were observed only in fetuses in the isobutylene groups, the incidence of fetuses affected was small and not dose-related and there were no minor changes in the appearance or ossification of the sternbrae to indicate that this area of the skeleton was adversely affected by isobutylene. Also, there was no evidence for an adverse effect of isobutylene on other ossification centres of the skeleton.

There was no effect of isobutylene on the percentage of fetuses with minor external/visceral defects; the proportion of fetuses with a minor defect was statistically significantly *lower* in the isobutylene treated groups in comparison with the control group. Consideration of the specific defects showed that the incidence of fetuses with a kinked ureter was *lower* in the treated groups compared to the control group.

The percentage and proportion of fetuses with external/visceral variants were statistically significantly higher in the 8000 ppm group in comparison with the control group. This difference from control was due to a higher incidence of fetuses with the umbilical artery positioned on the left side of the bladder. The position of the umbilical artery on the right or left side of the bladder is variable in this strain of rat (historical control range 8.1-18.2%) and an increase in incidence of this variation is considered to have occurred by chance and not as a result of exposure to isobutylene.

Isolated differences of other defects and variants from control were considered to be incidental. Thus, isobutylene at exposure concentrations of up to 8000 ppm did not have any adverse effects on fetal development.

Table 5. Intergroup comparison of foetal skeletal defects and variants in developmental toxicity study.

Parameter	Control	500 ppm	2,000 ppm	8,000 ppm
Major Skeletal Defects				
Prop. of fetuses affected	2/284	4/289	2/261	3/294
Percentage (mean)	0.9	1.6	0.9	1.2
Prop. of litters affected	1/24	4/24	2/24	3/24
Minor Skeletal Defects Only				
Prop. of fetuses affected	113/284	147/289	140/261	136/294
Percentage (mean)	48.4	51.0	53.2	45.4
Prop. of litters affected	24/24	23/24	23/24	24/24
Skeletal Variants				
Prop. of fetuses affected	210/284	230/289	199/261	232/294
Percentage (mean)	75.6	80.2	78.0	80.9
Prop. of litters affected	24/24	23/24	24/24	24/24

At the end of the 14-week NTP studies discussed in Section 3.3, samples were collected for sperm motility and vaginal cytology evaluations on 10 rats and mice exposed to 0 (controls), 2,000, 4,000, or 8,000 ppm isobutylene. The parameters evaluated for male animals included spermatid heads per testis, spermatid count, and epididymal spermatozoal concentration and motility. The left cauda epididymis, epididymis, and both left and right testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies from all female animals. The parameters evaluated were estrous cycle length and relative frequency of estrous stages. These data

for rats are presented in Tables 6 and 7 for male and female reproductive parameters, respectively, and discussed below.

In male rats, left epididymis weights were significantly increased and epididymal sperm motility was significantly decreased in the 8000 ppm exposure group. However, there was no statistically significant difference in left or right testis weight compared to controls. In female rats, the time spent in estrus was increased with a concurrent decrease in the time spent in diestrus, although the length of the average estrus cycle was not altered. There were no effects on the reproductive organs of rats of either sex that could be attributed to exposure to isobutylene.

There were no differences between control group and exposed mice of either sex for any of the measured parameters (data not shown). There were no effects on the reproductive organs of mice of either sex that could be attributed to exposure to isobutylene

Table 6. Summary of male rat reproductive parameters evaluated in NTP 14-week study.

Parameter	Control	2,000 ppm	4,000 ppm	8,000 ppm
Weights				
Necropsy body wt.	358 ± 8	364 ± 6	362 ± 7	366 ± 6
L. cauda epidymis	0.1742 ± 0.0063	0.1906 ± 0.0020	0.1838 ± 0.0065	0.1936 ± 0.0046*
L. epididymis	0.4650 ± 0.0067	0.4758 ± 0.0040	0.4601 ± 0.0107	0.4780 ± 0.0067
L. testis	1.4802 ± 0.0260	1.4905 ± 0.0079	1.4913 ± 0.0304	1.5185 ± 0.0211
R. testis	1.416 ± 0.031	1.412 ± 0.011	1.419 ± 0.016	1.445 ± 0.011
Spermatid measurements				
Sperm. Heads / testes	9.89 ± 0.34	10.11 ± 0.40	9.95 ± 0.28	9.97 ± 0.22
Sperm. Heads / testes	14.63 ± 0.54	15.07 ± 0.62	14.82 ± 0.44	15.15 ± 0.43
Sperm. Count (mean)	73.13 ± 2.68	73.35 ± 3.09	74.08 ± 2.18	75.75 ± 2.13
Epididymal spermatozoal measurements				
Motility (%)	91.15 ± 3.18	89.32 ± 2.01	88.04 ± 1.97	86.53 ± 1.90*
Conc (10 ⁶ /g cauda epid)	886 ± 55	836 ± 39	819 ± 66	840 ± 39

* Significantly different ($P \leq 0.05$) from chamber control.

Data are presented as mean ± std. error.

Table 7. Summary of female rat reproductive parameters evaluated in NTP 14-week study.

Parameter	Control	2,000 ppm	4,000 ppm	8,000 ppm
Necropsy body wt.	207 ± 4	213 ± 5	208 ± 4	217 ± 6
Estrous cycle length (days)	4.70 ± 0.15	4.80 ± 0.13	4.80 ± 0.11	4.80 ± 0.08
Estrous stages (% of cycle)				
Diestrus	40.0	38.3	38.3	39.2
Proestrus	17.5	18.3	18.3	13.3
Estrus	20.8	20.8	25.0	24.2
Metestrus	20.8	20.8	18.3	21.7
Uncertain diagnosis	0.8	1.7	0.0	1.7

Necropsy body weight and estrous cycle length data are presented as mean ± std. error.

Studies in Humans

There are no reproductive/developmental studies in humans.

Conclusion

Under the conditions of this prenatal developmental toxicity study, the inhalation exposure of pregnant Wistar rats to isobutylene on days 5 to 21 (inclusive) of gestation elicited no maternal toxicity, prenatal or developmental toxicity, or teratogenicity at all tested concentrations up to 8,000 ppm. There was no effect of isobutylene on the number, growth or survival of the fetuses *in utero* and no effect on fetal development.

These findings, along with the with findings of no biologically significant effects on male or female reproductive organs attributed to isobutylene exposure in repeated dose inhalation studies in two species, and the lack of significant effects on reproductive parameters (except for a minor weight increase in epididymus weight and decreased sperm motility in male rats exposed at 8,000 ppm) leads to a conclusion of low concern for reproductive toxicity.

3.2 Initial Assessment for Human Health

Isobutylene has a low order of acute toxicity. As isobutylene is a gas at normal temperature and pressure, ingestion or dermal absorption of this material is unlikely. Inhalation of isobutylene can produce central nervous system depression, anesthesia and/or asphyxiation. However, these effects are only seen at very high concentrations, i.e., 20% or higher. Isobutylene is predicted to produce narcosis in man at concentrations exceeding the lower exposure limit (LEL) of 18,000 ppm.

There are no data to evaluate the dermal or ocular irritation potential of isobutylene. However, should skin or eye contact occur to this chemical in its liquid state, tissue freezing, severe cold burn, and/or frostbite may result.

Repeated dose toxicity clearly demonstrated that isobutylene is not toxic to rodents at concentrations up to 2,000 ppm for 105 weeks. Although isobutylene produced an increase in follicular cell carcinomas of the thyroid in male rats, this only occurred at the highest exposure concentration, i.e., 8000 ppm. Thyroid tumors did not occur in female rats nor did they occur in male or female mice. This finding is of questionable relevance for humans. Overall, this data suggests that isobutylene has a low potential for carcinogenicity.

Test data clearly demonstrate that isobutylene is not genotoxic. Isobutylene was not mutagenic when tested in reverse mutation assays conducted in *Salmonella typhimurium* and *Escherichia coli* either in the presence or absence of metabolic activation at concentrations. In addition, isobutylene did not increase the number of transformed foci in C3H/10T1/2 clone 8 mouse embryo fibroblast cells. In the mouse lymphoma assay, there was no evidence of mutagenic activity in mouse lymphoma L5178Y cells either in the presence or absence of metabolic activation. In addition, isobutylene did not induce an increase in micronuclei formation in mouse bone marrow cells.

In a prenatal developmental toxicity study, inhalation exposure of pregnant Wistar rats to isobutylene on days 5 to 21 (inclusive) of gestation elicited no maternal toxicity at all tested concentrations up to 8,000 ppm. Furthermore, there was no effect of isobutylene on the number, growth or survival of the fetuses *in utero* and no adverse effects on fetal development.

These findings, along with the with findings of no biologically significant effects on male or female reproductive organs attributed to isobutylene exposure in repeated dose inhalation studies in two species, and the lack of significant effects on reproductive parameters (except for a minor weight

increase in epididymus weight and decreased sperm motility in male rats exposed at 8,000 ppm) leads to a conclusion of low concern for reproductive toxicity.

4 HAZARDS TO THE ENVIRONMENT

Measured data are not available for aquatic toxicity endpoints. However, structure-activity relationship (SAR) data developed with the ECOSAR model (Cash and Nabholz, 1990) are used to address selected acute and chronic endpoints for three aquatic trophic levels (The ECOSAR model was accessed in EPIWIN (1999)). The ECOSAR model is a reliable and valid SAR model to apply to isobutylene because it is based on a related chemical dataset that calculates the toxicity of neutral organic hydrocarbons whose toxic mode of action is non-polar narcosis. For this reason, no further testing is needed nor is the presentation of data from a close analogue necessary. The aquatic toxicity values were determined using the following measured constants: log K_{ow} = 2.34, water solubility = 263 mg/L, and melting point = -140.4°C (ECOSAR requires input of selected physicochemical data and chemical structure to run the model and calculate effect concentrations).

4.1 Aquatic Effects

Isobutylene is expected to exhibit a moderate to low order of aquatic toxicity based on calculated acute and chronic data.

Acute Toxicity Test Results

Isobutylene has a calculated 96-hour LC₅₀ fish toxicity value of 19.9 mg/L, a 48-hour LC₅₀ invertebrate toxicity value of 21.9 mg/L, and a 96-hour EC₅₀ alga toxicity value of 13.9 mg/L.

Chronic Toxicity Test Results

Calculated isobutylene chronic aquatic toxicity values include a 30-day value of 2.7 mg/L for fish (based on survival/growth), a 16-day value of 1.3 mg/L for invertebrates (based on survival/reproduction), and a 96-hour value of 1.7 mg/L for algae (based on growth).

4.2 Terrestrial Effects

Acute Toxicity Test Results

There are no experimental data available using standard testing procedures that can be used to assess the terrestrial hazard of isobutylene. However, there is a calculated (ECOSAR) earthworm 14-day LC₅₀ value of 271.2 mg/kg soil (Cash and Nabholz, 1990). This value was calculated using the following measured constants: log K_{ow} = 2.34, water solubility = 263 mg/L, and melting point = -140.4°C. The earthworm data suggest that isobutylene has a low order of toxicity to soil dwelling organisms.

4.3 Other Environmental Effects

Data on other environmental effects are not available.

4.4 Initial Assessment for the Environment

Results of distribution modelling show that isobutylene will partition primarily to the air compartment, with a negligible amount partitioning to water. In spite of its water solubility, wet deposition of isobutylene is not likely to play a significant role in its atmospheric fate because of rapid photodegradation. Volatilisation to the air will contribute to the rapid loss of isobutylene from aqueous and terrestrial habitats. In the air, isobutylene has the potential to rapidly degrade through indirect photolytic processes mediated primarily by hydroxyl radicals and ozone depending on their concentrations. The isobutylene half-life from hydroxyl radical attack ranges from approximately 3

to 8 hours, while the half-life as effected by reactions involving ozone is approximately 23 hours. Aqueous photolysis and hydrolysis will not contribute to the transformation of isobutylene in aquatic environments because it is either poorly or not susceptible to these reactions.

Isobutylene concentrations have been reported to range in urban air samples ranging from 1 to 10 ppb (Manufacturing Chemists Association, Inc., 1974).

Although the biodegradability of isobutylene has not been evaluated, studies have demonstrated that 1-butene can be degraded by bacteria isolated from soil and surface water samples. The results from these studies suggest that isobutylene may also be subject to microbial degradation because of the similarity between these two aliphatic alkenes. However, biodegradation is unlikely to contribute to the overall degradation of isobutylene in the environment because it is a gas. Isobutylene is not expected to sorb significantly to organic matter in soil, sediment, and wastewater solids based on a $\log K_{oc}$ of 1.55.

Due to the fact that isobutylene is a gas at ambient temperature and pressure and is expected to partition predominantly to the atmosphere, no aquatic toxicity testing has been conducted. The ECOSAR model was used to predict aquatic toxicity using the equation for neutral organics, a reliable estimation method for this class of substance. Calculated acute toxicity values for fish and invertebrates are 19.9 and 21.9 mg/L, respectively. For algae, the calculated 96-hr EC50 is 13.9 mg/L. Chronic toxicity values of 2.7, 1.3, and 1.7 mg/L are calculated for fish, invertebrates, and algae, respectively. Isobutylene has a low potential to bioaccumulate in aquatic species based on a calculated bioconcentration factor of 12.6.

In the terrestrial environment, isobutylene is expected to exhibit a low order of toxicity based on a calculated 14-day LC₅₀ value of 271.2 mg/kg soil for an earthworm.

5 RECOMMENDATIONS

The chemical is currently of low priority for further work.

The chemical may possess properties indicating a hazard for human health (carcinogenicity, although it is unknown if the findings related to carcinogenicity are of relevance to humans). Based on data presented by the sponsor country, exposure to human is anticipated to be low, and therefore, this chemical is currently of low priority for further work. Countries may desire to investigate any exposure scenarios that were not presented by Sponsor Countries.

The chemical possesses properties suggesting a hazard for the environment. Although this does not warrant further work (as it is related to acute aquatic toxicity which may become evident only at very high exposure levels), it should nevertheless be noted by chemical safety professionals and other users.

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ANNEX

A literature search was conducted on 4 October 2002 going back at least 10 years to update the IUCLID file. Search strategy included CAS number, chemical nomenclature, and key words relevant to the endpoints addressed in this SIAR. The databases searched included:

- Aquire (1992-2002)
- BIODEGRADATION DATA (BIODEG) (1992-2002)
- BIODEGRADATION BIBLIOGRAPHIC REFERENCES (BIOLOG) (1992-2002)
- Biological Abstracts - BIOSIS (1992-2002)
- Cancerlit (1992-2002)
- EMBASE (1992-2002)
- EMBSINFO (formerly RBird) (1992-2002)
- Engineering Index - Compendex (1992-2002)
- Enviroline (1992-2002)
- Environmental Bibliography (1992-2002)
- Gene-Tox (1992-2002)
- Medline (1992-2002)
- National Technical Information Service - NTIS (1992-2002)
- NIOSH (1992-1998)
- PASCAL (1992-2002)
- Pollution Abstracts (1992-2002)
- TERRETOX (1992-2002)
- TSCATS (1992-2002)
- Toxfile (1992-2002)

I U C L I D

Data Set

Existing Chemical	:	ID: 115-11-7
CAS No.	:	115-11-7
EINECS Name	:	2-methylpropene
EC No.	:	204-066-3
TSCA Name	:	1-Propene, 2-methyl-
Molecular Formula	:	C4H8
Producer related part		
Company	:	ExxonMobil Biomedical Sciences Inc.
Creation date	:	28.01.2003
Substance related part		
Company	:	ExxonMobil Biomedical Sciences Inc.
Creation date	:	28.01.2003
Status	:	
Memo	:	CEFIC LOSG for the ICCA HPV initiative
Printing date	:	10.12.2003
Revision date	:	
Date of last update	:	10.12.2003
Number of pages	:	37
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

Type :
Name : Coastal Chem Inc.
Contact person :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

28.01.2003

Type :
Name : Coastal Refining & Marketing, Inc.
Contact person :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

28.01.2003

Type :
Name : Enron Corp.
Contact person :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

28.01.2003

Type :
Name : Equistar
Contact person :
Date :
Street :
Town :
Country :
Phone :

Telefax :
Telex :
Cedex :
Email :
Homepage :

12.02.2003

Type :
Name : Exxon Corporation
Contact person :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

28.01.2003

Type :
Name : Shell Oil Co.
Contact person :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

28.01.2003

Type :
Name : Texas Petrochemicals Corp.
Contact person :
Date :
Street :
Town :
Country :
Phone :
Telefax :
Telex :
Cedex :
Email :
Homepage :

28.01.2003

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****1.1.1 GENERAL SUBSTANCE INFORMATION**

Purity type :
Substance type : Organic
Physical status : gaseous
Purity : > 99 % w/w
Colour :
Odour :

28.01.2003

1.1.2 SPECTRA**1.2 SYNONYMS AND TRADENAMES**

1,1-Dimethylethene

12.02.2003

1,1-Dimethylethene

06.10.2003

1,1-Dimethylethylene

28.01.2003

1-Propene, 2-methyl- (9CI)

12.02.2003

2-Methyl-1-Propen

12.02.2003

2-Methyl-1-propene

26.09.1993

2-Methyl-Propen

12.02.2003

2-Methylpropeen

12.02.2003

2-Methylpropen

12.02.2003

2-Methylpropene

12.02.2003

2-MeTHYLPROPENE

12.02.2003

2-Methylpropylene

12.02.2003

2-Metilpropene

12.02.2003

2-Metilpropeno

12.02.2003

2-Metylpropen

12.02.2003

2-Metyylipropeeni

12.02.2003

a-Butylen

12.02.2003

asym.-Dimethyl ethylene

12.02.2003

Butene

12.02.2003

Butylen

12.02.2003

Butylene

12.02.2003

i-Butylen

12.02.2003

Isobuten

12.02.2003

Isobutene

11.05.1994

Isobutylen

12.02.2003

Isobutylene

28.01.2003

Isopropylidenemethylene

12.02.2003

Metilpropeno

12.02.2003

Propene, 2-methyl

06.10.2003

Propene, 2-Methyl (Iso-Butylene)

12.02.2003

y-Butylen

12.02.2003

y-Butylene

12.02.2003

1.3 IMPURITIES

Purity :
CAS-No :
EC-No :
EINECS-Name : n-Butylenes
Molecular formula :
Value : < 1 % w/w

28.01.2003

Purity :
CAS-No : 106-97-8
EC-No :
EINECS-Name : Butane
Molecular formula :
Value : < 1 % w/w

Remark : EINECS No. 203-448-7

27.10.2003

1.4 ADDITIVES

Remark : No additives
28.01.2003

1.5 TOTAL QUANTITY

Remark : Worldwide, isobutylene production from all sources exceeds 10,000 kilotonnes/yr.
23.10.2003 (35)

Remark : For the year 2000, production in Japan was estimated at 1000 kilotonnes. In 2001, Western Europe produced 995 kilotonnes and the United States 8300 kilotonnes.
05.12.2003 (35)

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Specific limits : no
Symbols : F+, , ,
Nota : , ,
R-Phrases : (12) Extremely flammable
S-Phrases : (9) Keep container in a well-ventilated place
(16) Keep away from sources of ignition - No smoking
(33) Take precautionary measures against static discharges
12.02.2003 (16)

1.6.2 CLASSIFICATION

Classified : as in Directive 67/548/EEC
Class of danger : extremely flammable
R-Phrases : (12) Extremely flammable
Specific limits :
12.02.2003 (16)

1.6.3 PACKAGING

1.7 USE PATTERN

Type of use : use
Category :

Remark : General use of Isobutylene:

Isobutylene is only used as an intermediate. It is mainly used as a monomer or copolymer for the production of synthetic rubber and plastics. About 72% of the available isobutylene is used for the production of butyl rubber. About 17% is used for the production of antioxidants for food, food packaging, supplements and for plastics. Another 9% is used for the production of (polymer) fuel oil - or lube oil additives. A remaining 2% is used for various other specialist intermediate applications.

28.01.2003

1.7.1 DETAILED USE PATTERN

1.7.2 METHODS OF MANUFACTURE

1.8 REGULATORY MEASURES

1.8.1 OCCUPATIONAL EXPOSURE LIMIT VALUES

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

Type : Council Directive (EEC) No. 76/769
Additional information : EU. Restriction on Marketing and Use under Directive 76/769/EEC, 1976 O.J. (L 262) 201, 27 Sep 1976, as last amended by Directives 2002/45/EC and 2002/62/EC (20th amendment and 9th adaptation).

Remark : R59: Substances appearing in Annex I to Directive 67/548/EEC which are classified as flammable or extremely flammable and labeled as such or which are provisionally classified and labeled as flammable, highly flammable or extremely flammable according to Article 5(2) of 67/548/EEC may not be used as such or in the form of preparations in aerosol generators marketed and intended for sale to the general public for entertainment and decorative purposes such as: metallic glitter intended mainly for decoration; artificial snow and frost; whoopee cushions; silly string aerosols; imitation excrement; horns for parties; decorative flakes and foams; artificial cobwebs; stink bombs, and so forth. The packaging of such aerosol generators must be marked "For professional users only." [Directive 94/48/EC, 1994 O.J. (L 331) 7, 21 December 1994 (13th amendment to 76/769/EEC)].

Test substance	:	2-Methylpropene Cas No. 115-11-7
12.02.2003		
Type	:	
Additional information	:	EU. Monomers Directive (Food Contact). Directive 2002/72/EC relating to plastic materials & articles intended to come into contact with foodstuffs, 2002 O.J. (L 220) 18, 15 August 2002.
Remark	:	R1: Com Dir 2002/72/EC, 15.08.02.
Test substance	:	Isobutene CAS No. 115-11-7
12.02.2003		

1.9.1 DEGRADATION/TRANSFORMATION PRODUCTS

1.9.2 COMPONENTS

1.10 SOURCE OF EXPOSURE

Remark : There are neither National exposure limits nor an ACGIH TLV for isobutylene. Isobutylene is listed in EU Council Directive 98/24/EC on the protection of workers from the risks related to chemical agents at work, "Hazardous chemical agent" [art. 2(b)(i)]. 1998 O.J. (L 131) 11.

Based on physical properties, the primary workplace exposure would be by inhalation. Workplace industrial exposure by inhalation to isobutylene may occur in a number of ways. These include :

(i) Exposure linked to handling, transfer, loading and unloading of either (a) LPGs containing isobutylene or (b) pure isobutylene between vessels (e.g. pipe to sphere transfer). These types of exposure can occur due to losses of very volatile organic compounds (VVOCs) in plant equipment. Types of losses vary but historically these are known to occur through hose connections, within valves or seals in the loading/unloading system and through pressure relief valves. To some extent, replacement of hoses (and in particular flexible hoses) by hard piping has ameliorated these types of losses. Employees affected routinely tend to be supply, distribution or transport process technicians (i.e. including shipping, marine terminal and road car operating personnel). Maintenance technicians may also be affected although this would not be anticipated to be routine in nature.

(ii) Exposure due to fugitive emissions from fixed plant. Here, loss of LPGs containing isobutylene or pure isobutylene may occur from leaking valves, seals and sampling points. Key areas which have been historically associated with isobutylene loss include leaks in the storage and compressor systems (where relevant), and leaks associated with high service pumps with simple (i.e. single) mechanical seals. Leaks (as fugitive emissions) have also been identified in piping systems between vessels or fractionating towers (e.g. C3 / C4# separation). Both process and maintenance technicians, as well as non-affiliated plant workers, are potentially exposed.

(iii) Isobutylene is encountered in cat-cracked LPG streams and as a component in Rich and Spent C4#s streams at varying concentrations. Isobutylene is commercially separated from other C4 butenes by catalytic conversion to methyl tertiary butyl ether, MTBE, (98% conversion), followed

by further catalytically-controlled reaction back to isobutylene and methanol. Here, isobutylene is obtained at 99% purity for storage and subsequent use. Some exposure to isobutylene may be encountered in process sampling steps and in vessel maintenance tasks. However, exposure risk to isobutylene may be more pronounced in catalyst changeout activities as the catalyst is present as layers of "catalyst packs", sometimes referred to as "teabags" which require stepwise manual removal. Traces of isobutylene are found in catalyst even after thorough purging and preparation. Maintenance or contract workers normally carry out this task.

Isobutylene is the primary feed to several chemical manufacturing processes (e.g. Synthetic Rubber) where it is reacted with isoprene in a catalytically-mediated reaction to produce butyl rubber. Exposure may occur at various stages in the process, including fugitive emission, and where rubber mixtures (e.g. rubber cement) is sampled for process quality testing. Sampling takes place into bombs (300 ml) used in closed-loop mode for pure isobutylene and into containers or special bags for "rubber slurry" or "rubber cement" sampling. Volatilisation losses can give rise to a pathway for exposure by inhalation.

lv) Exposure during sampling tasks for (a) any LPG streams containing isobutylene and (b) pure isobutylene. Historically, sampling bombs for LPGs, including isobutylene, were required to be "open-atmosphere vented" to remove contaminants from the bomb and the sampling "deadleg" within the sampled line. However, despite improvements in exposure reduction with the advent of closed-loop sampling systems (where fitted), any wear or leakage in the joints within closed-loop systems have been known to result in employee exposure. Process technicians are primarily at risk of exposure although lab technicians who take samples are also possible affected. Similarly, persons carrying out lab testing of isobutylene by gas-chromatography are also at risk where the GC is not within a fumehood. For example, isobutylene streams are either direct-injected by bomb which is purged through an open vent in the gas-sample valve, or transferred via a bladder which is also prone to low-level leakage.

28.10.2003

(48)

Remark

: Isobutylene is produced commercially by catalytic or thermal cracking of high boiling petroleum fractions or steam cracking of a mixture of saturated hydrocarbons. Isobutylene (13 to 28% of the product stream of C4 hydrocarbons) is separated from the resultant product mixture of C4 hydrocarbons either by extraction into 45 to 65% sulfuric acid with subsequent regeneration of the isobutylene by steam tripping or by the removal of normal butenes by adsorption on molecular sieves (Kirk-Othmer, 1978).

Other processes that may be used to produce isobutylene include the dehydration of ter-butyl alcohol and the thermal dehydrogenation of isobutane.

11.08.2003

(34) (50)

1.11 ADDITIONAL REMARKS**Remark**

: The mode of disposal for isobutylene is by incineration.
Transport Information:

Land (railroad/road, such as RID/ADR):

ADR/RID Class: 2,3b;
Danger number: 23;
Substance ID number: 1055;
Danger label: 3.

Inland waterways (such as ADN/R):
ADN/R Class: I d;
Sea (IMDG):
UN number: 1055;
IMO Class: 2.1;
IMDG Code: 2147;
Risk Label: 2FG;
MFAG number: 310

11.08.2003 (17)

1.12 LAST LITERATURE SEARCH

Type of search : Internal and External
Chapters covered :
Date of search : 04.10.2002

Remark : Aquire (1992-2002)
BIODEGRADATION DATA (BIODEG) (1992-2002)
BIODEGRADATION BIBLIOGRAPHIC REFERENCES (BIOLOG) (1992-2002)
Biological Abstracts - BIOSIS (1992-2002)
Cancerlit (1992-2002)
EMBASE (1992-2002)
EMBSINFO (formerly RBird) (1992-2002)
Engineering Index - Compendex (1992-2002)
Enviroline (1992-2002)
Environmental Bibliography (1992-2002)
Gene-Tox (1992-2002)
Medline (1992-2002)
National Technical Information Service - NTIS (1992-2002)
NIOSH (1992-1998)
PASCAL (1992-2002)
Pollution Abstracts (1992-2002)
TERRETOX (1992-2002)
TSCATS (1992-2002)
Toxfile (1992-2002)

28.01.2003

1.13 REVIEWS

11.08.2003 (5)

2.1 MELTING POINT

Value	:	= -140.4 °C	
Sublimation	:		
Method	:	other: not specified	
Year	:		
GLP	:	no data	
Test substance	:	other TS: Isobutylene	
Test substance	:	Isobutylene purity is unknown.	
Reliability	:	(2) valid with restrictions The CRC Handbook of Chemistry and Physics is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.	
Flag	:	Critical study for SIDS endpoint	
11.08.2003			(37)
Value	:	= -140.4 °C	
Sublimation	:		
Method	:	other: not specified	
Year	:		
GLP	:	no data	
Test substance	:	other TS: Isobutylene	
Test substance	:	Isobutylene purity is unknown.	
Reliability	:	(2) valid with restrictions The value is cited in the EPIWIN experimental database (SRC Physprop Database) for isobutylene. Although the original reference was not retrieved and reviewed for quality, this robust summary has a reliability rating of 2 because the data are from a peer reviewed database.	
11.08.2003			(15)
Value	:	= -130.9 °C	
Sublimation	:		
Method	:	other: calculated	
Year	:		
GLP	:		
Test substance	:	other TS: Isobutylene	
Method	:	The calculated value was determined using MPBPWIN version 1.40, a subroutine within the computer program EPIWIN version 3.04. Melting Point estimations performed by MPBPWIN are based on the average result of the calculation methods of K. Joback and Gold and Ogle. Joback's Method is described in Joback, K.G. 1982. A Unified Approach to Physical Property Estimation Using Multivariate Statistical Techniques. In The Properties of Gases and Liquids. Fourth Edition. 1987. R.C. Reid, J.M. Prausnitz and B.E. Poling, Eds. The Gold and Ogle Method simply uses the formula $T_m = 0.5839T_b$, where T_m is the melting point in Kelvin and T_b is the boiling point in Kelvin.	
Reliability	:	(2) valid with restrictions The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are not measured.	
11.08.2003			(15)
Value	:	= -140 °C	
Sublimation	:		

Method : other: not specified
Year :
GLP : no
Test substance : other TS: Isobutylene

Remark : Physical-chemical data obtained from open literature and are generally based on accepted industry methods.
Test substance : Isobutylene purity is unknown.
Reliability : (4) not assignable
 This robust summary has a reliability rating of 4 because the data were not reviewed.

11.08.2003 (1)

2.2 BOILING POINT

Value : = -6.9 °C at 1013 hPa
Decomposition :
Method : other: not specified
Year :
GLP : no data
Test substance : other TS: Isobutylene

Test substance : Isobutylene purity is unknown.
Reliability : (2) valid with restrictions
 The CRC Handbook of Chemistry and Physics is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.

Flag : Critical study for SIDS endpoint
 11.08.2003 (37)

Value : = -6.9 °C at 1013 hPa
Decomposition :
Method : other: not specified
Year :
GLP : no data
Test substance : other TS: Isobutylene

Test substance : Isobutylene purity is unknown.
Reliability : (2) valid with restrictions
 The value is cited in the EPIWIN experimental database (SRC Physprop Database) for isobutylene. Although the original reference was not retrieved and reviewed for quality, this robust summary has a reliability rating of 2 because the data are from a peer reviewed database.

11.08.2003 (15)

Value : = 10.2 °C at 1013 hPa
Decomposition :
Method : other: calculated
Year :
GLP :
Test substance : other TS: Isobutylene

Method : The calculated value was determined using MPBPWIN version 1.40, a subroutine within the computer program EPIWIN version 3.04. Boiling Point estimations performed by MPBPWIN are based on the calculation method of S. Stein and R. Brown in "Estimation of Normal Boiling Points from Group Contributions". 1994. J. Chem. Inf. Comput. Sci. 34: 581-587.

Reliability : (2) valid with restrictions

05.12.2003 (15)
 The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are not measured.

Value : = -6.9 °C at 1013 hPa
Decomposition :
Method : other: not specified
Year :
GLP : no
Test substance : other TS: Isobutylene

Test substance : Isobutylene purity is unknown.
Reliability : (4) not assignable
 This robust summary has a reliability rating of 4 because the data were not reviewed.

11.08.2003 (1)

2.3 DENSITY

Type : density
Value : = .5879 g/cm³ at 25 °C
Method : other: not specified
Year :
GLP : no data
Test substance : other TS: Isobutylene

Test substance : Isobutylene purity is unknown.
Reliability : (2) valid with restrictions
 The Merck Index is a chemical handbook that is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.

Flag : Critical study for SIDS endpoint
 11.08.2003 (47)

Type : density
Value : = .5942 g/cm³ at 20 °C
Method : other: not specified
Year :
GLP : no data
Test substance : other TS: Isobutylene

Test substance : Isobutylene purity is unknown.
Reliability : (2) valid with restrictions
 The Merck Index is a peer reviewed publication. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.

11.08.2003 (47)

Type : density
Value : = .599 g/cm³ at 20 °C
Method : other: ASTM D4052
Year :
GLP : no
Test substance : other TS: Isobutylene

Test substance : Isobutylene purity is unknown.
Reliability : (4) not assignable
 This robust summary has a reliability rating of 4 because the data were not

11.08.2003 reviewed. (17)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : 2973 hPa at 25 °C
Decomposition :
Method : other (calculated)
Year :
GLP :
Test substance : other TS: Isobutylene

Method : Calculated values using MPBPWIN version 1.40, a subroutine of the computer program EPIWIN version 3.04. Vapor Pressure estimations performed by MPBPWIN are based on the average result of the calculation methods of Antoine and Grain. Both methods use boiling point for the calculation. The measured values for melting and boiling points of -140.4 and -6.9°C (Lide, 1997), respectively, were used with these methods.

The Antoine Method is described in the Handbook of Chemical Property Estimation. Chapter 14. W.J. Lyman, W.F. Reehl and D.H. Rosenblatt, Eds. Washington, D.C.: American Chemical Society. 1990.

A modified Grain Method is described on page 31 of Neely and Blau's Environmental Exposure from Chemicals, Volume 1, CRC Press. 1985.

Reliability : (2) valid with restrictions
 The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are not measured.

Flag : Critical study for SIDS endpoint
 06.10.2003 (15) (37)

Value : = 3080 hPa at 25 °C
Decomposition :
Method :
Year :
GLP : no data
Test substance : other TS: Isobutylene

Test substance : Isobutylene purity is unknown.
Reliability : (2) valid with restrictions
 The value is cited in the EPIWIN experimental database (SRC Physprop Database) for isobutylene. Although the original reference was not retrieved and reviewed for quality, this robust summary has a reliability rating of 2 because the data are from a peer reviewed database.

06.10.2003 (15)

Value : = 1013 hPa at -6.9 °C
Decomposition :
Method : other (measured)
Year :
GLP : no data
Test substance : other TS: Isobutylene

Method : Method not specified.
Remark : Measured data from several investigators were reviewed and analyzed for

confidence. Reliable data were identified and used to develop a temperature vs. vapor pressure matrix that provided the following data for isobutylene:

1013 hPa at -6.9° C
 267 hPa at -36.7° C
 80.0 hPa at -57.7° C
 26.7 hPa at -73.4° C
 6.7 hPa at -96.5° C

The following sources provided the measured data used by the author to develop the temperature vs. vapor pressure matrix:

American Petroleum Institute. 1946. Project 44, National Bureau of Standards.
 Coffin and Maass. 1926. J. Am. Chem. Soc. 50:1427-1437.
 Coffin and Maass. 1928. Chem. Zentr. I:1643.
 Coffin and Maass. 1927. Trans. Roy. Soc. Can. 21:33-40.
 Dow Chemical Co. files.
 Kraft. 1879. Ber. 12:1664-1668.
 Rossini. American Petroleum Institute. Research Project 44.

Test substance : Isobutylene purity is unknown.
Reliability : (2) valid with restrictions
 This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.
 06.10.2003 (56)

Value : = 2970 hPa at 25 °C
Decomposition :
Method : other (calculated)
Year :
GLP :
Test substance : other TS: Isobutylene

Method : Calculated values using MPBPWIN version 1.40, a subroutine of the computer program EPIWIN version 3.04.
 Vapor Pressure estimations performed by MPBPWIN are based on the average result of the calculation methods of Antoine and Grain. Both methods use boiling point for the calculation. The EPIWIN calculated values for melting and boiling points of -130.9 and 10.2°C, respectively, were used with these methods.
 The Antoine Method is described in the Handbook of Chemical Property Estimation. Chapter 14. W.J. Lyman, W.F. Reehl and D.H. Rosenblatt, Eds. Washington, D.C.: American Chemical Society. 1990.
 A modified Grain Method is described on page 31 of Neely and Blau's Environmental Exposure from Chemicals, Volume 1, CRC Press. 1985.

Reliability : (2) valid with restrictions
 The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are not measured.

06.10.2003 (15)

Value : = 2574 hPa at 20 °C
Decomposition :
Method : other (calculated): not specified
Year :
GLP : no
Test substance : other TS: Isobutylene

Remark : Physical-chemical data obtained from open literature and are generally based on accepted industry methods.

Vapor pressure at other temperatures: 4635 hPa at 40 degrees C; 7740 hPa at 60 degrees C; 18247 hPa at 100 degrees C.

Reliability : (4) not assignable
This robust summary has a reliability rating of 4 because the data were not reviewed.

06.10.2003 (14)

2.5 PARTITION COEFFICIENT

Partition coefficient :
Log pow : = 2.34 at °C
pH value :
Method : other (measured)
Year :
GLP : no data
Test substance : other TS: Isobutylene

Method : Shake-flask method.
Test substance : Isobutylene purity is unknown.
Reliability : (2) valid with restrictions
The value cited by the authors is a measured and preferred value. This robust summary has a reliability rating of 2 because the data were peer reviewed. This robust summary has a reliability rating of 2 because there is insufficient information available on the method and analytical procedure.

Flag : Critical study for SIDS endpoint
11.08.2003 (23)

Partition coefficient :
Log pow : = 2.23 at °C
pH value :
Method : other (calculated)
Year :
GLP :
Test substance : other TS: Isobutylene

Method : Calculated values using KOWWIN version 1.65, a subroutine of the computer program EPIWIN version 3.04
Octanol / Water Partition Coefficient estimations performed by KOWWIN are based on an atom/fragment contribution method of W. Meylan and P. Howard in "Atom/fragment contribution method for estimating octanol-water partition coefficients". 1995. J. Pharm. Sci. 84:83-92.

Reliability : (2) valid with restrictions
The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are not measured.

11.08.2003 (15)

Partition coefficient :
Log pow : = 2.11 at 23 °C
pH value :
Method : other (calculated):
Year : 1981
GLP : no data
Test substance : other TS: Isobutylene

Reliability : (4) not assignable
The value was calculated. This robust summary has a reliability rating of 4 because data were not reviewed and the calculation procedure used was not identified or information on the validity of the model was not provided.

06.10.2003

(31)

Partition coefficient :
Log p_{ow} : = 2.14 at °C
pH value :
Method : other (calculated)
Year :
GLP : no data
Test substance : other TS: Isobutylene

Remark : Partition-coefficient n-Octanol/water: 2.14
 Physical-chemical data obtained from open literature and are generally based on accepted industry methods.

Reliability : (4) not assignable
 The value was calculated. This robust summary has a reliability rating of 4 because data were not reviewed and the calculation procedure used was not identified or information on the validity of the model was not provided.

06.10.2003

(2)

2.6.1 SOLUBILITY IN DIFFERENT MEDIA

Solubility in : Water
Value : = 263 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: measured
Year :
GLP : no
Test substance : other TS: Isobutylene

Method : Isobutylene at one atmosphere was added to a glass equilibration bottle filled with distilled water by displacing water until the volume of the aqueous phase was 3/4 of the volume of the bottle. The gas was maintained over the water. A rubber balloon in the line from the gas cylinder to the bottle served as a reservoir and was remained in-line until the aqueous phase was sampled. The 3/4 full bottle was shaken for 5 to 10 minutes and then allowed to stand at least 30 minutes prior to analysis. Aqueous samples were taken using a Hamilton syringe and transferred to the gas chromatograph (GC).

Analysis was by gas chromatograph (GC) with a hydrogen-flame ionization detector (Beckman). The chromatographic column was 12 ft. x 0.25 in., stainless steel tubing packed with 25% SE 30 gum rubber on 30-60 mesh firebrick. Helium flow through the column was 65cc/min.

Aqueous samples were taken from the equilibration bottle through a septum in tubing at the base of the bottle using a Hamilton syringe and transferred to the GC. Aqueous phase concentrations of isobutylene were determined against a standard curve prepared from the gas sample used in the aqueous equilibration procedure.

Test substance : Isobutylene purity >99%

Reliability : (1) valid without restriction
 This robust summary has a reliability rating of 1 because the test procedure

and means of analysis suggest that the methodology was appropriate to evaluate the water solubility of a gaseous substance. There is otherwise no information in the article to suggest that the data are invalid.

Flag	:	Critical study for SIDS endpoint	
16.10.2003			(41)
Solubility in Value	:	Water	
pH value concentration	:	= 399.2 mg/l at 25 °C	
Temperature effects	:		
Examine different pol.	:	at °C	
pKa	:	at 25 °C	
Description	:		
Stable	:		
Deg. product	:		
Method	:	other: not specified	
Year	:		
GLP	:	no data	
Test substance	:	other TS: Isobutylene	
Test substance Reliability	:	Isobutylene purity is unknown.	
	:	(2) valid with restrictions	
		The value is cited in the EPIWIN experimental database (SRC Physprop Database) for isobutylene. Although the original reference was not retrieved and reviewed for quality, this robust summary has a reliability rating of 2 because the data are from a peer reviewed database.	
16.10.2003			(15)
Solubility in Value	:	Water	
pH value concentration	:	= 495.6 mg/l at 25 °C	
Temperature effects	:		
Examine different pol.	:	at °C	
pKa	:	at 25 °C	
Description	:		
Stable	:		
Deg. product	:		
Method	:	other: calculated	
Year	:		
GLP	:		
Test substance	:	other TS: Isobutylene	
Method	:	Water solubility calculated by WSKOWWIN, a subroutine of the computer program EPIWIN version 3.04. that is based on a Kow correlation method described by W. Meylan, P. Howard and R. Boethling in "Improved method for estimating water solubility from octanol/water partition coefficient". Environ. Toxicol. Chem. 15:100-106. 1995.	
Reliability	:	(2) valid with restrictions	
		The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are calculated and not measured.	
16.10.2003			(15)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value : = -76 °C
Type : closed cup
Method : other: TCC
Year :
GLP : no
Test substance : other TS: Isobutylene

Remark : Physical-chemistry data obtained from open literature and are generally based on accepted industry methods.

Test substance : Isobutylene purity is unknown.

Reliability : (4) not assignable

This robust summary has a reliability rating of 4 because the data were not reviewed.

11.08.2003

(17)

2.8 AUTO FLAMMABILITY**2.9 FLAMMABILITY**

Result : highly flammable
Method : other: not specified
Year :
GLP : no
Test substance : other TS: Isobutylene

Remark : % by Volume
Lower limit: 1.8%, Upper limit: 9.6% at 25 C

Test substance : Isobutylene purity is unknown.

Reliability : (4) not assignable

This robust summary has a reliability rating of 4 because the data were not reviewed.

11.08.2003

(17)

2.10 EXPLOSIVE PROPERTIES**2.11 OXIDIZING PROPERTIES****2.12 DISSOCIATION CONSTANT****2.13 VISCOSITY****2.14 ADDITIONAL REMARKS**

Remark : Vapor Density: 1.94

11.08.2003

(61)

Remark : Viscosity: 0.92 cSt at 25 degree C (57)
11.08.2003

Remark : Specific gravity: 0.5942 at 20 degree C (57)
11.08.2003

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	1500000 molecule/cm ³
Rate constant	:	= .000000000051672 cm ³ /(molecule*sec)
Degradation	:	= 50 % after 2.5 hour(s)
Deg. product	:	
Method	:	other (calculated): Calculated values using AOPWIN version 1.89, a subroutine of the computer program EPIWIN version 3.04
Year	:	
GLP	:	
Test substance	:	other TS: Isobutylene
Method	:	Calculated values using AOPWIN version 1.89, a subroutine of the computer program EPIWIN version 3.04
		Indirect photodegradation, or atmospheric oxidation potential, is based on the structure-activity relationship methods developed by R. Atkinson under the following conditions:
		Temperature 25°C
		Sensitizer OH- radical
		Concentration of Sensitizer 1.5E6 OH- radicals/cm ³
Conclusion	:	The half-life of isobutylene, based on a 12-hour day, is 0.21 days. The half-life is normalized to a 12-hour day because atmospheric oxidation reactions only take place in the presence of sunlight.
Reliability	:	(2) valid with restrictions The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are not measured.
Flag	:	Critical study for SIDS endpoint
17.10.2003		(45)
Type	:	air
Light source	:	
Light spectrum	:	nm
Relative intensity	:	based on intensity of sunlight
INDIRECT PHOTOLYSIS		
Sensitizer	:	OH
Conc. of sensitizer	:	500000 molecule/cm ³
Rate constant	:	= .0000000000514 cm ³ /(molecule*sec)
Degradation	:	= 50 % after 7.5 hour(s)
Deg. product	:	
Method	:	other (calculated)
Year	:	
GLP	:	no data
Test substance	:	other TS: Isobutylene
Test condition	:	The author applied a unit -weight least-squares analysis of degradation rate constants for organic chemicals by OH- developed by the following investigators at temperatures less than or equal to 467K: Morris and Niki (1971); Atkinson and Pitts (1975); Wu et al. (1976); Barnes et al. (1982); Ohta (1984). These data were evaluated in conjunction with data reported by Atkinson and Aschmann (1984) that were developed at 295K to derive a

	recommended Arrhenius expression that yielded the following rate constant for isobutylene at 298K: 5.14E-11 cm ³ molecule ⁻¹ sec ⁻¹ .
	Two experimental methods used to study the kinetics of OH ⁻ reactions with organic chemicals included absolute and relative rate constant techniques. The absolute methods have involved primarily the discharge flow and flash photolysis techniques. Several relative rate methods are available.
	Detection of OH ⁻ from an electric discharge in water using ultraviolet absorption was the first absolute method employed. A subsequent method involved an electric discharge in water vapor, which yielded a cleaner source of OH ⁻ . The flash photolysis method was adapted to monitor OH ⁻ , which were produced by photodissociation of H ₂ O and H ₂ O ₂ in vacuum- and far-ultraviolet, respectively. OH ⁻ concentrations were they monitored by kinetic spectroscopy.
	Numerous relative rate methods exist. However, the predominant method has involved monitoring the relative disappearance rates of two or more organic compounds in systems containing OH ⁻ .
Conclusion	: The half-life of isobutylene, based on a 12-hour day, is 0.63 days. The half-life is normalized to a 12-hour day because atmospheric oxidation reactions only take place in the presence of sunlight.
Reliability	: (1) valid without restriction Measured data from the author together with measured data from other investigators that were reviewed for reliability, were included in the development of rate constants for selected chemicals. Therefore, the value identified by the author represents a valid rate constant for isobutylene based on all valid studies at the time of publication.
Flag 06.10.2003	: Critical study for SIDS endpoint (3)
Type	: air
Light source	:
Light spectrum	: nm
Relative intensity	: based on intensity of sunlight
INDIRECT PHOTOLYSIS	
Sensitizer	: O ₃
Conc. of sensitizer	: 70000000000 molecule/cm ³
Rate constant	: = .00000000000000011 cm ³ /(molecule*sec)
Degradation	: = 50 % after 22.7 hour(s)
Deg. product	:
Method	: other (calculated)
Year	:
GLP	: no data
Test substance	: other TS: Isobutylene
Test condition	: The author applied an unweight least-squares analysis of degradation rate constants for organic chemicals by O ₃ developed by the following investigators: Hanst et al. (1958); Bufalini and Altshuller (1965); Becker et al. (1974); Grimsrud et al. (1975), Japar et al. (1974) and Huie and Herron (1975). These data were used to derive a recommended Arrhenius expression that yielded the following rate constant for isobutylene at 298K: 1.1E-17 cm ³ molecule ⁻¹ sec ⁻¹ .
	Two experimental methods used to study the kinetics of OH ⁻ reactions with organic chemicals included absolute and relative rate constant techniques. The absolute methods include static/stopped flow and flow systems. The author characterized the relative rate constant techniques as invalid due to confounding secondary reactions and those data were not included in analyses.

- Static/stopped flow systems monitor the rate of O₃ decay in the presence of a known excess concentration of the test sample. In comparison, flow systems include flow-tubes where known concentrations of O₃ and organic enter a reaction tube and final concentrations at the tube terminus are monitored, which can include a chemiluminescence analyzer for O₃ and gas chromatography for organics.
- Reliability** : (1) valid without restriction
Measured data from the author together with measured data from other investigators that were reviewed for reliability, were included in the development of rate constants for selected chemicals. Therefore, the value identified by the author represents a valid rate constant for isobutylene based on all valid studies at the time of publication.
- Flag** : Critical study for SIDS endpoint
17.10.2003 (4)
- Type** : air
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Deg. product :
Method :
Year :
GLP :
Test substance : other TS: Isobutylene
- Remark** : Direct photochemical degradation in aqueous solution occurs through the absorbance of solar radiation by a chemical substance. If the absorbed energy is high enough, then the resultant excited state of the chemical may undergo a transformation. A prerequisite for direct photodegradation is the ability of one or more bonds within a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range. Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds, and wavelengths below 290 nm are shielded from the earth by the stratospheric ozone layer.
An approach to assessing the potential for a substance to undergo photochemical degradation is to assume that degradation will occur in proportion to the amount of light wavelengths >290 nm absorbed by constituent molecules. Isobutylene does not absorb light within a range of 290 to 750 nm. These data indicate that photolysis will not significantly contribute to the degradation of isobutylene in the aquatic environment.
- Reliability** : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are not measured, but rather a technical discussion.
- Flag** : Critical study for SIDS endpoint
16.10.2003 (66)
- Type** : air
Light source :
Light spectrum : nm
Relative intensity : based on intensity of sunlight
Deg. product :
Method :
Year :
GLP :
Test substance : other TS: Isobutylene
- Remark** : Surface lifetime is estimated to be approximately 6 hours with a half-life of 4 hours (U.S. EPA, 1991). This is based on an estimated ozone addition rate constant of 1.3E-17 cm³/molecule-second. Experimental data indicate that the

ozone rate constant is 1.21E-17 cm³/molecule-second with an uncertainty of +/- 30% (Atkinson, et al., 1984). This is a moderately rapid reaction rate. Highly reactive species have half-lives of minutes, whereas non-reactive species have half-lives of months to years.

Test substance : Isobutylene purity is unknown.
Reliability : (4) not assignable
 This robust summary has a reliability rating of 4 because the data were not reviewed.

16.10.2003 (4) (58)

3.1.2 STABILITY IN WATER

Type : abiotic
t1/2 pH4 : at °C
t1/2 pH7 : at °C
t1/2 pH9 : at °C
Deg. product :
Method :
Year :
GLP : no data
Test substance : other TS: Isobutylene

Result : Hydrolysis of an organic molecule occurs when a molecule (R-X) reacts with water (H₂O) to form a new carbon-oxygen bond after the carbon-X bond is cleaved. Mechanistically, this reaction is referred to as a nucleophilic substitution reaction, where X is the leaving group being replaced by the incoming nucleophilic oxygen from the water molecule. The leaving group, X, must be a molecule other than carbon because for hydrolysis to occur, the R-X bond cannot be a carbon-carbon bond.

The carbon atom lacks sufficient electronegativity to be a good leaving group and carbon-carbon bonds are too stable (high bond energy) to be cleaved by nucleophilic substitution. Thus, hydrocarbons are not subject to hydrolysis and this fate process will not contribute to the degradative loss of isobutylene from the environment.

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

16.10.2003 (20) (24)

Deg. product :
Method :
Year :
GLP :
Test substance : other TS: Isobutylene

Remark : Hydrolysis of isobutylene is predicted to be an unlikely transformation process in the environment.

11.08.2003 (2)

3.1.3 STABILITY IN SOIL

3.2.1 MONITORING DATA

Type of measurement : other: U.S. urban atmosphere
Media : air

Concentration	:	
Method	:	
Remark	:	Isobutylene has been detected in the U.S. urban atmosphere at a low concentration of 1 to 10 ppb.
Test substance	:	Isobutylene
Reliability	:	(4) not assignable This robust summary has a reliability rating of 4 because insufficient information is available to assess the data for quality.
11.08.2003		(40)

3.2.2 FIELD STUDIES

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	
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: Henry's Law constant calculation
Year	:	
Result	:	The Henry's Law constant (HLC) representing volatility for isobutylene is 6.34E4 Pa-m ³ /mole at 25°C. The HLC was calculated using a water solubility of 263 mg/L, a vapour pressure of 2973 hPa, and a molecular weight of 56.11.
Test substance	:	other TS: Isobutylene
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data are based on measured water solubility and calculated vapour pressure data.
Flag	:	Critical study for SIDS endpoint
16.10.2003		

Type	:	
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: Calculation
Year	:	
Result	:	The volatilization half-life of isobutylene from a model river and lake is estimated to be approximately 46 minutes and 2.97 days, respectively.
Test substance	:	other TS: Isobutylene
Reliability	:	(2) valid with restrictions The data were calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are not measured.
Flag	:	Critical study for SIDS endpoint
23.10.2003		(15)

3.3.2 DISTRIBUTION

Media	:	air - biota - sediment(s) - soil - water	
Method	:	Calculation according Mackay, Level I	
Year	:		
Remark	:	Physicochemical data used in the calculation:	
		Parameter	Value w/ Units
		Molecular Weight	56.11
		Temperature	25°C
		Log Kow	2.34
		Water Solubility	263 g/m ³
		Vapor Pressure	2973 hPa
		Melting Point	-140.4°C
Result	:	Using the Mackay Level I calculation, the following distribution is predicted for Isobutylene:	
		% Distribution	Compartment
		99.99	Air
		0.01	Water
		0.00	Soil
		0.00	Sediment
		0.00	Suspended Sediment
		0.00	Biota
Test substance	:	other TS: Isobutylene	
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the distribution data are modeled.	
Flag	:	Critical study for SIDS endpoint	
17.10.2003			(39)
Media	:		
Method	:	other (calculation)	
Year	:		
Method	:	The calculated value was determined using PCKOCWIN version 1.66, a subroutine within the computer program EPIWIN version 3.04.	
Result	:	Koc = 35.04 Log Koc = 1.55	
Test substance	:	other TS: Isobutylene	
Reliability	:	(2) valid with restrictions The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are not measured.	
16.10.2003			(15)
Media	:		
Method	:	Calculation according Mackay, Level I	
Year	:		
Remark	:	Isobutylene released to the environment is expected to partition primarily to the atmosphere, based on the Mackay Level I Partitioning Fugacity Model. This model calculates the distribution of a compound in air, soil, water, suspended solids, aquatic biota and sediment. Isobutylene was calculated to partition 99.98% into the air with the remainder partitioning into the water (ASTER, 1991). Henry's Law constant, which is a measure of the tendency of a chemical to	

remain in aqueous solution, indicates that isobutylene will volatilize rapidly from open water surfaces (ASTER, 1991; Lyman et al., 1984) and not persist. Also, isobutylene is estimated to have a short half-life (U.S. EPA, 1991). Once in the atmosphere, isobutylene can degrade at a moderately rapid rate through ozone addition (Atkinson et al., 1984).

16.10.2003 (2) (4) (38) (58)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum :
Deg. product :
Method : other
Year :
GLP : no data
Test substance : other TS: 1-butene

Method : Seven strains of bacteria with typical characteristics of a Xanthobacter spp. were isolated from a culture enriched with propene and 1-butene. The bacteria demonstrated 5 to 7 hour generation periods and NADH-dependent mono-oxygenases.

The seven isolated strains were maintained on yeast/glucose medium slants. For the study, organisms were cultivated in a mineral medium enriched with either propene or 1-butene. The gas enrichment contained 10% (v/v) oxygen when organisms were grown under nitrogen-fixing conditions with (NH₄)₂SO₄ and NH₄Cl being replaced by MgSO₄ and NaCl in the medium. When evaluated, cell-free extracts prepared from cell suspensions were washed and dialysed by elution over a G-25 Sephadex column.

Cell suspensions of gas-grown cells were incubated in screw-cap bottles in a 30C water bath. 500 ppm of the selected gas was injected in the headspace and samples withdrawn at regular intervals for gas chromatographic analysis.

Result : Propene and 1-butene metabolism was based on parent chemical disappearance, which is a primary measure of loss. Bacterial strains from the genus Xanthobacter were identified as possessing the ability to metabolize gaseous alkenes, including propene and 1-butene, as carbon sources for growth. The bacterium was isolated from a soil enriched with an atmosphere containing the alkenes.

Conclusion : Selected stains of a bacterium demonstrated the ability to metabolize propene and/or 1-butene. Data support the presence of a hydrocarbon mono-oxygenase as the likely enzyme responsible for the metabolism of these alkenes to the epoxy form, which has been described as one of several degradative processes involved in the metabolism of alkenes (degradation is initiated by attack at the double bond to form the epoxide, once oxidized additional degradative steps can occur that result in the complete meabolism of the alkene).

Reliability : (2) valid with restrictions
 This robust summary has a reliability rating of 2 because the data were developed using non standardized test procedures, which in part based parent chemical metabolism on the loss of the parent chemical, which is a primary measure of biodegradation. However, the information is well

	documented and meets accepted scientific principles.	
Flag	: Critical study for SIDS endpoint	
16.10.2003		(59)
Type	: aerobic	
Inoculum	:	
Deg. product	:	
Method	:	
Year	:	
GLP	:	
Test substance	: other TS: Isobutylene	
Remark	: Alkene metabolism can be initiated by attack at the double bond. Four degradative processes have been identified:	
	· oxygnease attack upon a terminal methyl group to the corresponding unsaturated alcohol and acid,	
	· subterminal oxygenase attack to the corresponding alcohol and acid,	
	· oxidation across the double bond to the corresponding epoxide, and	
	· oxidation across the double bond to the corresponding diol.	
11.08.2003		(64)
Deg. product	:	
Method	: other: computer model and expert opinion	
Year	:	
GLP	:	
Test substance	: other TS: Isobutylene	
Remark	: The probability that isobutylene can be rapidly biodegraded is calculated as 0.721 by the linear model and 0.901 by the non-linear model, which suggest that isobutylene has the potential to biodegrade rapidly. In comparison, an expert survey identified a 3.8- and 21.5-day interval for the biodegradability of isobutylene, based on a primary survey model and an ultimate suvey model, respectively.	
Reliability	: (2) valid with restrictions	
	The value was calculated based on chemical structure as modeled by EPIWIN. This robust summary has a reliability rating of 2 because the data are not measured.	
11.08.2003		(15)
Type	: aerobic	
Inoculum	:	
Deg. product	:	
Method	: other	
Year	:	
GLP	:	
Test substance	: other TS: 1,2-epoxybutane; 2-methyl-1,2-epoxypropane	
Method	: other: Crude cell extracts were prepared from a bacterium, Xanthobacter Py2, that was isolated from an environmental sample. Extracts were prepared by ultrasonic disintegration of concentrated bacteria. Cell debris and unbroken cells wre removed by centrifugation. Glycerol was added to the cleaned cell extract at a concentration of 10% (v/v) to stabilize enzyme activity. The finished cell extracts were incubated with several epoxyalkanes including 1,2-epoxybutane and 2-methyl-1,2-epoxypropane to determine whether the bacterium was able to convert selected epoxyalkanes to their corresponding ketones. Epoxyalkane and corresponding ketone concentratons were determined by headspace, gas chromatographic analysis over time.	
Remark	: Epoxyalkanes are intermediates in the bacterial metabolism of aliphatic alkenes. The formation of the corresponding ketone from the epoxyalkane	

	using cell extracts shows that this can be a step in the catabolic pathway of alkenes.
	Information on 1,2-epoxybutane and 2-methyl-1,2-epoxypropane purity is not available; assumed to have used a commercial grade.
Result	: Cell extracts from a bacterium of the genus <i>Xanthobacter</i> was identified as possessing the ability to convert 1,2-epoxybutane to the corresponding ketone. The cell extracts did not convert 2-methyl-1,2-epoxypropane to the corresponding ketone.
Reliability	: (2) valid with restrictions This robust summary has a reliability rating of 2 because the data were developed using non standardized test procedures. However, the information is well documented and meets accepted scientific principles.
06.10.2003	(65)
Type	: aerobic
Inoculum	:
Deg. product	:
Method	: other
Year	:
GLP	:
Test substance	: other TS: 1-butene
Method	: Cell suspensions of 1-butene-grown cells were incubated in a mineral medium and 1-butene. Butene metabolism and epoxybutane formation was determined by gas chromatographic analysis over time.
Remark	: Information on 1-butene purity is not available; assumed to have used a commercial grade.
Result	: A bacterial strain from the genus <i>Mycobacterium</i> was identified as possessing the ability to convert 1-butene to epoxybutane. The bacterium was isolated from a soil enriched with 1-butene.
Reliability	: (2) valid with restrictions This robust summary has a reliability rating of 2 because the data were developed using non standardized test procedures. However, the information is well documented and meets accepted scientific principles.
06.10.2003	(21)
Type	: aerobic
Inoculum	:
Deg. product	:
Method	: other
Year	:
GLP	:
Test substance	: other TS: 1-butene
Method	: Cell suspensions of 1-butene-grown cells were incubated in a mineral medium and 1-butene. Butene metabolism and epoxybutane formation were determined by gas chromatographic analysis over time.
Remark	: Information on 1-butene purity is not available; assumed to have used a commercial grade.
Result	: Several bacterial strains were identified as possessing the ability to convert ethylene, propylene, 1-butene, and 1,3-butadiene to the respective epoxyalkanes or epoxyalkene. The bacteria were isolated from lake and soil samples enriched with propane.
Reliability	: (2) valid with restrictions This robust summary has a reliability rating of 2 because the data were developed using non standardized test procedures. However, the information is well documented and meets accepted scientific principles.
06.10.2003	(30)

3.6 BOD5, COD OR BOD5/COD RATIO

Remark : The BOD (Biological Oxygen Demand) half-life for isobutylene ranged from 3 to 17 days based on modelling.

Test substance : Isobutylene

Reliability : (2) valid with restrictions
The half-life was calculated using the ASTER (Assessment Tools for the Evaluation of Risk) computer model, which was developed by United States, Environmental Protection Agency.

23.10.2003 (2)

3.7 BIOACCUMULATION

Species : other: (see remark)

Exposure period : at °C

Concentration :

BCF : = 12.64

Elimination :

Method : other: calculation

Year :

GLP : no data

Test substance : other TS: Isobutylene

Remark : A log BCF of 1.10 (BCF = 12.64) is calculated. With respect to the log Pow = 2.34, bioaccumulation of isobutylene in the aquatic environment is expected to occur at low levels.

Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are calculated.

Flag : Critical study for SIDS endpoint

11.08.2003 (15)

BCF : = 19

Elimination :

Method : other: Calculated

Year :

GLP :

Test substance : other TS: Isobutylene

Remark : Calculated results (BCF): 19. Calculated from octanol/water partition coefficients (Veith, 1983). Measured data were not located. Exposure of aquatic organisms to isobutylene is not expected to occur for significant periods of time, based on a calculated Henry's Law constant of 0.178 (ASTER, 1991), which indicates that isobutylene will volatilize rapidly from surface waters (Lyman, 1982) and not persist. As a result, bioconcentration of isobutylene in aquatic environments is not expected to be significant.

Reliability : (2) valid with restrictions
The value was calculated. This robust summary has a reliability rating of 2 because the data are not measured.

11.08.2003 (2) (38) (60)

3.8 ADDITIONAL REMARKS

Remark	:	The photochemical ozone creation potential (POCP) index for a chemical provides a relative measure of its reactivity or ozone forming potential. The POCP index can also provide a means of ranking volatile organic compounds (VOCs) by their ability to form ozone in the troposphere. Reported POCP indices for isobutylene in northwestern Europe range from 62.7 to 70.3, in comparison with an POCP index of 100 for ethylene, the reference substance.
Reliability	:	(2) valid with restrictions The values were calculated. This robust summary has a reliability rating of 2 because the data are not measured.
23.10.2003		(12) (13)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	: other: Acute Fish Toxicity Calculation
Species	: other: fish
Exposure period	: 96 hour(s)
Unit	: mg/l
LC50	: = 19.9 calculated
Method	: other: ECOSAR Computer Model (in: EPIWIN Model)
Year	:
GLP	:
Test substance	: other TS: Isobutylene
Test condition	: A log Kow (octanol/water partition coefficient) value and a chemical structure are needed to complete the calculation with this model, which can be used with chemicals like hydrocarbons whose mode of toxic action is non polar narcosis. The log Kow value used was 2.34 (Hansch and Leo). The SMILES (Simplified Molecular Input Line Entry System) structure used with the model was: C=C(C)-C.
Reliability	: (2) valid with restrictions This robust summary has a reliability rating of 2 because the data are not measured.
Flag	: Critical study for SIDS endpoint
06.10.2003	(15) (22)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	: other: Acute Daphnid Toxicity Calculation
Species	: other: Daphnid
Exposure period	: 48 hour(s)
Unit	: mg/l
LC50	: = 21.9 calculated
Method	: other: ECOSAR Computer Model (in: EPIWIN)
Year	:
GLP	:
Test substance	: other TS: Isobutylene
Test condition	: A log Kow (octanol/water partition coefficient) value and a chemical structure are needed to complete the calculation with this model, which can be used with chemicals like hydrocarbons whose mode of toxic action is non polar narcosis. The log Kow value used was 2.34 (Hansch and Leo). The SMILES (Simplified Molecular Input Line Entry System) structure used with the model was: C=C(C)-C.
Reliability	: (2) valid with restrictions This robust summary has a reliability rating of 2 because the data are not measured.
Flag	: Critical study for SIDS endpoint
06.10.2003	(15) (22)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	: other algae: green alga
Endpoint	:
Exposure period	: 96 hour(s)
Unit	: mg/l
EC50	: = 13.9 calculated

Method	: other: Calculated ECOSAR Computer Model	
Year	:	
GLP	:	
Test substance	: other TS: Isobutylene	
Remark	: Test Type: Green Alga Toxicity Calculation	
Result	: 96-hour EC50 = 13.9 mg/l	
Test condition	: A log Kow (octanol/water partition coefficient) value and a chemical structure are needed to complete the calculation with this model, which can be used with chemicals like hydrocarbons whose mode of toxic action is non polar narcosis. The log Kow value used was 2.34 (Hansch and Leo). The SMILES (Simplified Molecular Input Line Entry System) structure used with the model was: C=C(C)-C.	
Reliability	: (2) valid with restrictions This robust summary has a reliability rating of 2 because the data are not measured.	
Flag	: Critical study for SIDS endpoint	(15) (22)
06.10.2003		
Species	: other algae: green alga	
Endpoint	:	
Exposure period	: 96 hour(s)	
Unit	: mg/l	
ChV*	: = 1.7 calculated	
Method	: other: ECOSAR Computer Model (in: EPIWIN Model)	
Year	:	
GLP	:	
Test substance	: other TS: Isobutylene	
Test condition	: The chronic value (ChV) was calculated using ECOSAR, which is a structure-activity relationship model that can estimate chronic toxicity values for selected groups of aquatic organisms (i.e., fish Daphnids, algae) and specific exposure durations. The ChV for fish, Daphnid, and algae are for survival/growth, survival/reproduction, and growth, respectively. A log Kow (octanol/water partition coefficient) value and a chemical structure are needed to complete the calculation with this model, which can be used with chemicals like hydrocarbons whose mode of toxic action is non polar narcosis. The log Kow value used was 2.34 (Hansch and Leo). The SMILES (Simplified Molecular Input Line Entry System) structure used with the model was: C=C(C)-C.	
Reliability	: (2) valid with restrictions This robust summary has a reliability rating of 2 because the data are not measured.	
Flag	: Critical study for SIDS endpoint	(15) (22)
16.10.2003		

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

4.5.1 CHRONIC TOXICITY TO FISH

Species	: other: fish
Endpoint	:
Exposure period	: 30 day(s)
Unit	: mg/l
ChV*	: = 2.7 calculated
Method	: other: ECOSAR Computer Model (in: EPIWIN)
Year	:

GLP	:		
Test substance	:	other TS: Isobutylene	
Remark	:	Test Type: Chronic Fish Toxicity Calculation	
Test condition	:	The chronic value (ChV) was calculated using ECOSAR, which is a structure-activity relationship model that can estimate chronic toxicity values for selected groups of aquatic organisms (i.e., fish Daphnids, algae) and specific exposure durations. The ChV for fish, Daphnid, and algae are for survival/growth, survival/reproduction, and growth, respectively. A log Kow (octanol/water partition coefficient) value and a chemical structure are needed to complete the calculation with this model, which can be used with chemicals like hydrocarbons whose mode of toxic action is non polar narcosis. The log Kow value used was 2.34 (Hansch and Leo). The SMILES (Simplified Molecular Input Line Entry System) structure used with the model was: C=C(C)-C.	
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data are not measured.	
Flag	:	Critical study for SIDS endpoint	
16.10.2003			(15) (22)

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species	:	other: Daphnid	
Endpoint	:		
Exposure period	:	16 day(s)	
Unit	:	mg/l	
Chv*	:	= 1.3	
Method	:	other: ECOSAR Computer Model (in: EPIWIN)	
Year	:		
GLP	:		
Test substance	:	other TS: Isobutylene	
Remark	:	Test Type: Chronic Daphnid Toxicity Calculation	
Test condition	:	The chronic value (ChV) was calculated using ECOSAR, which is a structure-activity relationship model that can estimate chronic toxicity values for selected groups of aquatic organisms (i.e., fish Daphnids, algae) and specific exposure durations. The ChV for fish, Daphnid, and algae are for survival/growth, survival/reproduction, and growth, respectively. A log Kow (octanol/water partition coefficient) value and a chemical structure are needed to complete the calculation with this model, which can be used with chemicals like hydrocarbons whose mode of toxic action is non polar narcosis. The log Kow value used was 2.34 (Hansch and Leo). The SMILES (Simplified Molecular Input Line Entry System) structure used with the model was: C=C(C)-C.	
Reliability	:	(2) valid with restrictions This robust summary has a reliability rating of 2 because the data are not measured.	
Flag	:	Critical study for SIDS endpoint	
16.10.2003			(15) (22)

4.6.1 TOXICITY TO SEDIMENT DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

28.01.2003

4.6.3 TOXICITY TO SOIL DWELLING ORGANISMS

Type : other: Earthworm Toxicity Calculation
Species : other: earthworm
Endpoint : mortality
Exposure period : 14 day(s)
Unit : other: ppm
LC50 : = 271.2 calculated
Method : other: ECOSAR Computer Model (in: EPIWIN)
Year :
GLP :
Test substance : other TS: Isobutylene

Test condition : A log Kow (octanol/water partition coefficient) value and a chemical structure are needed to complete the calculation with this model, which can be used with chemicals like hydrocarbons whose mode of toxic action is non polar narcosis. The log Kow value used was 2.34 (Hansch and Leo). The SMILES (Simplified Molecular Input Line Entry System) structure used with the model was: C=C(C)-C.

Reliability : (2) valid with restrictions
This robust summary has a reliability rating of 2 because the data are not measured.

Flag : Critical study for SIDS endpoint

06.10.2003 (15) (22)

4.6.4 TOX. TO OTHER NON MAMM. TERR. SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.0 TOXICOKINETICS, METABOLISM AND DISTRIBUTION

5.1.1 ACUTE ORAL TOXICITY

Type : other
Value :
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Method : other: not specified
Year : 1986
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Remark : Isobutylene (5% v/v in corn oil) was administered by oral gavage at a dose of 5ml/kg to 6 male and 6 female Sprague Dawley rats. The animals were sacrificed at different timepoints within 6 hours post dosing. Blood analysis showed very low levels of isobutylene in blood after dosing with 29.7 mg/kg (nominal) reaching a maximum of 1.2 ug/ml 20 min after dosing, and a maximum of 17% of the dose in the GI tract 20 min after dosing. No toxic effects were observed at the highest dose tested (0.25 ml/kg or 148.5 mg/kg).

Isobutylene is a gas at room temperature and pressure, therefore toxic dose levels were not attainable via the oral route.

Result : A nominal weight of 29.7 mg isobutylene was administered (in corn oil) at a constant volume of approximately 1 mL (5 mL/kg body weight) by oral gavage at a single dose of 5.0% (or 150 mg/kg/day) to 6 male and 6 female Sprague Dawley rats. Pairs (one male, one female) were sacrificed at different timepoints within 6 hours post dosing. Blood and urine samples were taken during necropsy from all animals. The maximum blood concentration reached was 1.2 ug/mL after 20 min in one male animal. There were no ketone bodies noted in urine analyses. No adverse clinical effects nor mortality occurred as a result of these exposures. The only treatment-related effects at necropsy was slight distension of the ileum and jejunum with some mucoid secretions noted in 7 of 8 animals killed up to 4 hours after dosing.

Test substance : Isobutylene
Reliability : (2) valid with restrictions
Flag : Critical study for SIDS endpoint

23.10.2003

(27)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Value : = 620 mg/l
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Doses :
Exposure time : 4 hour(s)

Method	:	other: not specified	
Year	:		
GLP	:	no	
Test substance	:	as prescribed by 1.1 - 1.4	
Result	:	Rats were exposed to varying concentrations of isobutylene vapors in order to determine the LC50. In these studies the 4-hour LC50 in rats was 270,000 ppm (620 mg/L) (Shugaev, 1969). It was reported that rats inhaling isobutylene for 1-hour at the LC50 were in a state of deep "narcosis."	
Reliability	:	(2) valid with restrictions	
Flag	:	Critical study for SIDS endpoint	
23.10.2003			(54)
Type	:	other: Acute Effects Evaluation	
Value	:		
Species	:	mouse	
Strain	:	no data	
Sex	:	no data	
Number of animals	:	64	
Vehicle	:	other: oxygen	
Doses	:		
Exposure time	:		
Method	:	other: No guideline specified, acceptable scientific method	
Year	:	1950	
GLP	:	no	
Test substance	:	other TS: Isobutylene 99.4% pure.	
Result	:	LC50s were not measured. For isobutylene, surgical anesthesia occurred at a concentration of 19.8% and respiratory arrest at 32% giving an anesthetic index of 1.6. Isobutylene demonstrated the widest range between anesthesia and respiratory arrest in this series, suggesting a better margin of safety.	
Test condition	:	The purpose of this research study was to compare the anesthetic properties of 20 different highly purified unsaturated hydrocarbons and carbon-oxygen ring compounds. Concentrations required for surgical anesthesia and for respiratory arrest were measured. Experiments were carried out in a large stoppered jar equipped with apparatus to introduce known quantities of oxygen (21%) or test compound at 25-27°C under atmospheric pressure. CO ₂ was absorbed with NaOH. Experiments were limited to concentrations causing anesthesia in 10 min. and were terminated after 20 min. Probit analysis was used to determine conc/effect relationships.	
Test substance	:	Purity determined by Nat'l Bureau of Standards freezing point method. CAS Number 115-11-7	
Conclusion	:	Results support the concept that narcotic potency increases with molecular weight and degree of unsaturation.	
Reliability	:	(2) valid with restrictions This is not a standard acute toxicity study. It is research study using non-standard methods. Mouse strain and sex were not specified. Methods were appropriate for the purpose.	
11.08.2003			(62)
Type	:	LC50	
Value	:	= 415 mg/l	
Species	:	mouse	
Strain	:		
Sex	:		
Number of animals	:		
Vehicle	:		
Doses	:		

Exposure time	:	2 hour(s)	
Method	:	other: not specified	
Year	:		
GLP	:	no	
Test substance	:	as prescribed by 1.1 - 1.4	
Remark	:	The following observations were made in an acute inhalation study with mice: at 30% isobutylene, no symptoms; at 40%, excitation after 7-8 minutes followed by narcosis; at 50%, narcosis after 2-2.25 min; at 60-70%, narcosis after 50-60 seconds.	
Result	:	Mice and rats were exposed to varying concentrations of isobutylene vapors in order to determine the LC50 for each species. In these studies, the 2-hour LC50 of isobutylene in mice was 180,000 ppm (415 mg/L) and the 4-hour LC50 in rats was 270,000 ppm (620 mg/L) (Shugaev, 1969). It was reported that rats inhaling isobutylene for 1-hour at the LC50 were in a state of deep "narcosis."	
Reliability	:	(2) valid with restrictions	
Flag	:	Critical study for SIDS endpoint	
11.08.2003			(54)
Type	:	other: Acute effects evaluation	
Value	:		
Species	:	dog	
Strain	:	no data	
Sex	:	no data	
Number of animals	:	4	
Vehicle	:	other: air	
Doses	:		
Exposure time	:		
Method	:	other: No guideline specified, acceptable scientific method	
Year	:	1950	
GLP	:	no	
Test substance	:	other TS: Isobutylene 99.4% pure	
Result	:	No LC 50 was determined. Arrhythmias of different levels of severity were produced with each agent. The arrhythmias were least severe with isobutylene, which produced only mild tachycardia and minor voltage changes after epinephrine injection in all 4 dogs, suggesting a wider margin of safety in exposure conditions.	
Test condition	:	This pharmacology study was performed to elucidate relationships between chemical structure and physiological activity. Of particular interest was the ratio of anesthetic to respiratory arrest concentrations (anesthetic index) in the mouse and the specific characteristic of inducing severe arrhythmia/fibrillation in surgically anesthetized dogs after IV injection of epinephrine. Dogs were administered each of the 9 test materials including isobutylene, 1-butene or 2-butene,cis, at sufficient dose and duration to induce an appropriate level of anesthesia followed by I.V. administration of epinephrine to produce cardiac stimulation. Reviewer comments: Compounds that can sensitize the heart in this test are believed to be ones that might induce heart irregularities under stressful conditions.	
Test substance	:	Purity determined by Nat'l Bureau of Standards freezing point method. CAS Number 115-11-7	
Conclusion	:	Irregularities of cardiac rhythm of at least moderate severity were produced with all compounds except isobutylene that caused only mild tachycardia and minor voltage changes after epinephrine injection.	
Reliability	:	(2) valid with restrictions	
11.08.2003		This is not a standard acute toxicity study. It is a research study using non-standard methods that were appropriate for the purpose.	(62)

Type	:	LC50
Value	:	= 620 mg/l
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Doses	:	
Exposure time	:	4 hour(s)
Method	:	other: not specified
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Mice were exposed to varying concentrations of isobutylene vapors in order to determine the LC50. In these studies the 2-hour LC50 of isobutylene in mice was 180,000 ppm (415 mg/L) (Shugaev, 1969).
Reliability	:	(2) valid with restrictions
Flag	:	Critical study for SIDS endpoint
23.10.2003		

(54)

5.1.3 ACUTE DERMAL TOXICITY

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

5.2.2 EYE IRRITATION

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Type	:	
Species	:	rat
Sex	:	male/female
Strain	:	Sprague-Dawley
Route of admin.	:	inhalation
Exposure period	:	13 weeks
Frequency of treatm.	:	6 hours/day, 5 days/week
Post exposure period	:	not applicable
Doses	:	0, 250, 1000, 8000 ppm (0, 0.57, 2.29, 18.4, mg/l, respectively)
Control group	:	yes
NOAEL	:	8000 ppm
Method	:	other: No guidelines specified, acceptable scientific method
Year	:	1982
GLP	:	yes
Test substance	:	other TS: Isobutylene
Method	:	Analysis performed for the following parameters: body weight, body weight gain, hematology, blood chemistry, organ weights, organ/body wt ratio,

	organ/brain wt. ratio. Analysis of variance used for normally distributed errors, t-test between control and treatment groups. For non-normal distributions, Kruskal-Wallis test was used; significance determined by the Wilcoxon rank sum test. All tests were two tailed.
Remark	: Toxicological significance of elevated ketones is unknown but the finding indicates absorption of the test article. Possibly urine ketone bodies were derived from metabolism of the 4-carbon isobutylene. It was likely that internal organ exposure was higher in this inhalation study than in the oral studies where ketone bodies were not found (#4298-13/19-20). However, blood and organ levels were not measured after inhalation.
Result	: No biologically significant treatment related effects were observed at any dose level. In the intermediate and high dose males and females, elevated ketones were detected in urine (Multistix, semi-quantitative method). No biologically significant treatment related effects were observed at any dose level. In the intermediate and high dose males and females, elevated ketones were detected in urine (Multistix, semi-quantitative method). Histopathological examination didn't reveal any treatment-related changes. The NOAEL was 8000 ppm.
Test condition	: Groups of rat (10 M, 10 F/group, approx. 47 days old at start) were exposed to isobutylene at 0, 250, 1000, 8000 ppm 6 hrs/day, 5 d/week for 13 wks. Water and pelleted diet were available ad lib. Rats were observed twice daily for morbidity and mortality. Body weight and food consumption were recorded weekly. Fasted blood was collected at initiation, wk 5, and wk 13 for hematology and chemistry. Urine samples were obtained during wk 13 for chemistry. At sacrifice bone marrow was collected, ophthalmoscopy and necropsies were performed, and tissues preserved for histopathology.
Test substance	: Isobutylene, 99.7% pure, provided by study sponsor, CAS Number 115-11-7
Conclusion	: No biologically significant treatment related effects were found. The 8000 ppm dose level was the highest that could be tested while ensuring that the chamber concentration would be below the lower explosive limit of isobutylene.
Reliability Flag	: (1) valid without restriction
05.12.2003	: Critical study for SIDS endpoint (25)
Type	:
Species	: rat
Sex	: male/female
Strain	: Sprague-Dawley
Route of admin.	: gavage
Exposure period	: 4 weeks
Frequency of treatm.	: once/day, 7 days/week
Post exposure period	: none
Doses	: 0, 1.49, 14.86, 148.55 mg/kg/day
Control group	: yes
NOAEL	: = 148.55 - mg/kg
Method	: other: No guidelines specified, acceptable scientific method
Year	: 1986
GLP	: yes
Test substance	: other TS: Isobutylene
Method	: Not specified. Group means and std. dev. calculated.
Result	: There were no deaths. There were no changes in body weight or food consumption. The only statistically significant treatment-related effects were a decrease in total white blood cell count of 11% (M, p<0.01) and 44% (F, p<0.01) in the 150 mg/kg/day group rats, predominantly in leucocytes and monocytes, however, this was not toxicologically significant. Differential counts of WBC cell types were performed but not analyzed statistically. Slight, non-significant increases in BUN (male) and blood glucose (female) were also observed in this group. The range

	finding study (#4298-13/19-20) showed very low levels of isobutylene in blood after dosing with 29.7 mg/kg (nominal) reaching a maximum of 1.2 µg/ml 20 min after dosing, and a maximum of 17% of the dose in the GI tract 20 min after dosing. No toxicologically significant changes were observed at dose levels up to 150 mg/kg/day administered over 28 days. Histopathological examination did not reveal any treatment-related changes. The NOAEL was 150 mg/kg/day.
Test condition	: Groups of rats (5 M, 5 F/group, approx. 42 days old at start) received a daily oral dose (5 ml/kg) of corn oil containing various levels of isobutylene, 7 days a week for 4 weeks. Pelleted diet and tap water were available ad lib. Rats were examined twice daily for morbidity and mortality. Body weights were recorded weekly. Blood for hematology and clinical chemistry was collected during week 4. At sacrifice, necropsies were performed and tissues preserved on all rats. Histopathologic evaluations were performed on tissues from all rats in group 1 (corn oil control) and group 4 (High dose).
Test substance	: Isobutylene, 99.7% pure, provided by study sponsor. CAS Number 115-11-7
Conclusion	: No toxicologically significant changes were observed at dose levels up to 148.6 mg/kg/day administered over 4 weeks. However, a statistically significant decrease in the white blood cell count was observed at the high dose, 148.6 mg/kg/day. Reviewer comments: A reasonable explanation for the low recovery of isobutylene might be that a considerable amount was lost back to the atmosphere via volatilization after instillation as a bolus dose in the warm stomach.
Reliability	: (2) valid with restrictions Statistical method used was not reported.
Flag 10.12.2003	: Critical study for SIDS endpoint (26)
Type	:
Species	: rat
Sex	: male/female
Strain	: Sprague-Dawley
Route of admin.	: gavage
Exposure period	: 7 days
Frequency of treatm.	: daily
Post exposure period	:
Doses	: 0, 1.49, 14.86, 148.6 mg/kg
Control group	: yes
Method	: other: not specified
Year	:
GLP	: yes
Test substance	: as prescribed by 1.1 - 1.4
Remark	: Isobutylene was administered in a range finding study to 4 groups of 2 male and 2 female rats at 0, 0.05, 0.5, or 5% (v/v) in corn oil. All animals survived with no significant changes in body weight, food consumption, clinical chemistry or gross pathology.
Reliability 28.10.2003	: (1) valid without restriction (27)
Type	:
Species	: rat
Sex	: male/female
Strain	: Fischer 344
Route of admin.	: other: inhalation (whole body)
Exposure period	: 14 weeks
Frequency of treatm.	: 6 hours/day 5 days/week
Post exposure period	: none

Doses	: 0, 500, 1000, 2000, 4000 or 8000 ppm (0, 1.14, 2.29, 4.59, 9.18, 18.4 mg/l, respectively)
Control group	: yes
Method	: other: NTP 90-Day Study
Year	: 1998
GLP	: yes
Test substance	: other TS: Isobutene, CAS No. 115-11-7; 99.9% purity

Method : Isobutene was manufactured by Exxon, Inc., supplied by Specialty Gas Concepts, and shipped through Norco in two lots. Lot SGC051091ECA was used during the 14-week study. Identity, purity, and stability analyses were conducted by the study laboratory.

The chemical, a colorless vapor at room temperature, was identified as isobutene by infrared and nuclear magnetic resonance spectroscopy. The purity of each lot was determined by gas chromatography relative to a reference standard with a declared purity of 99.9% purchased from Matheson Gas Products. Major peak comparisons by two systems indicated a relative purity of 100.0% by one system and 100.6% by the second system for lot SGC051091ECA relative to the reference standard.

During the studies, the bulk chemical was stored in its original shipping cylinders at approximately 22 degree C. Stability was monitored throughout the studies by the study laboratory with gas chromatography. No degradation of the bulk chemical was detected.

Isobutene was distributed under regulated pressure. Provided additional heat to replace the heat lost due to isobutene vaporization. The gas passed through a filter via a main on/off pneumatic valve and then was distributed by a manifold to five pairs of metering valves with corresponding flow meters. Isobutene was delivered to each exposure chamber through these flow meters via three-way solenoid valves located at the chamber end of the vapor delivery line. Isobutene vapor was diluted with conditioned air as it was injected into the chamber inlet duct.

Chamber concentrations of isobutene were monitored by an on-line gas chromatograph from each chamber approximately every 20 minutes during exposures. Chamber concentration uniformity was maintained throughout the studies.

Necropsy

Necropsy was performed on all animals the day following the last exposure. Organs weighed were the heart, liver, lung, right kidney, right testis, and thymus.

Clinical Pathology

Blood was collected from the retroorbital plexus of 10 male and 10 female special study rats at day 3 and day 23 and of core study rats at terminal sacrifice for hematology and clinical chemistry analyses.

Hematology: hematocrit (automated and manual); hemoglobin concentration; erythrocyte, reticulocyte, nucleated erythrocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; leukocyte count and differentials.

Clinical chemistry: urea nitrogen, creatinine, serum glucose, total protein, albumin, globulin, A/G ratio, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, bile acids.

Histopathology

Complete histopathology was performed on all core study chamber control and 8000 ppm rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with

marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung, lymph nodes (mandibular, mesenteric, bronchial, mediastinal), mammary gland (with adjacent skin), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testes (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, the nose of all male and female rats was examined.

Sperm Motility and Vaginal Cytology

At the end of the studies, sperm samples were collected from all male animals in the 0, 2000, 4000 and 8000 ppm exposure groups for sperm motility evaluations. The following parameters were evaluated: spermatid heads per testis, spermatid count, and epididymal spermatozoal concentration and motility. The left cauda epididymis, epididymis, and testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies from all females exposed to 0, 2000, 4000 and 8000 ppm for vaginal cytology evaluations. The following parameters were evaluated: estrous cycle length and relative frequency of estrous stages.

Organ and body weight data were analyzed with the parametric multiple comparison procedures (Dunnett, Williams). Hematology, clinical chemistry, urinalysis, spermatid, and epididymal spermatozoal data were analyzed using non-parametric multiple comparison methods (Shirley, Dunn). Treatment effects were investigated by applying a multivariate analysis of variance to the transformed data to test for simultaneous equality of measurements across exposure concentrations (Morrison).

Result

- : All rats survived to the end of the study. The final mean body weights and body weight gains of all exposed groups of males and females were similar to those of the chamber control groups. There were no clinical findings or effects on hematologic or clinical chemistry indices attributed to isobutene exposure. There were no biologically significant effects on male or female reproductive endpoints as a result of exposure to isobutene. The absolute right kidney weights of 4,000 and 8,000 ppm males and the relative right kidney weights of all exposed groups of males were greater than those of the chamber controls; however, the differences were no greater than 10% and 8%, respectively. No effects were observed on either the absolute or relative kidney weights of female rats. The absolute liver weights of females exposed to 1,000 ppm and above and the relative liver weights of all exposed groups of females rats were greater (up to 20%) than those of the chamber controls; however, the increases in absolute and relative liver weights did not occur in a concentration-related manner. There were no histopathologic effects associated with increased kidney or liver weights as a result of isobutene exposure. There were no exposure-related gross lesions in the rats. Some minimal hypertrophy of goblet cells lining the nasopharyngeal duct in the most caudal section of the nasal cavity was observed in all groups of exposed male and female rats (males: 0/10 in 0 ppm controls, 4/10 in 500 ppm, 7/10 in 1,000 ppm, 9/10 in 2,000 ppm, 8/10 in 4,000 ppm, 9/10 in 8,000 ppm; females: 0/10, 4/10, 8/10, 8/10, 7/10, 10/10, respective exposure groups).

In male rats, left epididymis weights were significantly increased and epididymal sperm motility was significantly decreased in the 8000 ppm exposure group. However, there was no statistically significant difference in left or right testis weight compared to controls. In female rats, the time spent in estrus was increased with a concurrent decrease in the time spent in diestrus, although the length of the average estrus cycle was not altered. There were no effects on the reproductive organs of rats of either sex that

Test condition	: could be attributed to exposure to isobutylene. F344/N rats (10 males and 10 females/group, 6 weeks of age) were exposed by inhalation for 6 hours/day, 5 days/week, 14 weeks to 0, 500, 1,000, 2,000, 4,000 or 8,000 ppm, isobutene. Isobutene concentrations in the exposure chambers were monitored by on-line gas chromatography approximately every 20 minutes during exposures.	
Test substance	: Isobutene, CAS No. 115-11-7 Lot Nos. SGCO51091ECA and SGCO20594ECA; 98% - >99% purity	
Conclusion	: These data demonstrate that isobutene is not toxic to rats exposed to concentrations up to 8,000 ppm for 14 weeks.	
Reliability	: (1) valid without restriction GLP Study.	
Flag 10.12.2003	: Critical study for SIDS endpoint	(46)
Type	:	
Species	: rat	
Sex	: male/female	
Strain	: Fischer 344	
Route of admin.	: inhalation	
Exposure period	: 105 weeks	
Frequency of treatm.	: 6 hours/day, 5 days/week	
Post exposure period	:	
Doses	: 500, 2000 or 8000 ppm	
Control group	: yes	
Method	: other: NTP Two Year Carcinogenicity Study	
Year	: 1998	
GLP	: yes	
Test substance	: other TS: Isobutene (CAS No. 115-11-7)	
Method	: Survival analysis was estimated by the product-limit procedure of Kaplan and Meier. Statistical analyses for possible dose-related effects on survival used Cox's method for testing two groups for equality and Tarone's life table test to identify dose-related trends. All reported P values for the survival analysis are two-sided. The Poly-k test was used to assess neoplasm and nonneoplastic lesion prevalence. Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure related trend. All reported P values are one-sided. Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data were analyzed with the parametric multiple comparison procedures (Dunnnett, Williams). Hematology, clinical chemistry, urinalysis, spermatid, and epididymal spermatozoal data were analyzed using non-parametric multiple comparison methods (Shirley, Dunn). Treatment effects were investigated by applying a multivariate analysis of variance to the transformed data to test for simultaneous equality of measurements across exposure concentrations (Morrison).	
Result	: The survival of exposed males and females was similar to that of the chamber controls. Mean body weights of exposed groups were generally similar to those of the chamber controls throughout the study. There were no exposure-related clinical findings. Exposure of rats to isobutene caused an increase, although marginal, in the incidences of hyaline degeneration of the olfactory epithelium of the nose in males and females; more importantly, the severities of this lesion (mild to moderate) were increased in exposed males and females in a concentration-related fashion [Males: Incidence: 43/49 (controls), 45/49 (500 ppm), 46/50 (2000 ppm), and 49/49 (8000 ppm); Severity: 1.3, 1.4, 2.2, and 2.6 out of 4, respectively. Females: Incidence: 44/50 (control), 47/50 (500 ppm), 48/50 (2000 ppm), 47/49 (8000 ppm); Severity: 1.5, 2.4, 2.8, and 2.8 out of 4, respectively].	

Test condition	:	Some minimal hypertrophy of goblet cells lining the nasopharyngeal duct in the most caudal section of the nasal cavity was observed in all groups of exposed male and female rats.
Test substance	:	F344/N rats (50 males and 50 females/group, 6 weeks of age) were exposed by inhalation for 6 hours/day, 5 days/week, 105 weeks to 0, 500, 2,000 or 8,000 ppm, isobutene. Isobutene concentrations in the exposure chambers were monitored by on-line gas chromatography approximately every 20 minutes during exposures.
Conclusion	:	Isobutene, CAS# 115-11-7 Lot Nos. SGCO51091ECA and SGCO20594ECA; 98% - >99% purity
Reliability	:	Under the conditions of this study, isobutylene produced a dose related increase in the incidence and severity of hyaline degeneration of the olfactory epithelium of the nose in males and females, which is considered an adaptive response.
Flag	:	(1) valid without restriction GLP Study.
10.12.2003		Critical study for SIDS endpoint
Type	:	
Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	other: inhalation (whole body)
Exposure period	:	14 weeks
Frequency of treatm.	:	6 hours/day, 5 days/week
Post exposure period	:	none
Doses	:	0, 500, 1000, 2000, 4000 or 8000 ppm (0, 1.14, 2.29, 4.59, 9.18, 18.4 mg/l, respectively)
Control group	:	yes
Method	:	other: NTP 90-Day Study
Year	:	1998
GLP	:	yes
Test substance	:	other TS: Isobutene, CAS No. 115-11-7
Method	:	Isobutene was manufactured by Exxon, Inc., supplied by Specialty Gas Concepts, and shipped through Norco in two lots. Lot SGC051091ECA was used during the 14-week study. Identity, purity, and stability analyses were conducted by the study laboratory.
		The chemical, a colorless vapor at room temperature, was identified as isobutene by infrared and nuclear magnetic resonance spectroscopy. The purity of each lot was determined by gas chromatography relative to a reference standard with a declared purity of 99.9% purchased from Matheson Gas Products. Major peak comparisons by two systems indicated a relative purity of 100.0% by one system and 100.6% by the second system for lot SGC051091ECA relative to the reference standard.
		During the studies, the bulk chemical was stored in its original shipping cylinders at approximately 22 degree C. Stability was monitored throughout the studies by the study laboratory with gas chromatography. No degradation of the bulk chemical was detected.
		Isobutene was distributed under regulated pressure. Provided additional heat to replace the heat lost due to isobutene vaporization. The gas passed through a filter via a main on/off pneumatic valve and then was distributed by a manifold to five pairs of metering valves with corresponding flow meters. Isobutene was delivered to each exposure chamber through these flow meters via three-way solenoid valves located at the chamber end of the vapor delivery line. Isobutene vapor was diluted with conditioned air as it was injected into the chamber inlet duct.

(46)

Chamber concentrations of isobutene were monitored by an on-line gas chromatograph from each chamber approximately every 20 minutes during exposures. Chamber concentration uniformity was maintained throughout the studies.

Necropsy

Necropsy was performed on all animals the day following the last exposure. Organs weighted were the heart, liver, lung, right kidney, right testis, and thymus.

Clinical Pathology

Blood was collected from the retroorbital plexus of 10 male and 10 female special study rats at day 3 and day 23 and of core study rats at terminal sacrifice for hematology and clinical chemistry analyses.

Hematology: hematocrit (automated and manual); hemoglobin concentration; erythrocyte, reticulocyte, nucleated erythrocyte, and platelet counts; mean cell volume; mean cell hemoglobin; mean cell hemoglobin concentration; leukocyte count and differentials.

Clinical chemistry: urea nitrogen, creatinine, serum glucose, total protein, albumin, globulin, A/G ratio, alanine aminotransferase, alkaline phosphatase, creatine kinase, sorbitol dehydrogenase, bile acids.

Histopathology

Complete histopathology was performed on all core study chamber control and 8000 ppm rats and mice. In addition to gross lesions and tissue masses, the following tissues were examined: adrenal gland, bone with marrow, brain, clitoral gland, esophagus, gallbladder (mice), heart, large intestine (cecum, colon, rectum), small intestine (duodenum, jejunum, ileum), kidney, larynx, liver, lung, lymph nodes (mandibular, mesenteric, bronchial, mediastinal), mammary gland (with adjacent skin), nose, ovary, pancreas, parathyroid gland, pituitary gland, preputial gland, prostate gland, salivary gland, spleen, stomach (forestomach and glandular), testes (with epididymis and seminal vesicle), thymus, thyroid gland, trachea, urinary bladder, and uterus. In addition, the nose of all male and female rats was examined.

Sperm Motility and Vaginal Cytology

At the end of the studies, sperm samples were collected from all male animals in the 0, 2000, 4000 and 8000 ppm exposure groups for sperm motility evaluations. The following parameters were evaluated: spermatid heads per testis, spermatid count, and epididymal spermatozoal concentration and motility. The left cauda epididymis, epididymis, and testis were weighed. Vaginal samples were collected for up to 12 consecutive days prior to the end of the studies from all females exposed to 0, 2000, 4000 and 8000 ppm for vaginal cytology evaluations. The following parameters were evaluated: estrous cycle length and relative frequency of estrous stages.

Organ and body weight data were analyzed with the parametric multiple comparison procedures (Dunnnett, Williams). Hematology, clinical chemistry, urinalysis, spermatid, and epididymal spermatozoal data were analyzed using non-parametric multiple comparison methods (Shirley, Dunn). Treatment effects were investigated by applying a multivariate analysis of variance to the transformed data to test for simultaneous equality of measurements across exposure concentrations (Morrison).

Result : All mice survived to the end of the study. The final mean body weights and body weight gains of all exposed groups of males and females were similar to those of the chamber controls. There were no clinical findings or biologically significant effects on male or female reproductive endpoints attributed to isobutene exposure.

	<p>The absolute and relative right kidney weights of 8,000 ppm males were greater (approximately 11%) than those of the chamber controls. The absolute and relative right kidney weights of all groups of exposed females were greater (up to 18%) than those of the chamber controls, but, in general, were not exposure concentration related. There were no lesions detected grossly at necropsy or microscopically that supported these increases.</p> <p>There were no differences between control group and exposed mice of either sex for any of the measured parameters (data not shown). There were no effects on the reproductive organs of mice of either sex that could be attributed to exposure to isobutylene.</p>
Test condition	: B6C3F1 mice (10 males and 10 females/group, 6 weeks of age) were exposed by inhalation for 6 hours/day, 5 days/week, for 14 weeks to 0, 500, 1,000, 2,000, 4,000 or 8,000 ppm, isobutene. Isobutene concentrations in the exposure chambers were monitored by on-line gas chromatography approximately every 20 minutes during exposures.
Test substance	: Isobutene, CAS No. 115-11-7 Lot Nos. SGCO51091ECA and SGCO20594ECA; 98% - >99% purity
Conclusion	: These data demonstrate that isobutene is not toxic to mice exposed to concentrations up to 8,000 ppm for 14 weeks.
Reliability	: (1) valid without restriction GLP Study.
Flag 10.12.2003	: Critical study for SIDS endpoint
	(46)
Type	:
Species	: mouse
Sex	: male/female
Strain	: B6C3F1
Route of admin.	: inhalation
Exposure period	: 105 weeks
Frequency of treatm.	: 6 hours/day, 5 days/week
Post exposure period	:
Doses	: 500, 2000 or 8000 ppm
Control group	: yes
Method	: other: NTP Two Year Carcinogenicity Study
Year	: 1998
GLP	: yes
Test substance	: other TS: Isobutene (CAS No. 115-11-7)
Method	: Survival analysis was estimated by the product-limit procedure of Kaplan and Meier. Statistical analyses for possible dose-related effects on survival used Cox's method for testing two groups for equality and Tarone's life table test to identify dose-related trends. All reported P values for the survival analysis are two-sided. The Poly-k test was used to assess neoplasm and nonneoplastic lesion prevalence. Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure related trend. All reported P values are one-sided. Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data were analyzed with the parametric multiple comparison procedures (Dunnett, Williams). Hematology, clinical chemistry, urinalysis, spermatid, and epididymal spermatozoal data were analyzed using non-parametric multiple comparison methods (Shirley, Dunn). Treatment effects were investigated by applying a multivariate analysis of variance to the transformed data to test for simultaneous equality of measurements across exposure concentrations (Morrison).
Result	: In this study, neither survival rates nor body weight gains of males were

significantly affected by isobutene exposure. Although survival rates for female mice were not affected by exposure, female mice exposed to 2,000 or 8,000 ppm weighed slightly less than the chamber controls in the second year of the study. There were no treatment-related clinical findings in mice. The only lesions associated with exposure in mice were nonneoplastic nasal lesions in all exposed groups of males and females. Nasal lesions included hyaline degeneration of the respiratory and olfactory epithelium; the lesions were minimal to mild in severity and the incidences increased with increasing exposure concentration:

Males

Respiratory Epithelium (Severity)	Olfactory Epithelium (Severity)
6/50 (1.0)	6/50 (1.0)
19/49 (1.2)	7/49 (1.1)
29/50 (1.5)	16/50 (1.6)
39/48 (1.8)	17/48 (1.4)

Females

Respiratory Epithelium (Severity)	Olfactory Epithelium (Severity)
21/47 (1.8)	17/47 (1.5)
39/50 (1.5)	19/50 (1.2)
41/49 (1.6)	24/49 (1.1)
48/50 (2.3)	27/50 (1.2)

Although they were not observed in the 14-week mouse study, these lesions are fairly common in long-term inhalation studies. No nasal neoplasms were observed in male or female mice.

- Test condition** : B6C3F1 mice (50 males and 50 females/group, 6 weeks of age) were exposed by inhalation for 6 hours/day, 5 days/week, 105 weeks to 0, 500, 2,000 or 8,000 ppm, isobutene. Isobutene concentrations in the exposure chambers were monitored by on-line gas chromatography approximately every 20 minutes during exposures.
- Test substance** : Isobutene, CAS# 115-11-7
- Conclusion** : Lot Nos. SGCO51091ECA and SGCO20594ECA; 98% - >99% purity
Under the conditions of this study, there was a dose related increase of nasal lesions (hyaline degeneration of the respiratory and olfactory epithelium) in male and female B6C3F1 mice exposed to 500, 2,000 or 8,000 ppm isobutylene. This is considered an adaptive response.
- Reliability** : (1) valid without restriction
GLP Study.
- Flag** : Critical study for SIDS endpoint
- 10.12.2003 (46)

5.5 GENETIC TOXICITY 'IN VITRO'

- Type** : Ames test
- System of testing** : Salmonella typhimurium TA 98, TA 100, TA 1535, TA 1537, TA 1538
- Test concentration** : 250 - 10000 ppm
- Cytotoxic concentr.** :
- Metabolic activation** : with and without
- Result** : negative
- Method** : other: not specified
- Year** :
- GLP** : no
- Test substance** : as prescribed by 1.1 - 1.4
- Remark** : A gaseous protocol was used with concentrations ranging from 250 ppm to 10000 ppm. The S-9 fractions were isolated from Sprague Dawley rats treated with polychlorinated biphenyl (500 mg/kg, five days before

Reliability	: sacrifice). : (4) not assignable Reference not available.	
28.10.2003		(53)
Type	: Mouse lymphoma assay	
System of testing	: Mouse lymphoma L5178Y TK+/TK- cell line from Clive	
Test concentration	: 6.25, 12.5, 25, 50, 100% isobutylene in 5% CO ₂ in air.	
Cytotoxic concentr.	:	
Metabolic activation	: with and without	
Result	: negative	
Method	: other: Adequate scientific method based on Clive et al (1972, 77, 79), Amacher et al (1979)	
Year	: 1981	
GLP	: yes	
Test substance	: other TS: Isobutylene, liquefied	
Method	: None employed. Positive response is defined as a doubling of mutant frequency (mutant colonies ÷ 105 survivors) compared to solvent controls with a dose response over two consecutive concentrations. An increase in absolute mutant colonies is highly desirable.	
Result	: Preliminary toxicity results in the absence of S-9 indicated severe toxicity at 100% isobutylene due either to isobutylene itself or prolonged hypoxia to cells caused by exposure to 100% test gas atmosphere. Varying degrees of toxicity also occurred at other doses, only the lowest dose 6.25% was non-toxic. In the first of two mutation tests without S-9, cultures treated with isobutylene induced more TFT resistant colonies than controls but no mutant frequencies reach doubling. Numbers of colonies on survival plates were lower than normal producing overall higher mutant frequencies. These unusual distributions were due to inadequate precleansing of cultures with methotrexate prior to use. In the second experiment, following two additional rounds of cleansing with methotrexate, the number of mutant colonies induced by isobutylene and those in the negative control cultures were much lower and the number of survival colonies much increased. No dose of isobutylene induced a mutant frequency greater than the negative control. Of three experiments performed with S-9, the first was rejected because incubation with S-9 for 24 hours killed 80-90% cells in all cultures including the positive controls, and inadequate cleansing with methotrexate resulted in excess mutant colonies in the negative control group. In the subsequent 2 tests, shorter exposure of 16 hours substantially reduced S-9 induced toxicity. Exposure to isobutylene at concentrations up to 100% did not result in any significant increase in mutant colonies compared to negative control (CO ₂ /air) cultures. Positive control treatment produced appropriate increases in mutant frequency.	
Test condition	: In the preliminary toxicity test, mouse lymphoma cells (3x10 ⁶ cells) in culture flasks were exposed to isobutylene at concentrations of 100 - 6.25% without metabolic activation in incubation jars. Concentrations were blended by passing air and isobutylene through flow meters into a mixing chamber, before delivery into the incubation jars. Flow meters were calibrated by comparing standard registered flow rates with actual flow rates measured by gas burette at atmospheric pressure and ambient temperature. Actual flow rates were obtained by multiplying registered flow rates by appropriate conversion factor. Approximately 25 l gas/air mixture was flushed through each 6.25 l jar during exposure. Actual gas concentrations in jars were not measured. Incubation was carried out with shaking for 24 hours at 37 degree C. After incubation, test atmosphere was removed and cells were harvested by centrifugation. Resuspended cells were transferred to fresh tissue culture flasks, gassed with 5% CO ₂ in air and incubated at 37 degree C. Cell density was measured each day for three days by counting with a Neubauer haemocytometer to determine toxicity. In the definitive mutation test, 10 ml of 3x10 ⁶ exponentially	

growing L5178Y cells were exposed to isobutylene at concentrations of 100%-6.25% with and without metabolic activation. All cultures were incubated with shaking (150 rpm) at 37 degree C for 24 hours. Positive control compound without S-9 was ethyl methane sulfonate (400, 200 µg/ml); with S-9, 2-acetyl amino fluorine (100, 50 µg/ml); cultures were treated for 3 hours. After incubation, cells were harvested by centrifugation, resuspended in fresh medium, and samples from each suspension plated on soft agar for varying times. For day 0 survival, cells were plated immediately after exposure (3 plates/dose level), allowed to set at 40 C, equilibrated with 5% CO2/air and incubated at 37 degree C for 10 days. For expression of genetic damage, cells multiplied in liquid medium for 3 days following exposure. On the third day, cell cultures were adjusted to 3x10⁵ cells/ml, diluted in cloning medium, dispensed to 3 plates/dose level and incubated at 37 degree C for 10 days to determine cell survival. For mutant colony selection, cells were dispensed into cloning medium containing 5 µg/ml trifluorothymidine (TFT), 3 plates/dose group, and incubated at 37 degree C for 7-10 days. At the end of incubation, mutant colonies were counted manually.

Test substance : Isobutylene, liquefied, from Essochem Europe, Inc. CAS Number 115-11-7

Conclusion : In both the absence and presence of S-9 mix, isobutylene showed no evidence of mutagenic activity in the mouse lymphoma assay.

Reliability : (2) valid with restrictions
No direct measurement of exposure concentration or analysis of incubation jar atmosphere was performed. Results of these tests are valid and the lack of mutagenic effect was reproducible despite poor initial cell cleansing and toxicity due to initial overexposure to S-9.

Flag : Critical study for SIDS endpoint
23.10.2003 (44)

Type : other: Transformation assay

System of testing : Mouse embryo fibroblast derived cell line

Test concentration : 25, 50, and 100% isobutylene in 5% CO2 in air.

Cycotoxic concentr. :

Metabolic activation : with and without

Result : negative

Method : other: Adequate scientific method based on Heidelberger

Year : 1981

GLP : yes

Test substance : other TS: Isobutylene, liquefied

Method : None employed. Positive response is defined as the presence of type II or type III transformed foci in treated cultures with evidence of dose response and reproducibility in repeat assay. Compounds which transform fibroblast cells have a high probability of inducing tumors if injected in immunosuppressed mice.

Result : In the preliminary toxicity test without S9, only 100% isobutylene caused cell toxicity either due to isobutylene itself or prolonged hypoxia resulting from exposure to 100% test gas atmosphere. In the transformation assay with or without metabolic activation, no transformed colonies were observed at any exposure level. Positive control compounds, known carcinogens in vivo, induced clear evidence of morphological transformation.

Test condition : Preliminary toxicity assay without metabolic activation was performed to establish a range of concentrations for the transformation assay. Five ml. Samples of cells from a culture at density of 200 cells/ml were pipetted into plastic tissue culture flasks, incubated in 5% CO2/air overnight for equilibration, then medium was replaced with fresh medium supplemented with fetal bovine serum (10% v/v). Flasks with caps screwed on lightly were placed in incubation jars which were flushed with 100% isobutylene or isobutylene mixed with 5% CO2/air to achieve concentrations ranging from 50%-6.25%. Concentrations were blended by passing air and isobutylene

	through flow meters into a mixing chamber, before delivery into the incubation jars. Flow meters were calibrated by comparing standard registered flow rates with actual flow rates measured by gas burette at atmospheric pressure and ambient temperature. Actual flow rates were obtained by multiplying registered flow rates by appropriate conversion factor. Approximately 25 l gas/air mixture was flushed through each 6.25 l jar during exposure. Actual gas concentrations in jars were not measured. Jars were sealed and incubated with shaking (50 rpm) at 37 degree C for 24 hours. Exposure medium was then replaced with fresh medium and culture flasks incubated for an additional 3 weeks. Cells were harvested with trypsin and counted for toxicity in Neubauer haemocytometers. For the transformation assay, cultures were treated as above, except that S-9 mix was added to one half flasks (6/dose group) and all flasks (12/dose group) were placed in incubation jars flushed with 100%, 50% or 25% isobutylene. After 24 hours incubation with shaking, medium was changed and cells were incubated in flasks for 8 weeks. Medium was changed twice weekly until cells reached confluence and weekly thereafter. At 8 weeks, cells were fixed in methanol, stained with Giemsa and scored for transformed foci. Positive control chemicals were 3-methylcholanthrene (30, 15 µg/ml), ethyl methane sulfonate (250, 125 µg/ml), 2-acetylaminofluorene (10, 5 µg/ml) and 2-aminoanthracene (5, 2.5 µg/ml). Negative controls were CO2/air, DMSO or acetone.
Test substance	: Isobutylene, liquefied, from Essochem Europe, Inc. CAS Number 115-11-7.
Conclusion	: By criterion used in this laboratory, isobutylene had no transforming effect in C3H/10T½ cells in the presence or absence of liver metabolic activation and is not considered a potential carcinogen in vivo.
Reliability	: (2) valid with restrictions No direct measurement of exposure concentration or analysis of incubation jar atmosphere was performed.
Flag 23.10.2003	: Critical study for SIDS endpoint (42)
Type	: Ames test
System of testing	: Salmonella typhimurium TA1535, TA1537, TA1538, TA100, TA98; E. coli WP2uvrA(pKM101)
Test concentration	: 5% - 100%
Cycotoxic concentr.	:
Metabolic activation	: with and without
Result	: negative
Method	: other: Comparable to standard bacterial mutation assays
Year	: 1981
GLP	: yes
Test substance	: other TS: Isobutylene, 99.8% liquefied
Method	: None employed. Criteria for positive responses were, for TA100 a 1.5 fold increase and for TA1535, TA1537, TA1538, TA98 and E.coli, a doubling of revertant colonies compared to mean negative control values at some dose. Tests were also observed for dose response.
Result	: No mutagenic activity was induced by isobutylene in any strain at any concentration in the first or second tests. Reduction in number of colonies in all strains indicative of toxicity and growth inhibition was observed with and without metabolic activation at 80% and 100% isobutylene.
Test condition	: Bacteria were freshly prepared by 16 hour culturing in nutrient broth prior to use and monitored for strain sensitivity. An agar overlay comprised of 2 ml agar, 0.5 ml S-9 mix or phosphate buffer, and 0.1 ml fresh bacteria was mixed and poured on minimal agar plates. When set, plates were inverted, placed in jars of known volume and exposed to isobutylene at 37 degree C for 48 hours, then incubated an additional 24 hours in fresh air. Concentrations of isobutylene were achieved by mixing hydrocarbon-free artificial air and test gas through flow meters before delivery into incubation jars. Flow meters were calibrated by comparing standard registered flow

	rates with actual flow rates measured by gas burette at atmospheric pressure and ambient temp. Actual flow rates were obtained by multiplying registered air flow rates by the appropriate conversion factor. Approx. 25 liters gas/air filled each 6.25 liter jar during exposure. Actual gas concentrations inside the incubation jars were not measured. Duplicate plates were used in the first trial for each test, only one plate was used at each dose in the repeat trial/test. Negative control: hydrocarbon free artificial air, Positive gas control: vinyl chloride 30% in air in TA 1535, TA100 ± S9, Other pos. controls: 4-actyl aminofluorene 1.0 mg/plate in TA1538, TA98 +S9; methyl methane sulfonate 100 µg/plate in E.coli -S9, and 9-amino acridine 20 µg/plate in TA1537 -S9.	
Conclusion	: Isobutylene was adequately tested at sufficiently high doses to induce toxicity, and is not mutagenic to bacteria in this test system.	
Reliability	: (2) valid with restrictions Only 2 plates/dose in initial trial and only 1 plate/dose in repeat trial of each test was used. Gas concentration within chambers was not measured.	
Flag 23.10.2003	: Critical study for SIDS endpoint	(43)
Type	: Ames test	
System of testing	: Salmonella typhimurium TA 100, TA 102, TA 1535	
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	: with and without	
Result	: negative	
Method	: other: not specified	
Year	:	
GLP	: no	
Test substance	: as prescribed by 1.1 - 1.4	
Remark	: Using a simple exposure system consisting of gastight tissue culture flasks the authors investigated isobutylene and its metabolite 2-methyl-1,2-epoxypropane. The test compounds were added to the bacteria via the septum of the flasks and the flasks were incubated for 72 hrs. Isobutylene was not mutagenic in the presence (TA 1535 only) or absence of S9 mix up to a concentration of 50000 ppm. For the epoxide 2-methyl-1,2-epoxypropane, a positive response was detected at 500 ppm in strain TA 1535 while in the other strains 5000 ppm were required for a positive response. Additions of S9 mix reduced the mutagenicity detected in strain TA 1535, probably due to the action of epoxide hydrolases and GSH-S-transferases. The authors stressed that 2-methyl-1,2-epoxypropane is much less potent than propylene oxide and that the epoxide concentration necessary to induce a mutagenic effect are extremely high in comparison with the small amounts formed during biotransformation in vivo.	
Reliability 28.10.2003	: (1) valid without restriction	(9)
Type	: Escherichia coli reverse mutation assay	
System of testing	: E. coli (WP2 uvrA)	
Test concentration	:	
Cycotoxic concentr.	:	
Metabolic activation	: with and without	
Result	: negative	
Method	: other: not specified	
Year	:	
GLP	: no	
Test substance	: as prescribed by 1.1 - 1.4	
Remark	: A gaseous protocol was used with concentrations ranging from 250 ppm to 10000 ppm. The S-9 fractions were isolated from Sprague Dawley rats treated with polychlorinated biphenyl (500 mg/kg, five days before	

Reliability : sacrifice).
: (4) not assignable
Reference not available.
28.10.2003 (53)

Type : Escherichia coli reverse mutation assay
System of testing : Escherichia coli (WP2 uvrA)
Test concentration : 5% to 100%
Cycotoxic concentr. :
Metabolic activation : with and without
Result : Negative
Method : other: not specified
Year :
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : Bacteria were exposed to concentrations ranging from 5% to 100% isobutylene. Bacterial toxicity was observed at 80%.

Reliability : (1) valid without restriction
28.10.2003 (43) (55)

Type : other: in vitro micronucleus test
System of testing : human lymphocytes
Test concentration :
Cycotoxic concentr. :
Metabolic activation : Without
Result : Negative
Method : other: not specified
Year :
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Remark : Isobutylene and its epoxide 2-methyl-1,2-epoxypropane were tested using a gaseous protocol. Isobutylene induced no micronuclei in contrast to the epoxide (no further details).

Reliability : (4) not assignable
Reference not available.
28.10.2003 (33)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : Mouse
Sex : Male
Strain : B6C3F1
Route of admin. : Inhalation
Exposure period : 2 days, 6 hours/day
Doses : 1000, 3260, 10,000 ppm in air
Result :
Method : other: Consistent with standard methods. Cites Heddle et al. 1983 Report of US EPA GeneTox Program Mut. Res. 123: 61-119 and Cunningham et al. 1986 Mutagenesis 1: 449-452
Year : 1990
GLP : Yes
Test substance : other TS: Isobutylene colorless gas, 100% pure

Method : Calculation of mean and std. dev. of micronuclei data. Test of equality of group means by standard ANOVA at each time period, followed by Duncan's Multiple Range test if ANOVA was significant. Standard

Result	: regression used for dose response. Residuals of ANOVA analyzed for normality by Wilk's Criterion. : NOAEL = 10,000 ppm Isobutylene did not induce a statistically significant positive response nor a dose-related increase in the number of micronuclei in PCEs of mouse bone marrow at any dose level. A significant regression coefficient ($p < 0.05$) for increased percentage of PCEs was observed. This event was within historical control values and is not considered biologically significant. Positive control 1,3-butadiene induced statistically significant increases in micronuclei and a reduced %PCE indicative of toxicity. Negative control values were within normal range.
Test condition	: Male mice (10/group) were exposed to isobutylene, 6 hours a day for two days at 0, 1000, 3260 or 10,000 ppm. Actual exposure concentrations were determined by on-line gas chromatography reported hourly. Nominal concentrations were calculated. Chamber homogeneity verified by GC in pretrials. All mice were killed 24 hours after second exposure. Bone marrow was removed from both femurs, slides were prepared and stained with acridine orange for fluorescence. 1000 polychromatic erythrocytes (PCEs) were examined for micronuclei. Ratio of PCEs to normochromatic erythrocytes (NCEs) was determined by counting 1000 erythrocytes (PCE + NCE).
Conclusion	: Isobutylene was not clastogenic in mouse bone marrow under conditions of this test system.
Reliability Flag	: (1) valid without restriction : Critical study for SIDS endpoint
11.08.2003	(49)

5.7 CARCINOGENICITY

Species	: Rat
Sex	: male/female
Strain	: Fischer 344
Route of admin.	: Inhalation
Exposure period	: 105 weeks
Frequency of treatm.	: 6 hours/day, 5 days/week
Post exposure period	:
Doses	: 500, 2000 or 8000 ppm
Result	: Negative
Control group	: Yes
Method	: other: NTP Two Year Carcinogenicity Study
Year	: 1998
GLP	: Yes
Test substance	: other TS: Isobutene, CAS# 115-11-7
Method	: Survival analysis was estimated by the product-limit procedure of Kaplan and Meier. Statistical analyses for possible dose-related effects on survival used Cox's method for testing two groups for equality and Tarone's life table test to identify dose-related trends. All reported P values for the survival analysis are two-sided. The Poly-k test was used to assess neoplasm and nonneoplastic lesion prevalence. Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure related trend. All reported P values are one-sided. Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data were analyzed with the parametric multiple comparison procedures (Dunnnett, Williams). Hematology, clinical chemistry, urinalysis, spermatid, and epididymal spermatozoal data were analyzed using non-parametric multiple

	comparison method (Shirley, Dunn). Treatment effects were investigated by applying a multivariate analysis of variance to the transformed data to test for simultaneous equality of measurements across exposure concentrations (Morrison).
Result	: The survival of exposed males and females was similar to that of the chamber controls. Mean body weights of exposed groups were generally similar to those of the chamber controls throughout the study. There were no exposure-related clinical findings. The combined incidence of C-cell adenomas and carcinomas plus follicular cell carcinomas was 6/48, 4/48, 7/48, 12/50 for control, 500, 2000, and 8000 ppm exposed male rats, respectively. Corresponding incidence for female rats was 1/48, 0/48, 0/48, and 5/50, respectively. Isobutene exposure caused an increased incidence of follicular cell carcinoma in the 8,000 ppm male group compared to the chamber controls. The histomorphology of the carcinomas in this group was similar to the morphologic spectrum typical of spontaneously developing follicular cell carcinomas. There were no concurrent increases in the incidences of thyroid gland follicular cell hyperplasia or adenoma in male rats, nor were there increased incidences of proliferative lesions of the thyroid gland in exposed female rats compared to the chamber controls. The historical control range for follicular cell carcinoma in male rats in inhalation studies is 0% to 4%, and the highest historical control incidence of this neoplasm by any route for male rats is 3/50 (6%) (in a dosed feed study). The five carcinomas in the 8,000 ppm male group were considered treatment related because of the significant increase over historical control rates for inhalation studies as well as all other routes of administration. Exposure of rats to isobutene caused an increase, although marginal, in the incidences of hyaline degeneration of the olfactory epithelium of the nose in males and females; more importantly, the severities of this lesion (mild to moderate) were increased in exposed males and females in a concentration-related fashion [Males: Incidence: 43/49 (controls), 45/49 (500 ppm), 46/50 (2000 ppm), and 49/49 (8000 ppm); Severity: 1.3, 1.4, 2.2, and 2.6 out of 4, respectively. Females: Incidence: 44/50 (control), 47/50 (500 ppm), 48/50 (2000 ppm), 47/49 (8000 ppm); Severity: 1.5, 2.4, 2.8, and 2.8 out of 4, respectively]. No nasal neoplasms were observed in exposed male or female rats.
Test condition	: F344/N rats (50 males and 50 females/group, 6 weeks of age) were exposed by inhalation for 6 hours/day, 5 days/week, 105 weeks to 0, 500, 2,000 or 8,000 ppm, isobutene. Isobutene concentrations in the exposure chambers were monitored by on-line gas chromatography approximately every 20 minutes during exposures.
Test substance	: Isobutene, CAS# 115-11-7
Conclusion	: Lot Nos. SGCO51091ECA and SGCO20594ECA; 98% - >99% purity Under the conditions of this study, there was some evidence of carcinogenic activity of isobutene in male F344/N rats at the highest dose based on an increased incidence of follicular cell carcinoma of the thyroid gland. There was no evidence of carcinogenic activity in female F344/N rats exposed to isobutene at concentrations of 500, 2,000 or 8,000 ppm.
Reliability	: (1) valid without restriction GLP Study.
Flag 27.10.2003	: Critical study for SIDS endpoint
	(46)
Species	: Mouse
Sex	: male/female
Strain	: B6C3F1
Route of admin.	: Inhalation
Exposure period	: 105 weeks
Frequency of treatm.	: 6 hours/day, 5 days/week
Post exposure period	:
Doses	: 500, 2000 or 8000 ppm

Result	: Negative																								
Control group	: Yes																								
Method	: other: Two Year Carcinogenicity Study																								
Year	: 1998																								
GLP	: Yes																								
Test substance	: other TS: Isobutene, CAS No. 115-11-7																								
Method	<p>: Survival analysis was estimated by the product-limit procedure of Kaplan and Meier. Statistical analyses for possible dose-related effects on survival used Cox's method for testing two groups for equality and Tarone's life table test to identify dose-related trends. All reported P values for the survival analysis are two-sided.</p> <p>The Poly-k test was used to assess neoplasm and nonneoplastic lesion prevalence. Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure related trend. All reported P values are one-sided.</p> <p>Two approaches were employed to assess the significance of pairwise comparisons between exposed and control groups in the analysis of continuous variables. Organ and body weight data were analyzed with the parametric multiple comparison procedures (Dunnett, Williams). Hematology, clinical chemistry, urinalysis, spermatid, and epididymal spermatozoal data were analyzed using non-parametric multiple comparison methods (Shirley, Dunn). Treatment effects were investigated by applying a multivariate analysis of variance to the transformed data to test for simultaneous equality of measurements across exposure concentrations (Morrison).</p>																								
Result	<p>: In this study, neither survival rates nor body weight gains of males were significantly affected by isobutene exposure. Although survival rates for female mice were not affected by exposure, female mice exposed to 2,000 or 8,000 ppm weighed slightly less than the chamber controls in the second year of the study. There were no treatment-related clinical findings in mice. The only lesions associated with exposure in mice were nonneoplastic nasal lesions in all exposed groups of males and females. Nasal lesions included hyaline degeneration of the respiratory and olfactory epithelium; the lesions were minimal to mild in severity and the incidences increased with increasing exposure concentration:</p> <table border="0" style="margin-left: 40px;"> <tr> <td colspan="2">Males</td> </tr> <tr> <td style="padding-right: 20px;">Respiratory Epithelium (Severity)</td> <td>Olfactory Epithelium (Severity)</td> </tr> <tr> <td>6/50 (1.0)</td> <td>6/50 (1.0)</td> </tr> <tr> <td>19/49 (1.2)</td> <td>7/49 (1.1)</td> </tr> <tr> <td>29/50 (1.5)</td> <td>16/50 (1.6)</td> </tr> <tr> <td>39/48 (1.8)</td> <td>17/48 (1.4)</td> </tr> <tr> <td colspan="2">Females</td> </tr> <tr> <td style="padding-right: 20px;">Respiratory Epithelium (Severity)</td> <td>Olfactory Epithelium (Severity)</td> </tr> <tr> <td>21/47 (1.8)</td> <td>17/47 (1.5)</td> </tr> <tr> <td>39/50 (1.5)</td> <td>19/50 (1.2)</td> </tr> <tr> <td>41/49 (1.6)</td> <td>24/49 (1.1)</td> </tr> <tr> <td>48/50 (2.3)</td> <td>27/50 (1.2)</td> </tr> </table> <p>Although they were not observed in the 14-week mouse study, these lesions are fairly common in long-term inhalation studies. No nasal neoplasms were observed in male or female mice.</p>	Males		Respiratory Epithelium (Severity)	Olfactory Epithelium (Severity)	6/50 (1.0)	6/50 (1.0)	19/49 (1.2)	7/49 (1.1)	29/50 (1.5)	16/50 (1.6)	39/48 (1.8)	17/48 (1.4)	Females		Respiratory Epithelium (Severity)	Olfactory Epithelium (Severity)	21/47 (1.8)	17/47 (1.5)	39/50 (1.5)	19/50 (1.2)	41/49 (1.6)	24/49 (1.1)	48/50 (2.3)	27/50 (1.2)
Males																									
Respiratory Epithelium (Severity)	Olfactory Epithelium (Severity)																								
6/50 (1.0)	6/50 (1.0)																								
19/49 (1.2)	7/49 (1.1)																								
29/50 (1.5)	16/50 (1.6)																								
39/48 (1.8)	17/48 (1.4)																								
Females																									
Respiratory Epithelium (Severity)	Olfactory Epithelium (Severity)																								
21/47 (1.8)	17/47 (1.5)																								
39/50 (1.5)	19/50 (1.2)																								
41/49 (1.6)	24/49 (1.1)																								
48/50 (2.3)	27/50 (1.2)																								
Test condition	<p>: B6C3F1 mice (50 males and 50 females/group, 6 weeks of age) were exposed by inhalation for 6 hours/day, 5 days/week, 105 weeks to 0, 500, 2,000 or 8,000 ppm, isobutene. Isobutene concentrations in the exposure chambers were monitored by on-line gas chromatography approximately every 20 minutes during exposures.</p>																								
Test substance	<p>: Isobutene, CAS# 115-11-7 Lot Nos. SGCO51091ECA and SGCO20594ECA; 98% - >99% purity</p>																								

Conclusion	:	Under the conditions of this study, there was no evidence of carcinogenic activity of isobutene in male or female B6C3F1 mice exposed to 500, 2,000 or 8,000 ppm.	
Reliability	:	(1) valid without restriction GLP Study.	
Flag 27.10.2003	:	Critical study for SIDS endpoint	(46)

5.8.1 TOXICITY TO FERTILITY

5.8.2 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	Rat	
Sex	:	Female	
Strain	:	Wistar	
Route of admin.	:	other: vapor exposure	
Exposure period	:	17 days (day 5 to 21 of gestation)	
Frequency of treatm.	:	6 hours/day	
Duration of test	:	21 days	
Doses	:	500, 2000 and 8000 ppm	
Control group	:	yes, concurrent no treatment	
Method	:	OECD Guide-line 414 "Teratogenicity"	
Year	:	2002	
GLP	:	Yes	
Test substance	:	other TS: Isobutene	
Method	:	<p>Maternal bodyweight was evaluated by analysis of covariance. Maternal food consumption, the numbers of implantations and live foetuses per female, gravid uterus weight, litter weight, mean foetal weights per litter, and mean manus and pes scores per litter were evaluated by analysis of variance.</p> <p>Pre-implantation loss, post-implantation loss, early intra-uterine deaths, late intra-uterine deaths, major external/visceral defects, minor external/visceral defects, external/visceral variants, major skeletal defects, minor skeletal defects, and skeletal variants were analysed as the proportion of fetuses with each individual manus and pes score, and the proportion of foetuses and the proportion of litters affected with each defect using FISHER'S EXACT test.</p>	
Result	:	<p>Exposure to isobutylene on days 5 to 21 (inclusive) of gestation did not elicit any maternal effects, i.e., there were no treatment-related changes in clinical condition, no effects on maternal body weight or food consumption and no macroscopic findings in tissues examined post mortem.</p> <p>There was no effect of isobutylene on the number, growth or survival of the fetuses in utero. There was no effect of isobutylene on fetal development. Although cleft sternebrae were observed only in fetuses in the isobutylene groups, the incidence of fetuses affected was small and not dose-related and there were no minor changes in the appearance or ossification of the sternebrae to indicate that this area of the skeleton was adversely affected by isobutylene. Also, there was no evidence for an adverse effect of isobutylene on other ossification centres of the skeleton. Isolated differences from control were considered to be incidental. Thus isobutylene at exposure concentrations of up to 8000 ppm is considered not to have any adverse effect on fetal development.</p>	
Test condition	:	<p>Twenty-four mated female Wistar rats per test group were exposed (whole-body) to dynamic atmospheres of isobutylene for 6 hours per day on days 5 through day 21 (inclusive) of gestation. The target concentrations were 500, 2000 and 8000 ppm. A concurrent control group was exposed to clean air. Chamber concentrations were determined analytically using a</p>	

gas chromatographic method.

Clinical observations were recorded for each animal at least once a day throughout the study (days 1-22 of gestation). On exposure days clinical observation was performed before, during and after exposure. Food consumption, water consumption and body weight of the animals was frequently determined.

On day 22 of gestation, all animals were sacrificed and assessed by gross pathology (including weight determinations of the unopened uterus and the placentae). For each dam, corpora lutea were counted and number and distribution of implantation sites (differentiated as resorptions, live and dead fetuses) was determined. The fetuses were removed from the uterus, sexed, weighed and further investigated for any external findings.

Thereafter, all fetuses were examined internally for visceral variation and abnormality, sexed and eviscerated. The fetuses were then fixed in 70% industrial methylated spirits. After approximately 24 hours, the head of each fetus was cut along the fronto-parietal suture line and the brain was examined for macroscopic abnormalities. The fetuses were then returned to the 70% methylated spirits, processed and stained with Alizarin Red S and Alcian Blue and then examined for variation and abnormality of bone and cartilage and the degree of ossification of the manus and pes was assessed.

- Conclusion** : Under the conditions of this prenatal developmental toxicity study, the inhalation exposure of pregnant Wistar rats to isobutylene on days 5 to 21 (inclusive) of gestation elicited no maternal toxicity at all tested concentrations up to 8,000 ppm.
There was no effect of isobutylene on the number, growth or survival of the fetuses in utero and no effect on fetal development.
- Reliability** : (1) valid without restriction
GLP Study.
- Flag** : Critical study for SIDS endpoint
11.08.2003 (7)

5.8.3 TOXICITY TO REPRODUCTION, OTHER STUDIES

5.9 SPECIFIC INVESTIGATIONS

5.10 EXPOSURE EXPERIENCE

- Remark** : Seven persons inhaled 100 ppm isobutylene and the difference between the concentrations inhaled and exhaled was determined. The value obtained after 20 minutes was defined as 80% value of the final absorption rate and was 17% for isobutylene.
15.04.1994 (63)

- Remark** : Isobutylene is a normal component of human breath and is present at a concentration of 0.43 +/- 0.09 nmol/liter. The breath concentration of isobutylene increased 10-fold when subjects were exposed to halothane anesthesia. The source of this isobutylene was speculated to be terpenes or ubiquinones; however the actual origin is unknown.

The concentrations of volatile hydrocarbons were studied in breath samples from patients before and after anesthesia. In patients to whom halothane was administered, there was a significant increase in the concentration of isobutylene exhaled (from 0.43 to 4.66 nmol/L). There

was no change in the concentration of isobutylene in six patients anaesthetized with ketamine and diazepam. The concentrations of ethane and pentane were not able to explain the origin of the isobutylene, but they suggest that it is formed endogeneously and that halothane administration inhibited the metabolism of the formed isobutylene which subsequently was exhaled.

Reliability : (4) not assignable
This entry was assigned a reliability rating of "4" because the full article was not available for review.

29.10.2003 (28)

Remark : 111 mg/m³ are reported as the limit for olfactory detection, and 1235 mg/(m³*2 min) is reported to be the lowest irritating concentration.

11.08.2003 (32)

5.11 ADDITIONAL REMARKS

Type : Metabolism

Remark : The biotransformation of isobutylene was qualitatively and quantitatively investigated using liver homogenates from C57 black female and CBA male mice and head space gas chromatography. Isobutylene was metabolized to its epoxide 2-methyl-1,2-epoxypropane in a NADPH-dependent reaction. The metabolism was inhibited by metyrapone and SKF 525A, inhibitors of monooxygenases. The epoxide was detoxified by hydrolysis, catalyzed by epoxide hydrolases, and by conjugation to GSH, catalyzed by GSH S-transferases. The involvement of these enzymes was demonstrated by addition of 3,3,3-trichlorpropene oxide as inhibitor of epoxide hydrolases and indomethacin as inhibitor of GSH S-transferases.

Reliability : (2) valid with restrictions
23.10.2003 (10)

Type : Toxicokinetics

Remark : Mice and rats were exposed to vapors of isobutylene at the LC50 level (415 mg/(L*2 hr) for mice, 620 mg/(L*4 hr) for rats) and the concentrations in tissues after the exposure were determined by GC after extraction. The concentrations in rat tissues were: brain - 126; liver - 77.4; kidneys - 63.7; spleen - 59.1; perinephric fat - 219.0 (mg/100 ml). In the brains of mice, 264.1 mg/100ml were measured. In addition, the distribution of isobutylene in various sections of the central nervous system of one cat was determined. The exposure concentration was set so that the animals died during the inhalation within one hour. The author interpreted the result as indicative of higher concentrations in those sections of the central nervous system containing substantia alba.

17.01.2003 (54)

Type : Toxicokinetics

Remark : A method for the simultaneous detection of various hydrocarbons in the breath of experimental animals and humans allowed the quantification of isobutylene. Whereas isobutylene was not detected in untreated rats, the compound was exhaled (2.27 nmol/kg*hr) after treatment with ethanol (5 g/kg). The authors were not able to attribute the origin of isobutylene to lipid peroxidation, since branched fatty acids are virtually not present in membranes and adipose tissues. They suggested that exhaled branched hydrocarbons may stem from radical-mediated decompositions of isoprenoid structures

04.12.2002 like precursors of the steroid biosynthesis. (18)

Type : Toxicokinetics

Remark : Isobutylene was detected in the breath of ethanol-treated Sprague-Dawley rats. The compound accumulated in the atmosphere if the animals were confined in a closed chamber until a steady state concentration was reached. This was indicative of metabolism of the compound superimposed upon exhalation. The elimination of isobutylene from a closed chamber by rats was measured and showed the highest elimination rate in comparison with ethane, propane, butane, and pentane (half life 1.3 h, K(elimination) 0.53 L/h, clearance 2.8 L/kg*hr). The metabolism of hydrocarbons was inhibited by administration of ethanol, tetrahydrofuran, or dithiocarb, known inhibitors of cytochrome P450-dependent monooxygenases. The authors suggested, that the ethanol inducible fraction of the monooxygenases is mainly responsible for the metabolism of hydrocarbons. The results show that the presence of hydrocarbons in breath may not uncritically be taken as proof for lipid peroxidation. An increased release of hydrocarbons into the gas phase, after treatment with compounds suspected to induce lipid peroxidation, may merely result from decreased metabolism. This may especially be important in the case of isobutylene that can not originate from the usual peroxidative breakdown of membrane lipids, since branched fatty acids are extremely rare in cell constituents.

04.12.2002 (19)

Type : Toxicokinetics

Remark : A two-compartment toxicokinetic model for inhalation was used to analyze the gas uptake of isobutylene in Sprague-Dawley rats and B6C3F1 mice. In each experiment 2 rats or 8 mice were exposed to isobutylene. The metabolism followed Michaelis-Menten kinetics. The maximal metabolic elimination rates were 340 umol/kg/hr for rats and 560 umol/kg/hr for mice. The atmospheric concentration at which $V_{max}/2$ was reached was 1200 ppm for rats and 1800 ppm for mice. At steady state, the rate of metabolism was directly proportional to the isobutylene concentration when the exposure concentration was below 500 ppm. The primary metabolite formed was the epoxide of isobutylene, 2-methyl-1,2-epoxypropane, which was detected in the exhaled air of animals exposed to isobutylene. The maximum isobutylene epoxide concentration after isobutylene exposure was only about 1/15 and 1/100 of the ethylene oxide or 1,2-epoxy-3-butene oxide concentrations observed after ethylene and butadiene exposure, respectively. This result was interpreted by the authors as indication of a very efficient detoxification of the isobutylene epoxide by epoxide hydrolases.

Reliability : (2) valid with restrictions
Only 2 rats or 8 mice used for each experiment.

23.10.2003 (11)

Type : Toxicokinetics

Remark : F-344/N rats were exposed to 40, 400, and 4000 ppm radioactively labelled (14-C) isobutylene for 6 hrs. The blood concentration of isobutylene was linearly related to the exposure concentration up to 400 ppm, but not at 4000 ppm, indicating saturation of uptake or metabolism. Total body burdens were nonlinearly related to exposure ppm at all three exposure concentrations with umoles isobutylene equivalents/ppm exposure = 0.47, 0.21, 0.076 with increasing exposure, respectively. Isobutylene

		equivalents were predominantly excreted in the urine. Less than 5% was metabolized to CO ₂ . Three major metabolites were detected in the urine. One of these appeared to be a sulfate conjugate, one a mercapturic acid of 1,2-epoxy-3-butene oxide. The urinary profile was the same at 40 and 400 ppm.	
Reliability	:	(2) valid with restrictions Abstract only.	
23.10.2003			(52)
Type	:	Toxicokinetics	
Remark	:	The authors investigated the origin of various volatile alkanes and alkenes exhaled in the breath of male rats (no strain mentioned). Isobutylene was detected in air exhaled from untreated rats and toxicokinetic parameters were determined. The amount exhaled was not affected by pretreatment with CC14, a compound known to induce lipid peroxidation. After ethanol pretreatment (5 g/kg) the exhalation of isobutylene was increased about 6-fold compared to not-treated animals. According to the authors these results suggest that isobutylene is formed physiologically, but that its formation is not due to lipid peroxidation. The treatment with ethanol inhibited the metabolism of isobutylene via P-450-dependent monooxygenases thus increasing the exhalation of the compound. Additional experiments suggested that the physiological formation of isobutylene is due to O ₂ -radical attack on leucine, either as amino acid or bound to a peptide or protein.	
04.12.2002			(51)
Type	:	Toxicokinetics	
Remark	:	Male F344 rats were exposed to 0, 40, 400, or 4000 ppm of isobutylene, and a time course evaluation of blood levels of isobutylene was performed. Three rats per time point were used to determine blood levels at 0.25, 0.5, 1.0, 2.0, 2.25, 2.75, 3.75 and 6.75 hours after initiation of the exposure. Blood levels of isobutylene were linearly related to exposure concentrations between 40 and 400 ppm but increased in a supralinear fashion at the highest concentration, suggesting saturation of metabolism. Total uptake, excretion patterns, and metabolic conversions were studied in rats exposed for up to 6 hours to 0, 40, 400, or 4000 ppm ¹⁴ C-labelled isobutylene. Absorption was approximately 8% up to 40 ppm isobutylene, but decreased at the higher concentrations. The amount of isobutylene metabolized per ppm hr of exposure was also linear up to 40 ppm but decreased at higher concentrations. Over 90% of the absorbed isobutylene was metabolized at exposure concentrations up to 400 ppm, but the exposure to ca. 4000 ppm resulted in approximately 20% of the absorbed dose exhaled as unmetabolized isobutylene. Two urinary metabolites were identified as isobutenediol and 2-hydroxyisobutyric acid. Two other urinary metabolites were tentatively identified as sulfate conjugates of isobutenediol. The authors reported a high background of isobutylene in the blood of the animals due to endogeneous formation of isobutylene. In an erratum they attributed most of this background to a systematic error in analysis.	
Reliability	:	(1) valid without restriction	
09.12.2003			(29)
Remark	:	A DNA binding study was conducted in male and female F-344 rats and B6C3F1 mice with inhaled [¹⁴ C] isobutylene. Animals were placed in a closed all-glass exposure system. After complete disappearance of isobutylene from the atmosphere, the animals were killed and DNA binding in the liver and lungs were measured. No incorporation of ¹⁴ C radioactivity	

	from isobutylene into the natural nucleosides (or bases) occurred and that specific DNA adducts were not detected.	
28.01.2003		(36)
Type	: Metabolism	
Remark	: The epoxidation of the gaseous alkene 2-methylpropene or isobutene was studied in vitro in rat lung tissue and rat liver. Lung and liver tissue was isolated from adult male Sprague Dawley reats and subcellular lung and liver fractions prepared for incubation with isobutylene. Incubations were carried out in gastight headspace vials containing a NADPH-generating system. The isobutylene concentration was measured by gas chromatogaphy. A comparison of the data from the lung and liver fractions indicates lung tissue appears to be less exposed to the toxic epoxide metabolite than is the case for liver tissue, oscillating around 15-20% of the concentrations present in the liver, but it reaches 40% of the hepatic level after an incubation time of 1 hour. The results are correlated with the low capacity of the mixed function oxidase system, expressed by means of the cytochrome P-450 content and the 7-ethoxycoumarin O-deethylase activity, to form reactive intermediates. The activities of the principal epoxide detoxifying enzymes, glutathione S-transferase and epoxide hydrolase, present in the lung represent only 5-10% of the values measured in rat liver.	
Reliability	: (2) valid with restrictions Not all study details were provided.	
23.10.2003		(8)
Type	: Metabolism	
Remark	: Inhalation uptake as well as exhalation of isobutene is around 2.1 times higher in mice than rats which correlates well with the higher respiratory frequency in mice. In addition, transformation of isobutene to its epoxide and accumulation in vivo of the epoxide also occur at higher rates in mice than in rats.	
Reliability	: (4) not assignable Review paper which discusses interspecies differences in metabolism of 1,3-butadiene, isobutene and styrene.	
28.10.2003		(6)

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