FOREWORD INTRODUCTION

HEXYLENE GLYCOL

CAS N°: 107-41-5

SIDS Initial Assessment Report for SIAM 13

(Bern, 6-9th November 2001)

Chemical Name: Hexylene Glycol

CAS No: 107-41-5

Sponsor Country: United Kingdom

National SIDS Contact Point in Sponsor Country:

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HISTORY:

This substance is sponsored by the UK under the ICCA Initiative and is submitted for first discussion at SIAM 13.

Since SIAM 13, an addendum to the original test report has been provided which confirms that specific staining of the acidophilic globules seen in male rats in the key repeat dose toxicity study were alpha 2 microglobulin. The presence of this material and the nature of the adverse effects seen in the kidney are consistent with a male rat specific phenomenom which is generally accepted of little relevance to human health. Therefore, the systemic NOAEL can now be confirmed as 450 mg/kg/day and the NOAEL for localised iritation of the GI tract remains at 50 mg/kg/day.

PEER REVIEW PROCESS:

The industry consortium collected new data and prepared the updated IUCLID, and draft versions of the SIAR and SIAP. UK government peer-reviewed the documents, audited selected studies and conducted separate literature searches.

TESTING: No testing (X) Testing ( )

COMMENTS: The industry contact point is Dr D E Owen, Shell Chemicals Ltd, UK, acting on behalf of the Lesser Ketones Manufacturing Association (consortium members: Shell Chemical Company, ATOFINA Chemicals Inc, ExxonMobil Chemical Company, Dow Chemical Co).

Deadline for circulation: 14/9/01, 8/2/02

Date of circulation: 14/9/01, 8/2/02

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	107-41-5
Chemical Name	Hexylene glycol (2-methyl pentane-2,4-diol)
Structural Formula	CH_3 CHOH CH_2 C (OH)$(CH3)_2$ (NB the commercial substance is a racemic mixture)

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Hexylene glycol is of relatively low acute toxicity to mammals, the acute oral LD_{50} is >2000 and <5000 mg/kg (range >2000-4700 mg/kg) while the dermal LD_{50} is >2000 mg/kg (range >1.84-12.3 g/kg). The acute inhalational LC_{50} is ≥ the saturated vapour concentration. Recent skin and eye irritation guideline studies indicate that hexylene glycol has low potential to irritate the skin and is slightly irritating to the eye. Skin and eye effects are reversible. Hexylene glycol is not a skin sensitiser.

Repeated exposure by oral gavage to rats at 50, 150 or 450 mg/kg/day hexylene glycol for 90 days, with additional animals at the top dose also allowed a 4 week exposure-free recovery period, resulted in hepatocellular hypertrophy and increased liver weight, male rat specific nephropathy and inflammatory changes in the forestomach and to a lesser extent the glandular stomach. The liver changes were reversible and considered an adaptive physiological response to increased metabolic demand. The male rat nephropathy was partially reversible and associated with an increased severity of acidophilic globules, subsequently identified by specific staining (Masson's trichrome) as alpha-2-microglobulins, and considered of questionable biological significance to humans. Changes in the stomach (reversible) and forestomach (partially reversible) were considered attributable to local irritation induced by the gavage procedure. The NOAEL for this local effect being 50 mg/kg/day. The systemic NOAEL for this guideline study is considered to be 450 mg/kg/day with a no effect level for local irritation to the stomach and forestomach of 50 mg/kg/day.

Hexylene glycol is not genotoxic in either mammalian or non-mammalian cells *in vitro*.

No standard fertility studies are available. No effects on the gonads were observed in a good quality 90-day oral gavage study in rats, which were, administered hexylene glycol at doses up to 450 mg/kg/day by oral gavage. Therefore no studies are required under the SIDS regarding fertility.

In a good quality developmental toxicity study, in which rats received 30, 300 or 1000 mg/kg/day hexylene glycol by oral gavage, the LOAEL for maternal toxicity was 1000 mg/kg/day, based on slightly reduced weight gain at this top dose level. Greater pre-implanation loss observed at this dose level may be regarded of questionable biological significance.

This dose level was also the LOAEL for foetotoxicity based on a, slight delay in ossification, a greater number of fetuses with extra thoraco-lumbar ribs, and a slight decrease (not statistically significant) in foetal body weight. There was no evidence of teratogenicity up to the limit dose of 1000 mg/kg.

Environment

The environmental effects database meets the requirements of the SIDS data package. Hexylene glycol is of low acute toxicity to aquatic organisms. The lowest valid 96h LC50 for fish was 8510 mg/l (Mosquito fish, *Gambusia affinis*) and the lowest valid 48h EC50 for invertebrates was 2800 mg/l (*Ceriodaphnia reticulata*). Tadpoles of the frog *Rana catesbiana* were tested, with a 96 hour EC_{50} = 11800 mg/l.

The 72 hour EC_{50} for the freshwater alga *Selenastrum capricornutum* is >429 mg/l (highest level tested) based on both growth rate and biomass.

The $PNEC_{aqua}$ derived from the lowest toxicity value is 4.3 mg/l, based on an assessment factor of 100 applied to the algal EC50, in accordance with OECD guidance. No data are available on terrestrial or sediment organisms but PNEC values have been derived for the sediment and terrestrial compartments using equilibrium partitioning, 0.295 mg/kg wt for sediment and 0.0786 mg/kg for soil.

Exposure

The combined market for hexylene glycol in Europe and the USA for 2000 is 15000 tonnes. The principal end uses are in industrial coatings (45%) and as a chemical intermediate (20%). Hexylene glycol occurs as a component in a large number of products for industrial and consumer use.

Hexylene glycol is a liquid, melting point – 50°C, boiling point 197.5°C, vapour pressure 0.07hPa at 20°C, it is fully miscible in water and has a calculated n-octanol water partition coefficient (log K_{ow}) of 0.58. There are no aqueous streams from the production process but small amounts of hexylene glycol will be present in the output to the wastewater treatment plant from spills and cleaning operations. Hexylene glycol can also enter the aqueous and terrestrial environment from end uses such as in agricultural products and down hole lubricants for oil and gas fields. Under normal manufacturing practices there should be no emissions to the atmosphere. Low levels of emissions may occur as a result of spills and cleaning operations. The main application is in industrial surface coatings and there is potential here for release to the atmosphere.

There is a potential for occupational and consumer exposure through inhalation and skin contact although exposures through inhalation are expected to be low due to the low vapour pressure. Consumer exposure to hexylene glycol will occur principally through its use in cosmetics, antifreezes and hydraulic fluids. Exposure to aerosols is possible as a result of industrial spraying with paints containing hexylene glycol. Indirect exposures via the environment (e.g. ingestion of surface water contaminated with hexylene glycol) are also possible.

The calculated half-life for the photo-oxidation (reaction with hydroxyl radicals) of hexylene glycol in air is 9 hours. Hexylene glycol is not expected to undergo direct photolysis and is not susceptible to hydrolysis.

Hexylene glycol is predicted to distribute in the environment primarily to water or water and soil. Based on a calculated log K_{ow} of 0.58 which suggests a log K_{oc} of <1, hexylene glycol has

low potential to bioaccumulate (BCF=3) and low potential for sorption to soil. In water, hydrolysis and photodegradation are not expected to occur. Hexylene glycol is at least inherently biodegradable.

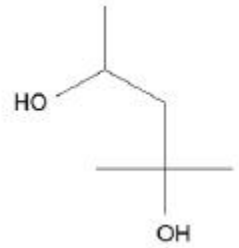
NATURE OF FURTHER WORK RECOMMENDED

No further work is indicated.

SIDS INITIAL ASSESSMENT REPORT

1. IDENTITY

Hexylene glycol (CAS no. 107-41-5) is a colourless liquid having the following physical–chemical properties and characteristics, which have been obtained from various reference sources or calculated using Syracuse quantitative structure activity relationships (see the IUCLID for further details).

PROPERTY	VALUE
Chemical formula	$C_6H_{14}O_2$
Molecular formula	CH_3 CHOH CH_2 C (OH)$(CH_3)_2$
Molecular weight	118.18
Structural formula	
Conversion factors	1 ppm = 4.83 mg/m^3 1 mg/m^3 = 0.206 ppm
Saturation conc.	66 ppm at 20°C
Physical form	Liquid at room temperature
Purity	>99% w/w 2-methyl-2,4-pentanediol
Typical impurities	water, acetone, propan-2-ol, 4-methylpentan-2-ol, 4-methylpentan-2-one, 4-hydroxy-4-methylpentan-2-one, Together totalling <1% w/w
Melting point	-50°C
Boiling point	197.5°C at 1013 hPa
Density	0.923 g/cm^3 at 20°C
Vapour pressure	0.07 hPa at 20°C (used for modelling)
n-octanol –water partition coefficient	log Kow 0.58 calculated Syracuse (used for modelling)
Water solubility	Miscible (1 x 10^5mg/l used for modelling)
Flash point	93°C closed cup
Autoflammability	306°C at 1013 hPa
Viscosity	36 mPa.s at 20°C
Synonyms	2,4-dihydroxy-2-methyl pentane 2-methyl 2,4 pentanediol 4-methyl 2,4 pentanediol 2-methyl-pentane-2,4-diol 1,1,3-trimethyl trimethylene glycol 1,1,3-trimethyl trimethylenediol α,α,α-trimethyltrimethylenediol trimethyltrimethylene glycol Diolane Isol Pinakon

The product currently produced contains >99% 2-methyl 2,4-pentanediol, which exists in enantiomeric form. Based on chemical principles equal amounts of enantiomeric products are formed when two achiral reagents react to give a chiral product. Hexylene glycol is formed from hydrogen and diacetone alcohol, both achiral reagents. Therefore commercial hexylene glycol as covered by CAS no. 107-41-5 may be described as a racemic mixture containing equal amounts of two enantiomers. Unless otherwise specified, it is assumed that all testing was conducted using this commercial material. [Note:]

Values used for monitoring are explained further in section 2.1.

[Note:] The R(-) form has the CAS no. 99210-90-9 and the S(+) form has the CAS no. 99210-91-0. CAS no. 99113-75-4 is the deleted CAS Registry number for 107-41-5. No specific property data are available for either of the two enantiomers.

2. GENERAL INFORMATION ON EXPOSURE

Estimated Production or Import Volume

In 2000 the estimated market for hexylene glycol in the USA was 7000 tonnes and in Europe 8000 tonnes. No information is currently available on the total global production tonnage, or trends. Hexylene glycol is not produced in the UK.

Uses

The single largest end use is in industrial coatings, this accounting for about 45% of the total production. An approximate breakdown of end uses is given in the table below.

TYPE OF END USE[#]	% (approx)	SPECIFIC APPLICATIONS
Industrial coatings	**45**	Paints, lacquers and varnishes as a solvent plasticiser in surface coatings. Used in both oil and water-based paints and in paint strippers.
Chemical intermediate	**20**	Chemical synthesis
Down hole lubricant for oil and natural gas fields	**10**	Ingredient in grinding and extrusion aids. As a down hole lubricant for oil and natural gas fields.
Leather & Textile processing	**7**	As a moistening and softening agent for composition cork, casein, leather, paper and textile fibres
Antifreezes	**7**	Antifreezes Hydraulic fluids as a coupling agent
Cosmetics	**6**	Cosmetics including fragrances, bath and hair preparations, eye makeup, soaps and skin care preparations at concentrations from 0.1-25% (CIR, 1985).
Agricultural/biocidal uses	**5**	As a wetting agent in pesticide formulations. Industrial cleaning/washing agents and disinfectants.
Minor uses		As a wetting or dispersing agent in polishes and cleaners. Solvent use in preparation of dyes, synthetic resin-base and steam set inks.

[#] 232 products on the Swedish Products Register (2001) contain hexylene glycol, 13 of which are consumer products. The main use indicated is as a solvent for industrial cleaners, hardeners. Information from the Danish Products Register also reflects the uses indicated above

No information is available on the typical concentration of the substance in consumer products other than cosmetics.

2.1 Environmental Exposure and Fate

Hexylene glycol is miscible in water, has a vapour pressure of 0.07 hPa at 20°C and a calculated Henry's Law constant of 8.27E-03 Pa.m3/mol. The Henry's Law constant was calculated using the maximum solubility permitted in the EUSES model (100,000 mg/l). The following values were used in environmental fate and distribution modelling:

Parameter	Value	Discussion
Vapour pressure	0.07 hPa	This value, obtained from reference texts, is comparable to the estimated value (Syracuse Epiwin) of 0.078 hPa and greater than measured values for the comparable products hexane-1,6-diol of <0.01 hPa and 3-methyl-1,5-pentanediol of 0.0072 hPa. The differences have a negligible effect on modelling output.
Solubility	100,000 mg/l	Hexylene glycol is miscible. For modelling the maximum solubility permitted in EUSES has been used.
Log Kow	0.58	Estimated value consistent with measured values for other isomers, 0 for hexane-1,6-diol and -0.03 for 3-methyl-1,5-pentanediol.
Biodegradability	Inherent	Based on data indicating that hexylene glycol is at least inherently biodegradable.

2.1.1 Sources of Potential Release to the Environment

Manufacturing process

There are no aqueous streams from the production process but small amounts of hexylene glycol will be present in the output to the wastewater treatment plant from spills and cleaning operations.

Under normal manufacturing practices emissions to the atmosphere are minimal. Low levels of emissions may occur as a result of spills and cleaning operations.

Downstream uses

Hexylene glycol can enter the aqueous and terrestrial environment from end uses such as in agricultural products and down hole lubricants for oil and gas fields.

The main application is in industrial surface coatings and there is potential here for release to the atmosphere. Other downstream uses may also contribute to atmospheric emissions.

No information is available on levels in production plant effluent, or losses from processing end use.

2.1.2 Photodegradation

The calculated half-life for the photo-oxidation (reaction with hydroxyl radicals) of hexylene glycol in air is 9.040 hours (Syracuse APOWIN 2.0).

2.1.3 Stability in water

Alcohols and ethers do not absorb light in the environmentally significant range (>290 nm). Therefore hexylene glycol should not undergo direct photolysis in the environment. Glycols have no hydrolysable groups and are therefore not susceptible to hydrolysis.

2.1.4 Transport between environmental compartments

Using a fugacity based model (Mackay level 1) hexylene glycol is predicted to appear mainly in the aqueous compartment (99.5%) with 0.34% in the soil, 0.17% in air and minimal amounts distributed to sediment. However the distribution of hexylene glycol in the environment as estimated by Level III fugacity modelling is dependent on inputs to the different compartments:

	Input (%)			Distribution (%)			
	Air	Water	Soil	Air	Water	Soil	Sediment
Scenario 1	100	0	0	<1	56	43	<1
Scenario 2	0	100	0	<1	100	<1	<1
Scenario 3	0	0	100	<1	55	44	<1

Consideration of the downstream applications indicates that emissions will be primarily to air with smaller amounts to water and soil. The overall environmental distribution is therefore likely to be closer to Scenario 1 than Scenario 2.

The calculated log Kow of 0.58 suggests a log Koc <1 (EU TGD QSAR, chapter 4 section 4.3) indicating a low potential for sorption to soil.

The distribution in a sewage treatment plant has been estimated using the SIMPLETREAT model to be 59% degraded, 41% to water, based on inherent biodegradability, log Kow = 0.58, water solubility = $1x10^5$ mg/l and vapour pressure =0.07 hPa.

Conclusions: Based on the relevant physical-chemical properties and the fact that hexylene glycol is at least inherently biodegradable, hexylene glycol will partition primarily to water or water and soil. In the sewage treatment plant hexylene glycol will degrade (59%) and be present in the effluent (41%).

2.1.5 Biodegradation

A number of biodegradation assays have been carried out with hexylene glycol, including a 'round-robin' assessment of methods for determination of biodegradability (Blok, 1985). The report of the 'round-robin' tests provided summary data only, however the weight of evidence shows that hexylene glycol is at least inherently biodegradable. In the ready biodegradability assays assessed by Blok the results were somewhat variable. Pass rates (% tests showing pass) were (14, 17, 60 and 69% for MITI I (n=7), Closed bottle (n=6), Sturm non-adapted (n=5) and modified OECD (n=16) respectively. Two tests for inherent degradability were included in the round-robin, the Zahn-Wellens test (n=5) and a MITI II assay (n=8) with respective pass rates of 100 and 50%. There was insufficient experimental detail particularly in terms of determining whether the 10-day window criterion had been satisfied to conclude that hexylene glycol is readily biodegradable.

Conclusions: Based on evidence from a number of studies hexylene glycol is considered to be at least inherently biodegradable.

2.1.6 Bioaccumulation

The calculated bioconcentration factor is 3.162 (Syracuse Aopwin V1.85).

Conclusions: Based on Log Kow 0.58 from which the BCF of 3.162 is calculated, hexylene glycol is not expected to bioaccumulate.

2.2 Human Exposure

Hexylene glycol is widely used in industrial and household cleaners. It is used as an industrial solvent and in printing inks. It has application in the automotive industry as an hydraulic fluid and in the textile and shoe making industry as a process chemical. Consumer exposure to hexylene glycol will occur principally through its use in cosmetics, antifreezes and hydraulic fluids. There is potential for worker and consumer exposure through inhalational and dermal exposure. Exposure to aerosols is possible as a result of industrial spraying with paints containing hexylene glycol. Indirect exposures via the environment (eg ingestion of surface water contaminated with hexylene glycol) are also possible.

2.2.1 Occupational Exposure

The primary occupational exposure and exposure during manufacturing is via skin contact and to a lesser extent, as hexylene glycol has a low vapour pressure, through inhalation of the vapours. Personal monitoring data are available from 6 operators occupationally exposed to hexylene glycol. These personnel were monitored in 1994 while collecting process samples containing hexylene glycol, a task with one of the greatest exposure potentials. This was a short duration task (15 minutes or less) and all samples were below the limit of detection, typically 1.5 ppm.

Typical occupational exposure limits are as follows (Ariel, 2001):

Authority	Limit ppm(mg/m^3)	Ceiling ppm(mg/m^3)
UK EH40/2000	8 hour TWA 25 (123)	STEL 25 (123) - 15 minute reference period
Belgium 1999		25 (123)
Denmark 1996	TWA 25 (123)	Yes
France 1999	VLE 25 (125)	
Finland 1998	8 hour limit 25 (120)	15 minute limit 40 (200)
Germany 10/2000	TRGS limit (125)	
Netherlands MAC list 2000	MAC (TGG) 25 (125)	Yes
Switzerland 1999	TWA 10 (49)	STEL 20 (98)
US, ACGIH		25 (121)

According to the ACGIH documentation of Threshold Limit Values their ceiling limit of 25 ppm is set to avoid eye irritation, which has been reported in volunteer studies at 50 ppm and nasal irritation and respiratory discomfort observed at 100 and 1000 ppm. As the saturated calculated vapour concentration at ambient temperature is 66 ppm, exposure at 100 and 1000 ppm was probably to a super-saturated mist.

3. HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics

3.1.1.1 Animal studies

Larsen, 1958 reported that male rats receiving 200 mg/day excreted 40% of the administered dose in the urine, of this about 4% was in the form of free glycol. Diechmann & Dierker, 1946 cited in Jacobsen, 1958, reported a substantial increase in the levels of glucuronates in the plasma and urine of rats and rabbits fed hexylene glycol. Gessner et al, 1960 also reported excretion of glucuronate in the urine of rabbits administered about 118 mg/kg by stomach tube. 67% of the dose was recovered from the urine in conjugated form. They were unable to characterise the conjugate.

3.1.1.2 Human studies

Five male volunteers were given single and repeated oral daily doses of 1-5 g hexylene glycol as a 10% aqueous solution as a drink. Both free and conjugated hexylene glycol was recovered from the urine, about 20-35% of the ingested dose being excreted, half in the conjugated form. Elimination continued for 5-10 days after cessation of exposure (Jacobsen, 1958). Urinary excretion only was investigated.

3.1.2 Acute Toxicity

3.1.2.1 Animal studies

Hexylene glycol is of relatively low acute toxicity to mammals. Single lethal dosages of hexylene glycol to laboratory animals (table 3.1.2) range from > 2.0 to 4.7 g/kg (LD_{50}) for oral exposure and greater than 2.0 g/kg (LD_{50}) for dermal exposure (Woodard *et al*, 1945; Smyth and Carpenter, 1948; Opdyke, 1978, Gardner 1996 a,b). The key studies indicated in the table 3.1.2 are the OECD guideline studies, the values obtained are supported by the older studies which were not carried out to current regulatory guidelines but provide valuable supporting evidence.

Inhalation exposure to saturated hexylene glycol vapour at room temperature (approximately 50 - 60 ppm) or vapour heated to 170°C (18000 ppm) did not produce acute intoxication or lethality to laboratory animals (Smyth and Carpenter, 1948).

The clinical signs observed in animals acutely intoxicated with hexylene glycol are predominately of central nervous system (CNS) depression and include decreased activity, muscle incoordination and flaccidity, palpebral closure, pilo-erection, narcosis and anaesthesia. Woodard et al, 1945 report that at doses near the LD_{50} blood was observed in the urine and there was some evidence of histopathological changes in the liver, lung and kidneys. No macroscopic lesions were noted at necropsy in the majority of rats receiving 2000 mg/kg HG orally or topically in recently conducted acute toxicity studies (Gardner, 1996a,b).

Conclusion: Hexylene glycol is of relatively low acute toxicity to mammals, the acute oral LD_{50} is >2000 and < 5000 mg/kg (range >2000-4700 mg/kg) while the dermal LD_{50} is >2000 mg/kg (range >1.84-12.3 g/kg). The acute inhalational LC_{50} is ≥ the saturated vapour concentration.

Table 3.1.2 Summary of acute oral and dermal toxicity data (key studies emboldened)

SPECIES	EXPOSURE	LD50	REFERENCE
ORAL			
Rat	**2000 mg/kg [GLP guideline OECD 420]**	**> 2.0 g/kg**	**Gardner (1996a)**
Rat		4.47 g/kg	Industrial Biotest, 1970 reported by BIBRA, 1991 & German MAK Commission, 1997
Rat		4.70 g/kg	Smyth and Carpenter (1948)
Rat		3.7 g/kg	RTECS online
Rat		4.76 g/kg	Union Carbide, 1949
Rat Mouse Rabbit Guinea pig		4.0 ml/kg (3.68 g/kg) 4.5 ml/kg (4.14 g/kg) 3.2 ml/kg (2.94 g/kg) 2.8 ml/kg (2.6 mg/kg)	Woodard et al (1945)
Mouse		3.8 ml/kg (3.5 g/kg)	SCC (1958) Anderson & McOmie, (1946)
Mouse		3.097 g/kg	Wenzel & Koff, 1956 RTECS on line
Mouse		3900 mg/kg	CIR, 1985
DERMAL			
Rat	**2000 mg/kg [GLP guideline OECD 402]**	**> 2 g/kg**	**Gardner (1996b)**
Rabbit		> 5 g/kg	Moreno reported in Opdyke (1978)
Rabbit	1.84 g/kg	>1.84 g/kg	SCC (1958)
Rabbit		13.3 ml/kg (12.3 g/kg)	Smyth and Carpenter, (1948)
Rabbit		>9.4 ml/kg (8.68 g/kg)	Anderson & McOmie, (1946)
Rabbit		8.56 ml/kg (7.90 g/kg)	Reported by BIBRA, 1991

3.1.2.2 Human experience

Hexylene glycol was at one time used to impregnate burn dressings (presumably for its hygroscopic property) and there are reports of toxic effects in patients to whom these dressings had been applied. Fisher et al, 1968 reported on an adult in whom delirium and ataxia developed progressively following application of the impregnated dressing. A full recovery was made following removal of the dressing. Procter, 1966 had previously reported coma and death in children with burns to which hexylene glycol dressings had been applied. Fischer et al, 1968 calculated that a 15 kg individual with a body surface of 0.64 m^2 and 25% burns could receive a dose of 2-7 g/kg hexylene glycol, depending on how many layers of dressing were applied.

3.1.3 Repeated dose toxicity

3.1.3.1 Animal studies

Hexylene glycol was administered by oral gavage in a 90 day study carried out in Sprague-Dawley rats at dose levels of 50, 150 and 450 mg/kg/day to OECD guideline 408 (Fabreguettes, 1999b). This study included a functional observational battery (FOB), which gave no evidence of neurotoxic effects. The NOAEL for systemic toxicity in this study is 450 mg/kg/day. Hepatocellular hypertrophy coupled with increased liver weight was observed at 450 mg/kg/day in both sexes and in males only at 150 mg/kg/day.

In the absence of degenerative or necrotic change this was considered an adaptive response to increased metabolic demand. At 150 and 450 mg/kg/day kidney histopathology (higher incidence and severity of acidophilic globules in the tubular epithelium) and increased kidney weights observed in male rats only are suggestive of male rat specific alpha-2-microglobulin nephropathy, this was subsequently confirmed by specific staining with Massons Trichrome stain.

Local changes in the forestomach (hyperplasia, hyperkeratosis, inflammatory cell infiltration and oedema of mucosa and sub-mucosa) and the glandular stomach (inflammatory cell infiltration and oedema of the sub-mucosa) observed in both sexes at 450 and 150 mg/kg/day are indicative of a local irritative effect resulting from the oral gavage procedure. No effect was observed at 50 mg/kg/day.

Observed effects were either fully or partially reversible over the 4-week recovery period (Fabreguettes, 1999b). There were no adverse effects on other organs including the reproductive organs. This is considered the key study in the assessment of the longer term effects of hexylene glycol.

Similar changes in the liver and kidneys were noted in the 14 day range-finder (Fabreguettes, 1999a) for the 90 day assay. Information is also available from the 14 day rat gavage study carried out to establish the toxicity of hexylene glycol for the developmental toxicity study (Clode, 1997). The main findings were dose related increases in adrenal and kidney weights in both sexes, statistically significant only at 1000 mg/kg/day. Mean liver weights were increased in all male treatment groups and top dose females. Statistical significance was attained in top dose groups of both sexes and males at 300 mg/kg/day. No histopathological examination was carried out.

A number of older studies have been reported but are not considered reliable indicators of the systemic effects of hexylene glycol following repeated administration, because of limited exposure duration, limited toxicity assessments, and/or deficient experimental design. The effects they do report are consistent with those observed in the key study.

In a 9 day inhalation study (Union Carbide, 1976) rats and 1 rabbit (no controls) were exposed to an aerosol of hexylene glycol (mean droplet size 1µm) at a concentration of 0.7 mg/l (140 ppm). Changes in the upper respiratory tract indicative of mild respiratory tract irritation were reported.

Conclusions: Repeated exposure by oral gavage to 50, 150 or 450 mg/kg/day hexylene glycol for 90 days resulted in hepatocellular hypertrophy and increased liver weight, male rat specific nephropathy and inflammatory changes in the forestomach and to a lesser extent the glandular stomach. The liver changes were considered an adaptive physiological response to increased metabolic demand, while the changes in the stomach were considered attributable to local irritation induced by the gavage procedure. The systemic NOAEL for this good quality study conducted to OECD guideline 408 is therefore considered to be 450 mg/kg/day and a no effect level for local irritation to the stomach and forestomach is considered to be 50 mg/kg/day.

3.1.3.2 Observations in man

There is one report available that assesses the effects of repeated oral exposure to humans. Five human subjects given oral doses of 37 g of hexylene glycol daily for 24 days (estimated daily dosage 14-28 mg/kg body weight) reported no subjective symptoms that could be attributed to the intake of hexylene glycol (Jacobson, 1958). Additionally, no alterations in urine parameters were detected in this study.

3.1.4 Genotoxicity

Hexylene glycol has been tested *in vitro* in mammalian and non-mammalian cells. No *in vivo* testing has been carried out.

3.1.4.1 Bacterial mutation assay

Hexylene glycol did not induce reverse gene mutation in *Salmonella typhimurium* strains TA1535, 1537, 1538, 98 and 100 or *Escherichia coli* WP_2 uvrA pKM101 when tested according to OECD guideline 471. HG was added to the test system at concentrations up to 4000 µg/plate in the presence or absence of metabolic activation. Hexylene glycol was soluble in the aqueous medium. There was no evidence of cytotoxicity at any dose level. There was no increase in reverse mutation rate with any of the bacterial strains tested in the presence or absence of metabolic activation (Meyer *et al*, 1985; Brooks *et al*, 1988).

3.1.4.2 Mitotic gene conversion

Mitotic gene conversion in the yeast *Saccharomyces cerevisiae* JD1 was measured in the liquid suspension assay at concentrations up to 5.0 mg/ml in the presence and absence of rat liver S9 according to OECD guideline 480. There was no significant effect on cell viability and no increase in the rate of mitotic gene conversion was observed (Meyer *et al*., 1985; Brooks *et al*., 1988).

3.1.4.3 Mammalian cells in vitro

Hexylene glycol was tested according to OECD guideline 473 in Chinese Hamster Ovary (CHO) cell cultures at concentrations up to 5000 µg/ml in the presence or absence of metabolic activation. There was no evidence of cytotoxicity at any dose level and no increase in numbers of chromosome aberrations was detected (Meyer *et al*., 1985; Brooks *et al*., 1988).

Conclusions: In guideline studies hexylene glycol does not induce gene mutations in bacterial strains, mitotic gene conversion in yeast or chromosome aberrations in CHO cell *in vitro*.

3.1.5 Carcinogenicity

No data are available.

3.1.6 Reproductive Toxicity

No standard fertility studies are available. No effects on the gonads were observed in a good quality 90-day oral gavage study in rats which were administered hexylene glycol at doses up to 450 mg/kg/day by oral gavage. Reproductive organs examined were the testes, prostate, seminal vesicles, epididymes, ovaries, vagina and uterus. Therefore no additional studies are required under the SIDS programme regarding fertility.

3.1.7 Developmental Toxicity

Pregnant Sprague-Dawley rats received 30, 300 and 1000 mg/kg by oral gavage on gestation days 6-15 in a study meeting OECD guideline 414 (Clode, 1997). The NOAEL for maternal toxicity is 300 mg/kg bw based on a reduction in group mean body weight gain and food consumption at the 1000 mg/kg/level. There was a marginal, non-statistically significant lowering of foetal body weight at the top dose level. Some evidence was found of marginally higher incidences of foetal variations (skeletal, incomplete ossification and extra thoraco-lumbar ribs) at 1000 mg/kg, some of which attained statistical significance. These observations were considered by the authors as related to a delay in normal ossification process possibly due to the reduced maternal body weight gain at

this dose level. Greater preimplantation loss observed at this dose level may be regarded of questionable significance. The NOAEL for foetotoxicity was considered to be 300 mg/kg.
No evidence of teratogenicity was found in this study. LOAELs were 1000 mg/kg for maternal toxicity and foetotoxicity.

A further developmental toxicity study was carried out under the FDA guidelines for Reproduction studies, 1966 (Denny, 1996). In this study Sprague-Dawley rats received hexylene glycol by oral gavage at dose levels of 500, 1200 and 1600 mg/kg/day on gestation days 6-17. There was overt evidence of maternal toxicity with the NOAEL for this parameter being 500 mg/kg based on overt clinical signs of intoxication with reduced weight gain and food consumption at 1200 and 1600 mg/kg. There was no statistically significant increase in total external, visceral and skeletal malformations or variations. However sporadic low occurrences of developmental abnormalities were observed at 1200 and 1600 mg/kg. At 1600 mg/kg there was an increased incidence of skeletal variations (delayed ossification, extra ribs) when analysed on a foetal basis. A NOAEL could not be assigned, as foetuses at the lower dose levels were not examined internally. The NOAEL indicated by the range-finding study (Satala, 1996) was 1000 mg/kg for both developmental and maternal toxicity).

In view of the unexpected maternal toxicity in this FDA guideline study, attempts were made to repeat the findings at 1200 and 1600 mg/kg but were unsuccessful (G. Daston - personal communication, 1999).

Conclusions: In guideline studies minor foetotoxicity is observed at maternally toxic dose levels. The NOAEL for foetoxicity is 300 mg/kg based on a slight increase in delayed ossification, a greater number of foetuses with extra thoraco-lumbar ribs and a slight non-statistically significant decrease in foetal body weight at the top dose level of 1000 mg/kg (LOAEL). Greater preimplantation loss observed at 1000 mg/kg may be regarded of questionable biological significance. The NOAEL for maternal toxicity is also 300 mg/kg based on slightly reduced weight gain at 1000 mg/kg and this was considered to be the LOAEL. There was no evidence of teratogenicity.

3.1.8 Other

3.1.8.1 Skin Irritation

Animal studies

In a study carried out to OECD guideline 404, 0.5 ml pure hexylene glycol was applied undiluted to the skin of 3 rabbits in a 4 hour semi-occlusive exposure. Group mean 24+48+72 hour scores were 0.4 for erythema and 0 for oedema with a maximum individual score of 1, effects were reversible. Hexylene glycol is not a skin irritant under the conditions of this study (Parcel, 1995). Studies carried out under cosmetic guidelines using both single 24 hr and repeated exposure confirmed the low level of irritation potential (Guillot et al, 1982). Further data are available from an OECD guideline 402 acute dermal toxicity study in rats (Gardner, 1996) where no irritation was observed following a 24 hour covered application to 2000 mg/kg undiluted product. Slight to moderate irritation following 24 hour exposure to hexylene glycol has been reported in secondary sources in the absence of further experimental detail therefore an independent assessment cannot be made as to the validity of this data and they are not considered key to the evaluation of the irritation potential of hexylene glycol.

Conclusions: The data available from guideline studies indicate that hexylene glycol has a low potential to irritate the skin and that effects are reversible.

Human studies

Human volunteers exposed to 20% hexylene glycol in petrolatum for a 48-hr closed-patch test experienced no irritation of the skin (Epstein, 1978).

Studies of groups of 37 and 39 human subjects with apparently healthy skin also demonstrated that hexylene glycol is not an irritant. Irritation scores for HG were 0.11 for a 24-hour occluded patch test and 0.02 for a semi-occluded patch, when rated on a scale of 0 to 4 (CIR, 1985).

A study conducted in 823 eczema patients reported that hexylene glycol used in patch testing (48 hour occlusive) at aqueous concentrations of 30 or 50% caused oedema and erythema of the skin in 2.8% of the patients tested (Kinnunen & Hannuksela, 1989). The authors considered this indicative of irritation due to application of hexylene glycol.

Conclusions: While hexylene glycol produces minimal irritation to healthy human skin, some irritation may be experienced in a small proportion of people with pre-existing eczema.

3.1.8.2 Eye irritation

Animal studies

In a study carried out to OECD guideline 405, undiluted hexylene glycol was found to be slightly irritating to the eye. Group mean 24+48+72 hour scores were corneal opacity 0.8, iritis 0, conjunctival redness 0.9, chemosis 0.9. Maximum individual 24+48+72 hour scores were corneal opacity 1 (observed in 1 rabbit only), iritis 0, conjunctival redness 1, chemosis 1.3. All signs of irritation had fully resolved by 72 hours in 2 rabbits and by day 8 in the third rabbit (Gardner, 1996c).

An earlier study (Coombs, 1978) carried out prior to GLP regulations, had several deficiencies; it was terminated at day 7 when effects, although reduced, were not completely resolved, the individual animal data was not reported and a test volume of 0.2 ml was used. Group mean 24+48+72 hour scores were corneal opacity 1.4, iritis 0.8, conjunctival redness 1.8, chemosis 1.4.

Studies carried out under national cosmetic guidelines indicated that undiluted hexylene glycol caused initial irritation which was reversible within 7 days (Guillot et al, 1982).

Several earlier studies report eye irritation of varying degrees, however these studies were all to non-standard protocols which do not allow us to interpret the methodology and scoring systems used in terms of internationally agreed criteria for assessing eye irritation.

Conclusions: The data available indicate that hexylene glycol has some potential to irritate the eyes. Recent guideline studies indicate that irritation is slight and reversible within 8 days.

Human studies

In a poorly reported study Silverman et al, (1946) some volunteers exposed to 50 ppm (near saturation) hexylene glycol vapours, experienced slight eye irritation. Assessment of the degree of irritation was subjective with no independent clinical assessment of the eyes. The majority of these volunteers indicated that they would find 50 ppm acceptable for an 8-hour working day suggesting that the effects on the eye were minimal. In a later study slight eye irritation was reported in only 1/7 volunteers exposed to 100 ppm (Hine et al, 1955), in this case the eyes were examined visually post-exposure. Following exposure to 1000 ppm varying degrees of irritation were reported in the absence of any experimental details (ACGIH). Exposure at 100 and 1000 ppm was probably to a mist see 3.1.3.8.

Conclusions: Exposure to saturated vapours or mists of hexylene glycol produces at most slight eye irritation based on subjective reporting of the volunteers at concentrations up to 100 ppm.

3.1.8.3 Sensory Irritation

Limited studies with human volunteers (number unspecified), in which vapour concentrations were not accurately measured, indicate that a 15 minute exposure to concentrations of ≥50 ppm hexylene glycol is at most slightly irritating to the eye, nose and respiratory tract. Exposure to 50 ppm caused slight eye irritation in some volunteers, while nose and throat irritation was observed at >50 ppm (concentration not reported). The volunteers estimated that a concentration of 50 ppm was satisfactory for an 8 hour exposure. (Silverman et al, 1946). Assessment of the effects was by self reporting, there was no other assessment of the degree of irritation caused.

At 100 ppm for 5 minutes some volunteers reported slight nasal irritation and respiratory discomfort with eye irritation in only 1/7 cases (Hine et al, 1955), while a 5 minute exposure to 1000 ppm produced eye and nasal irritation and respiratory discomfort (ACGIH). The saturated vapour concentration for hexylene glycol is 66 ppm so exposure to the higher concentrations was probably to a supersaturated mist (ACGIH).

No effect was observed on the CNS (Silverman et al, 1946; Hine et al, 1955).

Conclusion: Subjective reporting by human volunteers suggests that near saturation concentration (50 ppm) produces at most slight eye, nasal and respiratory tract irritation.

3.1.8.4 Skin sensitisation

Animal studies

A skin sensitisation assay following the method of Buehler (OECD 406) was carried out in guinea pigs under GLP. There was no evidence of delayed contact hypersensitivity (Gardner, 1996d). The undiluted product was used for both topical induction and challenge applications. Challenge was also carried out using a 50% aqueous solution. There were no positive responses in either test or control groups.

Conclusions: Hexylene glycol is not a skin sensitiser in guinea pigs using the Buehler assay.

Human studies

Volunteer studies (33 tested) indicate that hexylene glycol applied at a concentration of 20% in petrolatum does not cause skin sensitisation when applied to human skin using a maximization procedure (Epstein, 1976). CIR, 1985 report on repeated insult patch tests with several personal care formulations containing hexylene glycol. There was no evidence of skin sensitisation.

Kinnunen and Hannuksela (1989) studied eczema patients with positive patch test reactions to 30 or 50% hexylene glycol and found a positive ROAT (Repeated Open Application Test) in 1 of 7 patients. The authors hypothesized the reaction in this patient may be due to cross-sensitivity. Alomar et al, 1985 used hexylene glycol (10% aqueous) as a standard patch test in a group of 230 patients exposed to cutting oils who had been diagnosed with occupational dermatitis. 9 patients gave a positive response to challenge with hexylene glycol (3.9% of the total number tested).

Conclusions: Occasional positive responses have been observed in some workers diagnosed with occupational dermatitis. Taking all the available information into account hexylene glycol does not appear to be a skin sensitiser.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

Data are available on the acute toxicity of hexylene glycol to fish, crustacea and algae. Hexylene glycol has not been assessed in chronic studies.

4.1.1 Fish and invertebrates

Several fish and invertebrate species have been tested. These studies, which are summarised in table 4.1.1 below, are of varying quality none being strictly to current guidelines and none obviously to GLP. However the weight of evidence indicates that hexylene glycol is of low acute toxicity to aquatic organisms with LC_{50}/EC_{50} values being in excess of 2800 mg/l. There appears to be no significant difference in acute toxicity between fresh and salt or brackish water species. [1]

Given that all results indicate a similar low order of acute toxicity, the key studies are selected as those carried out using species recommended in OECD guidelines and acceptable methodology. These are emboldened in the table 4.1.1.

Conclusions: Hexylene glycol is of low acute toxicity to fish and aquatic invertebrates, including larval forms of the insect Tanytarsus. LC/EC_{50} values are all in excess of 2800 mg/l. There is no significant difference in toxicity between the fresh and brackish/salt water organisms tested.

[1] Data exist on the toxicity of hexylene glycol to sea urchin embryos based on inhibition of tritiated thymidine incorporation, indicating effects at concentrations similar to those observed with other aquatic species (Jackim & Nacci, 1984; Nacci & Jackim, 1985).

Table 4.1.1 Summary of acute toxicity values for fish and invertebrates (key studies emboldened)

Species	Common name	96 hr LC_{50} mg/l	Water type	Reli-ability	Primary reference
FISH					
Pimephales promelas	**Fathead minnow**	**8690**	**Fresh**	**2**	**Thurston et al, 1975**
Pimephales promelas	**Fathead minnow**	**10700**	**Fresh**	**2**	**Brooke et al, 1984**
Oncorhynchus mykiss	**Rainbow trout**	**9450**	**Fresh**	**2**	**Thurston et al, 1975**
Lepomis macrochirus	Bluegill sunfish	**12800**	**Fresh**	**2**	**Thurston et al, 1975**
Lepomis macrochirus	Bluegill sunfish	>10000	Fresh	4	Dawson et al, 1975
Carassius auratus	Goldfish	>5000 (24hr)	Fresh	2	Bridie et al, 1979
Carassius auratus	Goldfish	12000	Fresh	2	Thurston et al, 1975
Gambusia affinis	Mosquito fish	8510	Fresh	2	Thurston et al, 1975
Ictalurus punctatus	Channel catfish	11200	Fresh	2	Thurston et al, 1975
Alburnus alburnus	Bleak	8000	Brackish	4	Linden et al, 1979
Menidia beryllina	Tidewater silversides	10000	Estuarine /marine	4	Dawson et al, 1975
INVERTEBRATES		**48 hr EC_{50}**			
Daphnia magna	Common water flea	**3200**	**Fresh**	**2**	**Elnabarawy et al, 1986**
Daphnia pulex	Water flea	3300	Fresh	2	Elnabarawy et al, 1986
Ceriodaphnia reticulata	Water flea	2800	Fresh	2	Elnabarawy et al, 1986
Daphnia magna	Common water flea	5410	Fresh	2	Thurston et al, 1975
Artemia salina	Brine shrimp	5900 (24 hr)	Marine	4	Price et al, 1974
Nitocra spinipes	Shrimp	7600	Brackish	4	Linden et al, 1979
Oronnectes immunis	Crayfish	16500 (96 hr)	Fresh	2	Thurston et al, 1975
Tanytarsus dissimilis[#]	Tanytarsus (insect larva)	4310	Fresh	4	Thurston et al, 1975

[#] *considered to be an aquatic toxicity test – dosing was via water, sand was used as the substrate and little sorption is expected based on the low Kow.*

4.1.2 Algae

The toxicity to algae (*Selenastrum capricornutum*[2]) has been evaluated in a recent guideline study (OECD 201) carried out under GLP. No other studies are available. Hexylene glycol is of low toxicity, the 72 hour EC_{10} and EC_{50} (based on both growth rate and biomass) being >429 mg/l, the highest concentration tested (Thiebaud & Chedaille, 1999). The highest concentration tested was not the highest achievable concentration based on solubility but is considered sufficient to demonstrate the low toxicity of hexylene glycol to algae.

Conclusions: Hexylene glycol is of low toxicity to algae, the EC_{50} for growth and biomass being >429 mg/l, the highest dose level tested.

4.1.3 Bacteria

In a 10 day study hexylene glycol was found to support growth of *Pseudomonas aeruginosa* at concentrations up to 2000 ppm. 2000 ppm and above was inhibitory.
The NOEC was 1000 mg/l (a PNEC of 100 mg/l can be derived according to EU, Technical guidance). The optimum concentration for growth was 200 ppm (Daugherty, 1980).

[2] Now known as *Pseudokirchneriella subcapitata*.

Conclusions: Hexylene glycol is of low toxicity to bacteria with a NOEC of 1000 mg/l.

4.1.4 Other

Thurston et al (1975) evaluated the toxicity of hexylene glycol to frog tadpoles (*Rana catesbiana*). In a 96 hour flow through assay the LC_{50} was 11800 mg/l confirming the low toxicity to aquatic organisms.

Conclusions: Tests on frog tadpoles confirm the low toxicity of hexylene glycol to aquatic organisms.

4.1.5 Determination of PNEC aqua

Data are available from short term tests at 3 trophic levels. Based on the lowest value obtained for aquatic organisms (algal EC_{50} >429 mg/l, highest concentration tested) and applying an assessment factor of 100 in accordance with the OECD guidance the resultant $PNEC_{aqua}$ is >4.3 mg/l. The same assessment factor would be recommended using the EU TGD as hexylene glycol has a narcotic effect, there does not appear to be any significant difference in sensitivity between species tested and no adverse effects were seen at the highest dose level tested for the critical organism (*Selenastrum capricornutum*[2]).

Using the more conservative assessment factor of 1000 often applied to acute toxicity data in the EU TGD, a PNEC of 0.43 mg/l is derived.

Conclusions: The PNECaqua is 4.3 mg/l using *Selenastrum capricornutum* as the critical organism and applying an assessment factor of 100.

4.2 Terrestrial and Sediment Effects

There are no terrestrial and sediment effects data. Based on the low aquatic toxicity and low log K_{ow} effects on terrestrial and sediment organisms would be expected to occur only at very high concentrations. PNEC values derived using equilibrium partitioning as defined in the EU TGD are 0.295 mg/kg wt for sediment and 0.0786 mg/kg wt for soil.

4.3 Other Environmental Effects

Based on the calculated log K_{ow} of 0.58 and a resulting bioconcentration factor of 3.162, hexylene glycol is not expected to bioaccumulate significantly.

4.4 Initial Assessment for the Environment

Hexylene glycol is at least inherently biodegradable and with a Log K_{ow} of <1 is not expected to bioaccumulate. Environmental monitoring data are not available but fugacity based modelling (Mackay level 1) indicates that hexylene glycol will partition to water compartments in the environment. Hexylene glycol is of low acute toxicity to aquatic organisms and based on the lowest toxicity value a $PNEC_{aqua}$ of 4.3 mg/l was derived. The substance is of low priority for further work for the environment.

[2] Now known as *Pseudokirchneriella subcapitata*.

5. CONCLUSIONS AND RECOMMENDATIONS

5.1 Conclusions

Hexylene glycol is currently of low priority for further work.

The combined market for hexylene glycol in Europe and the USA for 2000 is 15000 tonnes. The principal end uses are in industrial coatings (45%) and as a chemical intermediate (20%). Hexylene glycol occurs as a component in a large number of products for industrial and consumer use. There is a potential for occupational and consumer exposure through inhalation and skin contact. There is potential exposure to the aquatic and soil compartments and to the atmosphere arising from the use of this substance.

Hexylene glycol is a liquid of vapour pressure 0.07 hPa, is fully miscible with water and has Log Kow of 0.58 (calculated). It has a calculated half-life for photo-oxidation of 9 hours and is not susceptible to hydrolysis. There is insufficient experimental data to determine whether hexylene glycol is readily biodegradable, but it is considered at least inherently biodegradable. Fugacity modelling (Mackay Level 1) predicts that hexylene glycol will partition predominantly to the aquatic compartment (99.5%). It has a low potential for sorption to soil (predicted Log Koc <1).

Human Health

Hexylene glycol is absorbed following ingestion and partly excreted in the urine of experimental animals and man both as free hexylene glycol and in conjugated form. There are no data on other possible routes of elimination.

Hexylene glycol is of a relatively low order of acute oral and dermal toxicity with LD_{50} values in excess of 2000 mg/kg. The inhalational LC_{50} is in excess of the saturated vapour concentration. Signs of intoxication at high dose levels are indicative of depression of the central nervous system.

Recent skin and eye irritation guideline studies indicate that hexylene glycol has low potential to irritate the skin and is slightly irritating to the eye. Skin and eye effects are reversible.

Sensory irritation was self reported by human volunteers at vapour concentrations of ≥50 ppm (this is near the calculated maximum attainable concentration of 66 ppm). This was confined to "slight" eye irritation at 50 ppm with nasal irritation and respiratory "discomfort" being observed at 100 and 1000 ppm.

Hexylene glycol is not a skin sensitiser in guinea pigs when tested using the Buehler test or in human volunteers using a maximisation assay. Occasional positive responses have been observed in some workers diagnosed with occupational dermatitis probably due to a cross reaction.

Hexylene glycol does not induce gene mutations in bacterial strains, mitotic gene conversion in yeast or chromosome aberrations in CHO cell *in vitro*.

No standard fertility studies are available. No effects on the gonads were observed in a good quality 90-day oral gavage study in rats which were administered hexylene glycol at doses up to 450 mg/kg/day by oral gavage. Therefore no additional studies are required under the SIDS programme regarding fertility.

Repeated exposure by oral gavage to 50, 150 or 450 mg/kg/day for 90 days resulted in hepatocellular hypertrophy and increased liver weight, male rat specific nephropathy and inflammatory changes in the forestomach and to a lesser extent the glandular stomach.
The liver changes were considered an adaptive response to increased metabolic demand, while the changes in the stomach were considered attributable to local irritation induced by the gavage procedure. The systemic NOAEL for this guideline study was therefore considered to be 450 mg/kg/day with and a no effect level for local irritation to the stomach and forestomach is considered to be 50 mg/kg/day.

In a good quality developmental toxicity study the NOAEL for maternal toxicity, was 300 mg/kg based on slightly reduced weight gain at the top dose level of 1000 mg/kg. The dose level of 300 mg/kg is also the NOAEL for foetotoxicity based on slight delayed ossification effect and a slight decrease (not statistically significant) in foetal body weight (LOAEL = 1000 mg/kg). There was no evidence of teratogenicity.

Environment

Hexylene glycol is of low acute toxicity to aquatic organisms, the lowest LC/EC_{50} is a 72h EC_{50} of >429 mg/l for the algae *Selenastrum capricornutum*[2]. No long-term toxicity data is available. There are no sediment or terrestrial effects data, but PNEC values have been derived for the sediment and terrestrial compartments using the equilibrium partitioning method as defined in the EU guidance: 0.295 mg/kg wt for sediment and 0.0786 mg/kg wt for soil. Hexylene glycol is at least inherently biodegradable and has low potential for bioaccumulation, based on a predicted BCF of 3.

5.2 Recommendations

No further testing is required.

5.3 Search criteria

Physical-chemical properties are obtained from standard reference works such as Kirk-Othmer, Hawleys Condensed Chemical Dictionary, Sax, Riddick et al, also some calculated values are given obtained mostly using Syracuse prediciton software.

The following data bases were searched under the CAS number 107-41-5 in December 2000:
STN easy on line; Poltox CD-ROMs 1966-2000; EPA Ecotoxicology Database ECOTOX; RTECS HSDB

Additionally Toxline was searched in December 2000 using the name hexylene glycol. No relevant references were identified using the CAS numbers for the individual enantiomers R(-) form 99210-90-9 & S(+) form 99210-91-0.

[2] Now known as *Pseudokirchneriella subcapitata*.

6. REFERENCES

American Conference of Governmental Industrial Hygienists (ACGIH) Documentation of Threshold Limit Values.

Alomar, A. et al (1985). Occupational dermatoses from cutting oils. Contact Dermatitis 12:129-138.

Anderson, H.H. and McOmie, W.A. (1946). Hexylene glycol. Report UC 86, University of California Medical School

Blok, J. et al (1985). Harmonisation of ready biodegradability tests. Chemosphere 14(1/12):1805-1820

Bridie A.L., Wolff, C.J.M. and Winter, M, 1979. The acute toxicity of some petrochemicals to goldfish. Water Research, 13(7: 623-626.

British Industrial Biological Research Association (BIBRA) Toxicity profile Hexylene glycol. 1991 Reporting unpublished data from the Mellon Institute (Union Carbide)

Brooke, L.T., Call, D.J., Geiger, D.L. and Northcott,C.E. (Editors) 1984. Acute toxicities of organic chemicals to fathead minnows (Pimephales promelas), Vol.1. Center for lake Superior Environmental Studies, University of Wisconsin-Superior: p181.

Brooks, T.M. et al., (1988) The genetic toxicology of some hydrocarbon and oxygenated solvents. Mutagenesis, 3(3): 227-232

Brown B, Schaffarzick RW and Dreisbach RH. (1955). Anticonvulsant properties of certain secondary and tertiary alcohols. J. Pharmacol. Exp. Ther. 115:230-239.

Cavender, F.L.; Sowinski, E.J. (1994) Glycol. Chapter 49 in Patty's Industrial Hygiene and Toxicology, 4th edition Editors Clayton, G.D. & F.E., Wiley-Interscience.

CIR Expert Panel. (1985). Final report on the safety assessment of butylene glycol, hexylene glycol, ethyoxydiglycol and dipropylene glycol. J Am Coll Toxicol, 4:223-248.

Clode SA. (1997). Hexylene glycol: 14 day Oral (gavage administration) toxicity study in the rat. Covance Laboratories, Ltd, North Yorkshire England, Report No. CHE121/28. Study sponsored by Shell Chemicals Europe Ltd (Toxicology Report No. 97.1195).

Clode SA. (1997). Hexylene glycol: Oral (gavage) study of embryo-foetal development in the rat. Covance Laboratories, Ltd, North Yorkshire England report No. 121/27. Study sponsored by Shell Chemicals Europe Ltd (Toxicology Report No. 97.1195).

Coombs, A.D. (1978) Toxicity of solvents: Eye irritation study on hexylene glycol. Shell Research Ltd, Sittingbourne Research Centre, Report No. TLGR.0035.78

Daston, G. Letterdated June 23rd 1999 from G. Daston, Procter and Gamble Co. to M.Banton, Shell Chemical Co.

Dawson, G.W., Jennings, A.L., Drozdowski, D. and Didier, (1975/77). The acute toxicity of 47 industrial chemicals to fresh and saltwater fishes. J. Hazardous Materials, 1(4):303-318

Daugherty, L.C., 1980. The growth of Pseudomonas aeruginosa on glycols of industrial importance. Lubrication Engin., 36, 718-723.

Diechmann WB and Dierker M. (1946). The spectrophotometric estimation of hexuronates (expressed as glucuronic acid) in plasma or serum. J. Biol. Chem. 163:753

Denny, K.H (1996) Developmental toxicity study in rats. Test article: D1748.01 (hexylene glycol). Report from MPI Research formerly International Research and Development Corporation, Mattawan, MI, USA. Study no. 191-1606 to The Procter & Gamble Co (sponsors).

Elnabarawy, M.T., Welter, A.N. and Robideau, R.R., 1986. Relative sensitivity of three daphnid species to selected organic and inorganic chemicals. Environ. Toxicol. Chem., 5(4), 393/398.

Epstein WL. (1976). Report to RIFM, August 16, 1976. Quoted by Opdyke, 1978

EU TGD Technical Guidance Document in support of Commission directive 93/67/EEC on risk assessment for new notified substances and Commission regulation (EC) No. 1488/94 on risk assessment for existing substances. 1996

Fabreguettes, C. (1999b) Hexylene glycol: 13-week study by oral administration (gavage) to rats followed by a four-week treatment-free period. Report from CIT study number 15837 TSR (and addendum) to Elf Atochem SA, France, Sponsor.

Fabreguettes, C. (1999a) Hexylene glycol: Two-week range-finding toxicity study by oral administration (gavage) in rats. Report from CIT study number 15836 TSR to Elf Atochem SA, France, Sponsor.

Gardner, J.R. (1996a) Hexylene glycol: Acute oral toxicity study in the rat. Report No. 1439/15-1032 from Corning Hazelton (Europe) to Shell Chemicals Europe Ltd October 1996 Shell Toxicology Report No. 96.1248

Gardner, J.R. (1996b) Hexylene glycol: Acute dermal toxicity study in the rat. Report No. 1439/16-1032 from Corning Hazelton (Europe) to Shell Chemicals Europe Ltd, October 1996 Shell Toxicology Report No. 96.1249

Gardner, J.R. (1996c) Hexylene glycol eye irritation study in the rabbit. Report no. 1439/17-1032 from Corning Hazelton to Shell Chemicals Europe Ltd, Toxicology report No. 96.1250

Gardner, J.R. (1996d) Hexylene glycol: Skin sensitisation study in the guinea pig (Buehler method) Report no. 1439/018-1032 from Corning Hazelton to Shell Chemicals Europe Ltd, Toxicology report No. 96.1251

German MAK Commission (1997) Hexylene glycol

Gessner P.K.; Parke, D.V.; Williams, R.T. (1960) Studies in detoxification 80. The metabolism of glycols. . Biochem. J. 74:1-5

Guillot JP et al. (1982) Safety evaluation of some humectants and moisturizers used in cosmetic formulations. Int. J. Cos. Sc. 4:67-80.

Hine CH, Anderson HH and Kodama, JK (1955). Sensory thresholds with certain Shell organic solvents. Report UC 247, University of California Medical School.

Howard, P.H. (Editor) (1993) Handbook of environmental fate and exposure data for organic chemicals. Lewis publishers

Kinnunen T and Hannuksela M. (1989). Skin reactions to hexylene glycol. Contact Dermatitis, 21:154-158.

Jackim, E.; Nacci, D. (1984) A rapid aquatic assay utilizing labelled thymidine incorporation in sea urchin embryos. Env. Toxicol. Chem. 3:631-636

Jacobson E. (1958). The excretion of hexylene glycol (2-methyl-2,4-pentane diol) in man. Acta Pharmacol et Toxicol, 14:207-213.

Larsen V. (1958). The toxicity of 2-methyl-pentan-2,4-diol (Hexylene glycol) by chronic oral administration to rats and mice. Acta Pharmacol et Toxicol, 14:341-349.

Linden, E., Bengtsson, B.E., Svanberg, O. and Sundstrom, G., 1979. The acute toxicity of 78 chemicals and pesticides formulations against two brackish water organisms, Chemosphere, 8(11/12), 843/851

Meyer, A.L; Brooks, T.M; Wiggins, D.E. (1985) Genotoxicity studies with hexylene glycol. Shell Research Ltd, Sittingbourne Research Centre Report No. SBGR.85.253.

Nacci, D.E.; Jackim, E. (1985) Rapid aquatic toxicity assay using incorporation of tritiated-thymidine into sea urchin Arbacia puntulata embryo: Evaluation of toxicant exposure procedures. Aquatic Toxicology and Hazard Assessment 8th Symposium ASTM STP 891, Bahner, R.C. & Hansen, D.J. Eds. ASTM pp382-394

Opdyke, D. (1978) Fragance Raw Material Monographs : Hexylene Glycol. Food & Cosmet. Tox., 16(1):777-778.

Parcell, B.I. (1995) Hexylene glycol: Skin irritation in the rabbit. Report No. SLL 302/950034/SE from Huntingdon Research Centre to SIPM B.V.

Price, K.S., Waggy, G.T. and Conway, R.A., (1974). Brine shrimp bioassay and seawater BOD of petrochemicals. J Water Pollut. Control Fed., 46(1) 63-77.

R.T.E.C.S. on line database 2001

SCC (Shell Chemical Corporation). (1958). Industrial Hygiene Bulletin. Hexylene Glycol, SC:57-101 and SC:57-102.

Satala, B.S. (1995) Range-finding developmental toxicity study in rats. Test article: D1748.01 (hexylene glycol). Report from International Research and Development Corporation, Mattawan, MI, USA. Study no. 191-1605 to the Procter & Gamble Co (sponsors).

Silverman L, Schulte HF, and First MW. (1946). Further studies on sensory response to certain industrial solvent vapors. J Ind Hyg Toxicol. 28:262-266.

Smyth, H.F.; Carpenter, C.P. (1948) Further experience with the range-finding test in the industrial laboratory. J. Ind. Hyg. Tox. 30(1): 63-68

Thiebaud, H.; Chedaille, D. 1999 Hexylene glycol inhibition de la croissance des algues. Elf Atochem S.A. Centre d'application de Levallois Study no. 4116/97/A

Thurston, R.V., Gilfoil, T.A., Meyn, E.L., Zajdel, R.K., Aoki, T.I. and Veith, G.D., 1985. Comparative toxicity of ten organic chemicals to common aquatic species. Water Research, 19(9), 1145/1155.

Union Carbide (1949) The acute and subacute toxicity of methyl pentane diol. Mellon Institute of Industrial Research, Special report 12-54,

Union Carbide Corporation (1976) Hexylene Glycol 9-day repeated aerosol inhalation by rats. Carnegie-Mellon Institute of Research, Special Report 39-42, April 7, 1976

Woodard, G.; Johnson, V.D.; Nelson, A.A. (1945) Acute toxicity of 2-methyl-2,4-pentanediol. Fedn Proc Fedn Am Soc Exp Biol 4:142-143.

I U C L I D Data Set

Existing Chemical	:	ID: 107-41-5
CAS No.	:	107-41-5
EINECS Name	:	2-methylpentane-2,4-diol
EINECS No.	:	203-489-0
TSCA Name	:	2,4-Pentanediol, 2-methyl-
Molecular Formula	:	C6H14O2

Producer Related Part

Company	:	Shell Chemicals Ltd.
Creation date	:	24.01.2001

Substance Related Part

Company	:	Shell Chemicals Ltd.
Creation date	:	24.01.2001
Memo	:	Revised dataset with robust summaries prepared on behalf of the Lesser Ketones Manufacturing Association for their HPVC commitment under the ICCA program.
Printing date	:	30.10.2001
Revision date	:	
Date of last Update	:	30.10.2001
Number of Pages	:	315
Chapter (profile)	:	
Reliability (profile)	:	
Flags (profile)	:	

1.0.1 OECD and Company Information

Type	:	lead organisation
Name	:	Lesser Ketones Manufacturing Association
Partner	:	Atofina Chemicals Inc Dow Chemical Co ExxonMobil Chemical Co Shell Chemical Co
Date	:	
Street	:	1250 Connecticut Avenue, N.W., Suite 700
Town	:	DC- 20036 Washington, DC
Country	:	United States
Phone	:	+1 (202) 637-9040
Telefax	:	+1 (202) 637-9178
Telex	:	
Cedex	:	
Remark	:	This revised dataset including robust summaries for key SIDS endpoints, was prepared in 2001 by Shell Chemicals Ltd on behalf of the Lesser Ketones Manufacturing Association as part of their HPVC commitment under the ICCA program. The dataset was based initially on the EC version from the Year 2000 edition CD-ROM. This was extensively revised and rewritten.
Source	:	Shell Chemicals Ltd
05.07.2001		

Type	:	sponsor country
Name	:	The Environment Agency, United Kingdom
Partner	:	
Date	:	
Street	:	Evenlode House, Howbery Park
Town	:	OX10 8BD Wallingford
Country	:	United Kingdom
Phone	:	+44 (0) 1491 828 559
Telefax	:	+44 (0) 1491 828 556
Telex	:	
Cedex	:	
Source	:	Shell Chemicals Ltd
05.07.2001		

1.0.2 Location of Production Site

Reliability	:	(1) valid without restriction
Remark	:	There are production sites in the USA, The Netherlands and France. We do not have information on production sites in other areas.
10.09.2001		

1.0.3 Identity of Recipients

1.1 General Substance Information

Substance type	:	organic
Physical status	:	liquid
Purity	:	> 99 % w/w

Remark : The product contains >99% w/w 2-methyl 2,4-pentanediol, which exists in enantiomeric form. Based on chemical principles equal amounts of enantiomeric products are formed when two achiral reagents react to give a chiral product.
2-methyl 2,4-pentanediol is formed from hydrogen and diacetone alcohol, both achiral reagents. Therefore 2-methyl 2,4-pentanediol may be described as a racemic mixture containing equal amounts of two enantiomers.

We can assume from applying these chemical principles and based on the above mentioned production method, that where 2-methyl 2,4-pentanediol is tested the 2-methyl 2,4-pentanediol content of the product will be a 50:50 racemic mixture as described above. What may differ is the level of impurities. For many older studies particularly from published sources detailed information on impurities may not be available.

Purity will obviously differ between producers and time of production. Recent toxicological testing has been carried out on products containing >99.5% w/w enantiomeric 2-methyl 2,4-pentanediol as described above.

Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chimie Rueil Mailmaison

22.08.2001

1.1.0 Details on template

1.1.1 Spectra

1.2 Synonyms

HEXYLENE GLYCOL
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
05.07.2001

(+-)-2-methyl-2,4-pentanediol
Source : STN Easy Search Result 08/09/2000
21.08.2001

2-methylpentane-2,4-diol
Source : STN Easy Search Result 08/09/2000
21.08.2001

4-methyl-2,4-pentanediol
Source : STN Easy Search Result 08/09/2000
21.08.2001

2,4-dihydroxy-2-methylpentane
Source : STN Easy Search Result 08/09/2000
21.08.2001

1,1,3-trimethyltrimethylenediol
Source : DOSE October 2000
21.08.2001

alpha,alpha,alpha'-trimethyltrimethylene glycol
Source : STN Easy Search Result 08/09/2000
21.08.2001

Diolane
Source : STN Easy Search Result 08/09/2000
21.08.2001

Isol
Source : RTECS Search Result 14/08/2001
21.08.2001

Pinakon
Source : RTECS Search Result 14/08/2001
21.08.2001

1,1,3-trimethylene glycol
Source : STN Easy Search Result 08/09/2000
10.09.2001

1.3 Impurities

CAS-No : 7732-18-5
EINECS-No : 231-791-2
EINECS-Name : Water
Contents : < .1 % w/w

Reliability : (1) valid without restriction
Source : Shell Chimie Rueil Mailmaison
21.08.2001

CAS-No : 123-42-2
EINECS-No : 204-626-7
EINECS-Name : 4-hydroxy-4-methylpentan-2-one
Contents : % w/w

Reliability : (1) valid without restriction

Remark : This impurity and the others listed below are typical of the impurities which may occur in current production of hexylene glycol. They are present at very low levels comprising a maximum total of <1% and commonly less than this. Higher levels of impurities may have been present historically.
Source : Shell Chemicals Ltd
31.08.2001

CAS-No : 108-10-1
EINECS-No : 203-550-1
EINECS-Name : 4-methylpentan-2-one
Contents : % w/w

Reliability : (1) valid without restriction
Source : Shell Chemicals Ltd
31.08.2001

CAS-No : 108-11-2
EINECS-No : 203-551-7
EINECS-Name : 4-methylpentan-2-ol
Contents : % w/w

Reliability : (1) valid without restriction
Source : Shell Chemicals Ltd
31.08.2001

CAS-No : 67-63-0
EINECS-No : 200-661-7
EINECS-Name : propan-2-ol
Contents : % w/w

Reliability : (1) valid without restriction
Source : Shell Chemicals Ltd
31.08.2001

CAS-No : 67-64-1
EINECS-No : 200-662-2
EINECS-Name : acetone
Contents : % w/w

Reliability : (1) valid without restriction
Source : Shell Chemicals Ltd
31.08.2001

1.4 Additives

1.5 Quantity

Production during the last 12 months :
Import during the last 12 months :
Quantity : 10 000 - 50 000 tonnes in
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
10.02.2000

1.6.1 Labelling

Labelling : as in Directive 67/548/EEC
Symbols : Xi
Nota :
Specific limits : yes
R-Phrases : (36/38) Irritating to eyes and skin
S-Phrases : (2) Keep out of reach of children

Remark : Annex 1 as last amended by Directive 2000/32/EC (26th ATP)

Specific limits C>=10% requires classification as for undiluted product. Note 8 Substance added by Directive 79/370/EEC, Article 1.4 and Annex.
(Source Ariel on line)
Source : Shell Chemicals Ltd
12.07.2001

1.6.2 Classification

Classification : as in Directive 67/548/EEC
Class of danger : irritating
R-Phrases : (36/38) Irritating to eyes and skin
Source : Shell Chimie Rueil Mailmaison

12.07.2001

Classification : as in Directive 67/548/EEC
Class of danger : irritating
R-Phrases : (36/38) Irritating to eyes and skin
Source : EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
10.02.2000

1.7 Use Pattern

Type : type
Category : Non dispersive use
Source : Shell Chimie Rueil Mailmaison
29.06.2001

Type : type
Category : Use resulting in inclusion into or onto matrix
Source : EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
29.06.2001

Type : type
Category : Wide dispersive use
Source : Shell Chimie Rueil Mailmaison
29.06.2001

Type : industrial
Category : Agricultural industry
Source : Lesser Ketones Manufacturing Association
04.07.2001

Type : industrial
Category : Chemical industry: used in synthesis
Source : Shell Chimie Rueil Mailmaison
22.02.2001

Type : industrial
Category : Leather processing industry
Source : Lesser Ketones Manufacturing Association
04.07.2001

Type : industrial
Category : Paints, lacquers and varnishes industry
Source : Shell Chimie Rueil Mailmaison
23.02.1994

Type : industrial
Category : Textile processing industry
Source : Lesser Ketones Manufacturing Association
04.07.2001

Type : use
Category : Anti-freezing agents
Source : Shell Chemicals Ltd
29.06.2001

Type : use
Category : Cleaning/washing agents and disinfectants
Source : EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

10.02.2000

Type : use
Category : Cosmetics
Source : Shell Chemicals Ltd
26.06.2001

Type : use
Category : Dustbinding agents
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
10.02.2000

Type : use
Category : Hydraulic fluids and additives
Source : Shell Chemicals Ltd
29.06.2001

Type : use
Category : Intermediates
Source : Shell Chimie Rueil Mailmaison
29.06.2001

Type :
Category : Solvents
Source : Shell Chimie Rueil Mailmaison
04.07.2001

1.7.1 Technology Production/Use

1.8 Occupational Exposure Limit Values

Type of limit : MAC (NL)
Limit value : 125 mg/m3
Short term exposure
Limit value : 125 mg/m3
Schedule :
Frequency : times

Remark : Use local exhaust ventilation.
Hand protection : PVC, nitrile or neoprene gloves.
Eye protection : safety monogoggles.
Body protection : chemicals resistant shoes or boots.
jacket or trousers-nitrile rubber.
Source : Shell Chimie Rueil Mailmaison
29.06.2001

Type of limit : OES (UK)
Limit value : 123 mg/m3
Short term exposure
Limit value : 123 mg/m3
Schedule : 15 minute(s)
Frequency : times
Country : UK
Reference : (1)
05.07.2001

Type of limit : TLV (US)
Limit value :

Short term exposure
Limit value : 121 mg/m3
Schedule : 15 minute(s)
Frequency : times

Remark : Basis of limit is sensory irritation.
Source : Shell Chemicals Ltd
Reference : (2)
29.06.2001

Type of limit : other
Limit value :
Short term exposure
Limit value : 125 mg/m3
Schedule : 15 minute(s)
Frequency : 4 times
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
Country : France
Reference : (3)
29.06.2001

1.9 Source of Exposure

Memo : Description of likely sources of contact.

Remark : Inhalation or skin contact when loading, unloading, using the product.
In case of accidental release, product may contaminate the environment.
Source : SHELL FRANCE Rueil Malmaison
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
05.07.2001

Memo : Description of the process and likely losses to the atmosphere.

Remark : Batch closed process.
Hydrogenation of 2-Pentanone, 4-hydroxy-4-methyl-.
Purification by distillation.
One production site.
Personal protective measures: gloves, glasses and goggles.
Ambient protective measures: fumes detectors.
Losses in atmosphere: less than 0.0001% of the production (# 1000 - 5000 tons per year)
Losses in water very low.
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
05.07.2001

1.10.1 Recommendations/Precautionary Measures

1.10.2 Emergency Measures

1.11 Packaging

1.12 Possib. of Rendering Subst. Harmless

1.13 Statements Concerning Waste

1.14.1 Water Pollution

Classified by	:	other: assume WGK
Labelled by	:	
Class of danger	:	1 (weakly water polluting)
Remark	:	The original entry did not specify the source of classification but it appears to be the German WGK. Since this entry was made the WGK have changed their classification scheme. Under the new scheme hexylene glycol is classifiied as 1 - Low hazard to waters.
Source	:	Shell Chemicals Ltd

05.07.2001

1.14.2 Major Accident Hazards

1.14.3 Air Pollution

1.15 Additional Remarks

Remark	:	DISPOSAL : Recover or recycle if possible. Otherwise : incineration. Use only in a well ventilated place. Earth all equipment. Do not use compressed air or oxygen for filling, discharging or handling the product. Avoid sparks. Remove ignition sources. Avoid naked flames. Do not smoke. Transport Information Not dangerous for convoyance under UN, IMO and ICAO codes. Rail/Road (RID/ADR) Class : 3 Item : 32 c) Symbol : None Proper shipping name : Hexylene glycol Kemler Plate : 30/1987
Source	:	Shell Chimie Rueil Mailmaison

26.05.1994

Remark	:	DISPOSAL : Recover or recycle if possible. Otherwise : incineration. Use only in a well ventilated place. Earth all equipment. Do not use compressed air or oxygen for filling, discharging or handling the product. Avoid sparks. Remove ignition sources. Avoid naked flames. Do not smoke. Transport Information

Not dangerous for convoyance under UN, IMO and ICAO codes.

Rail/Road (RID/ADR)
Class : 3
Item : 32 c)
Symbol : None
Proper shipping name : Hexylene glycol
Kemler Plate : 30/1987

Source : SHELL FRANCE Rueil Malmaison
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

26.05.1994

1.16 Last Literature Search

Type of Search : Internal and External
Chapters covered : 2
Date of search : 30.06.2001

Reliability : (1) valid without restriction

Remark : Physical-chemical properties are obtained from standard reference works such as Kirk-Othmer, Hawleys Condensed Chemical Dictionary, Sax, Riddick et al, also some calculated values are given obtained mostly using Syracuse prediction software. These values published in the open literature for the molecule hexylene glycol are considered representative of the product produced by the different consortium manufacturers, which are currently >99% hexylene glycol (minimum value) actually >99.5% or higher.

Source : Shell Chemicals Ltd
04.09.2001

Type of Search : Internal and External
Chapters covered : 3, 4, 5
Date of search : 21.12.2000

Reliability : (1) valid without restriction

Remark : The following data bases were searched under the Cas number 107-41-5 in December 2000.

STN easy on line
Poltox CD-ROMs 1966-2000
EPA Ecotoxicology Database ECOTOX
RTECS
HSDB

Additionally Toxline was searched in December 2000 using the name hexylene glycol.

No relevant references were identified using the Cas numbers for the individual enantiomers R(-) form 99210-90-9 & S(+) form 99210-91-0.

The Cas No 99113-75-4 is obsolete and has been replaced by Cas no 107-41-5

Source : Shell Chemicals Ltd
31.08.2001

1.17 Reviews

Memo : Cosmetic Ingredients Review, 1985
Source : Shell Chemicals Ltd
Reference : (4)
11.07.2001

Memo : Patty's Industrial Hygiene and Toxicology Vol IIC 3rd edition 1981 and Vol IIF 4th edition 1994
Reference : (5) (6)
11.07.2001

Memo : German MAK Commission, 1997
11.07.2001

Memo : BIBRA Toxicity Profile Hexylene glycol, 1991
Reference : (7)
11.07.2001

Memo : Fragrance Raw Materials Monograph Hexylene Glycol
Reference : (8)
11.07.2001

1.18 Listings e.g. Chemical Inventories

2.1 Melting Point

Value	:	= -50 ° C
Sublimation	:	
Method	:	other: No data
Year	:	
GLP	:	no data
Test substance	:	
Reliability	:	(4) not assignable
Remark	:	Reported as freezing point value -50C (glass)
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reference	:	(9)

21.08.2001

2.2 Boiling Point

Value	:	= 197.5 ° C at 1013 hPa
Decomposition	:	
Method	:	other: No data
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable
Remark	:	This value was chosen as representative as we have information on the vapour pressure at which it was determined.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reference	:	(10)

12.09.2001

Value	:	= 197.1 ° C at
Decomposition	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable
Source	:	Shell Chemicals Ltd
Reference	:	(11)

12.09.2001

Value	:	= 195 - 200 ° C at
Decomposition	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	ASTM D1078
Reliability	:	(4) not assignable

Source : Shell Chemicals Ltd
Reference : (12)
12.09.2001

Value : = 198.3 ° C at
Decomposition :
Method :
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Source : Shell Chemicals Ltd
Reference : (13)
12.09.2001

2.3 Density

Type : density
Value : = .92 - .923 g/cm3 at 20° C

Method : ASTM D -4052

Reliability : (4) not assignable
Source : Shell Chemicals Ltd
Reference : (12)
06.02.2001

Type : density
Value : = .923 g/cm3 at 20° C
Method : other: No data
Year :
GLP : no data
Test substance :

Reliability : (4) not assignable
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reference : (10)
06.02.2001

Type : density
Value : = .9234 g/cm3 at 20° C

Reliability : (4) not assignable
Source : Shell Chemicals Ltd
Reference : (11)
06.02.2001

Type : density
Value : = 5.17 kg/m3 at 20° C
Method : other: No data
Year :
GLP : no data
Test substance :

Reliability : (4) not assignable

Remark : Density of vapour
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reference : (10)
06.02.2001

Type : density
Value : = 921 kg/m3 at 20° C
Method :
Year :
GLP : no data
Test substance :

Reliability : (4) not assignable
Source : Shell Chemicals Ltd
Reference : (9) (14)
12.07.2001

Type : density
Value : = .9216 g/cm3 at ° C

Reliability : (4) not assignable
Source : Shell Chemicals Ltd
Reference : (13)
06.02.2001

2.3.1 Granulometry

2.4 Vapour Pressure

Value : = .07 hPa at ° C
Decomposition :
Method
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable

Remark : This value has been used for environmental modelling purposes and is widely reported in secondary references. We have also looked at the related compounds hexane-1,6-diol and 3-methyl-1,5-pentane diol and compared the calculated (Epiwin) vapour pressure data (in hPa) with the values given in the respective SIARs as follows:

hexane-1,6-diol calc vp 0.0077 SIAR value <0.01
3-methyl-1,5-pentane diol calc vp 0.016; SIAR value 0.0072
2-methyl-2-4-pentane diol calc vp 0.078; SIAR value 0.07

The exact value chosen for vapour pressure will have a negligible effect on volatilisation due to the very high water solubility (miscible). Henry's Constant, assuming the maximum solubility permitted in EUSES of 100,00 mg/l and vp of 7 Pa is 8.27X10-3 Pa.m3/mol. If the vp is <0.07hPa (read across to hexane-1,6-diol and 3-methyl-1,5-pentane diol) this will result in an even lower Henry's constant. Fugacity modelling and Sewage Treatment Plant fate have been calculated using a vapour pressure of 0.07 hPa and the results show minor distribution to air (0.17%).
Source : Atochem Paris la Defense

EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reference : (10)
12.09.2001

Value : = .067 hPa at 20° C
Decomposition :
Method
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Source : Shell Chemicals Ltd
Reference : (11)
21.08.2001

Value : = .0777 hPa at 25° C
Decomposition :
Method other (calculated)
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Method : Syracuse using mean VP of Antoine & Graine methods

Reliability : (2) valid with restrictions
Source : Shell Chemicals Ltd
12.09.2001

2.5 Partition Coefficient

Log pow : = .58 at ° C
Method other (calculated)
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable

Remark : This value is used for environmental monitoring purposes because it was calculated using a respected prediction method for Log Kow.
Reference : (15)
12.09.2001

Log pow : < -.14 at ° C
Method other (calculated)
Year :
GLP : no data
Test substance :

Reliability : (4) not assignable

Remark : Calculated from partition in ethyl ether using correlation equation for acidic solutes.
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reference : (16)
12.09.2001

2.6.1 Water Solubility

Value	:	at 20 ° C
Qualitative	:	miscible
Pka	:	at 25 ° C
PH	:	at and ° C
Method	:	other: No data
Year	:	
GLP	:	
Test substance	:	
Reliability	:	(4) not assignable
Remark	:	For environmental modelling purposes a solubility value of 100,000 mg/l has been used which is the maximum value allowed in the EUSES model.
Source	:	Shell Chemicals Ltd
Reference	:	(12)

10.09.2001

2.6.2 Surface Tension

Test type	:	other: (no data)
Value	:	= 33.1 mN/m at 20 ° C
Concentration	:	
Reliability	:	(4) not assignable
Source	:	Shell Chemicals Ltd
Reference	:	(14)

12.07.2001

2.7 Flash Point

Value	:	= 93 ° C
Type	:	closed cup
Method	:	other: ASTM D 3828 - IP 303 - ISO DIN 3679
Year	:	
GLP	:	no data
Test substance	:	
Reliability	:	(4) not assignable
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reference	:	(10)

06.02.2001

Value	:	= 93 ° C
Type	:	closed cup
Method	:	other: ASTM D -93
Year	:	
GLP	:	
Test substance	:	
Reliability	:	(4) not assignable
Source	:	Shell Chemicals Ltd
Reference	:	(12)

06.02.2001

Value : = 93 ° C
Type : open cup
Method : other: No data
Year :
GLP :
Test substance :

Reliability : (4) not assignable
Source : Shell Chemicals Ltd
Reference : (13)
06.02.2001

Value : = 96.1 ° C
Type : open cup

Reliability : (4) not assignable
Source : Shell Chemicals Ltd
Reference : (11)
06.02.2001

2.8 Auto Flammability

Value : = 306 ° C at 1013 hPa
Method : other: No data
Year :
GLP : no data
Test substance :

Reliability : (4) not assignable
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
Reference : (10)
06.02.2001

2.9 Flammability

2.10 Explosive Properties

Method : other: No data
Year :
GLP : no data
Test substance :

Reliability : (4) not assignable

Remark : Explosive limits of vapours in air : more than 1.27 % vol.
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
Reference : (10)
06.02.2001

Method : other
Year :
GLP :

Test substance :

Reliability : (4) not assignable

Remark : Explosive limits of vapours in air : lower limit 1% v/v, upper limit 9.9% v/v
Source : Shell Chemicals Ltd
Reference : (12)
06.02.2001

2.11 Oxidizing Properties

2.12 Additional Remarks

Memo : Viscosity

Reliability : (4) not assignable

Remark : Viscosity : 36 mPa.s at 20°C.; Cubic dilatation coefficient : 0.00072 per °C.
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
06.02.2001

Memo : Viscosity

Reliability : (4) not assignable

Remark : Dynamic viscosity 38.9 mPa.s at 20 degrees C (ASTM D-455)
Source : Shell Chemicals Ltd
Reference : (12)
06.02.2001

3.1.1 Photodegradation

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	1500000 molecule/cm3
Rate constant	:	cm3/(molecule*sec)
Degradation	:	% after
Deg. Product	:	
Method	:	other (calculated)
Year	:	
GLP	:	
Test substance	:	
Remark	:	Estimated using Syracuse Aopwin V1.85. Overall OH rate constant = 14.1981 E-12 cm3/molecule-sec Half-life 9.040 hours
Source	:	Shell Chemicals Ltd

26.10.2001

3.1.2 Stability in water

Type	:	abiotic
t1/2 pH4	:	at degree C
t1/2 pH7	:	at degree C
t1/2 pH9	:	at degree C
Reliability	:	(4) not assignable
Remark	:	Alcohols and ethers do not absorb light in the environmentally significant range (>290 nm). Therefore hexylene glycol should not undergo direct photolysis in the environment. Glycols have no hydrolysable groups and are therefore not susceptible to hydrolysis.
Source	:	Shell Chemicals Ltd
Reference	:	(17)

03.09.2001

3.1.3 Stability in soil

Remark	:	No data
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

26.04.1994

3.2 Monitoring data

Remark	:	No data
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

26.04.1994

3.3.1 Transport between environmental compartments

Remark : No data
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)

26.04.1994

3.3.2 Distribution

Media : air - biota - sediment(s) - soil - water
Method : Calculation according Mackay, Level I
Year :
Remark : Input data used:

Molecular weight = 118.18
Data temperature = 20C
Log Kow = 0.58 calculated value
Water solubility = 100,000 mg/l(hexylene glycol is miscible this value was selected as the highest permissible in the EUSES model)
Henry's Law Constant = 8.27e-3 Pa/m3/mol (calculated assuming a vp of 0.07hPa and water solubility of 100,000 mg/l)
Vapour pressure = 0.07 hPa (see below)
Melting point = 10C Note: this value was arbitarily selected to indicate that hexylene glycol is a liquid at room temperature.

The % environmental distribution calculated from the above parameters using the MacKay level 1 model is as follows:

Air	0.169
Water	99.5
Soil	0.335
Sediment	0.0074
Fish	1.89E-05

Comment on value used for vapour pressure. This value has been used for environmental modelling purposes and is widely reported in secondary references. We have also looked at the related compounds hexane-1,6-diol and 3-methyl-1,5-pentane diol and compared the calculated (Epiwin) vapour pressure data (in hPa) with the values given in the respective SIARs as follows:

hexane-1,6-diol calc vp 0.0077 SIAR value <0.01
3-methyl-1,5-pentane diol calc vp 0.016; SIAR value 0.0072
2-methyl-2-4-pentane diol calc vp 0.078; SIAR value 0.07

The exact value chosen for vapour pressure will have a negligible effect on volatilisation due to the very high water solubility (miscible). Henry's Constant, assuming the maximum solubility permitted in the EUSES model of 100,00 mg/l and vp of 7 Pa is 8.27X10-3 Pa.m3/mol. If the vp is <0.07hPa (read across to hexane-1,6-diol and 3-methyl-1,5-pentane diol) this will result in an even lower Henry's constant. Fugacity modelling and Sewage Treatment Plant fate have been calculated using a vapour pressure of 0.07 hPa and the results show minor distribution to air (0.17%).

The calculated value for Log Kow has been used, this compares with calculated values for hexane-1,6-diol of -.92 and .198 and a measured value of 0. For 3-methyl-1,5-pentane diol the measured log Kow is -0.03. We have therefore taken the worst case option for the environmental modelling.

Source : Shell Chemicals Ltd

3.4 Mode of degradation in actual use

3.5 Biodegradation

Type	:	aerobic
Inoculum	:	
Contact time	:	
Degradation	:	% after
Result	:	inherently biodegradable
Deg. Product	:	
Method	:	other: various methods used in OECD round-robin test
Year	:	1979
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Test substance	:	Test substance reported as 4-methyl-2,4-pentanediol, no other details available.
Result	:	Hexylene glycol has been subjected to biodegradation testing in an attempt to harmonise experimental procedures for various tests for biodegradability as part of the 2nd OECD round-robin test 1979-1980. % Tests showing pass for ready biodegradability (n = number of replicates) Modified Zahn Wellens 100% DOC removal (n=5) Sturm non-adapted 60% CO2 removal/TOC (n=5) MITI II 50% BOD/ThOD (n=8) MITI 1 14% BOD/ThOD (n=7) Modified OECD 69% DOC removal (n=16) Closed Bottle 17% ThOD (n=6) It is not clear whether those 'pass' results from tests for ready biodegradability were obtained within the 10 day window and it is therefore not possible to deduce from the data available that hexylene glycol is readily biodegradable. However hexylene glycol passed both tests for inherent biodegradability (Zahn Wellens and MITI 11).
Reliability	:	(2) valid with restrictions Reliability level 2 has been assigned. Although full experimental details were not given this round robin test was designed to evaluate OECD test methods and an assumption has been made that the studies were conducted to acceptable standards. These data provide good supporting evidence for the inherent biodegradability of hexylene glycol.
Flag	:	Critical study for SIDS endpoint
Reference	:	(18)
10.09.2001		
Type	:	aerobic
Inoculum	:	activated sludge
Concentration	:	100mg/l related to Test substance related to
Contact time	:	28 day
Degradation	:	= 34 - 76 % after 28 day
Result	:	other: see RS
Deg. Product	:	
Method	:	OECD Guide-line 301 C "Ready Biodegradability: Modified MITI Test (I)"
Year	:	1981

GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Test condition	:	Concentration of activated sludge (as the concentration of suspended solid) 30 mg/l indicating that this is a MITI 1 test. Test volume 300 ml, temperature 25C.
Result	:	Results for each of two replicates are as follows: BOD 76% and 34% mean 55% TOC 97% and 44% mean 71% GC 100% and 47% mean 74% The validity of these test results are questionable as the difference between replicates is >20%. While the results suggest that hexylene glycol is biodegradable they do not support a conclusion of ready biodegradability
Reliability	:	(3) invalid
Reference	:	(19)
30.10.2001		
Type	:	aerobic
Inoculum	:	other: No data
Contact time	:	
Degradation	:	% after
Result	:	other: reported as degradable
Deg. Product	:	
Method	:	other: MITI test
Year	:	1980
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable
Remark	:	Test carried out using a MITI protocol but reported in summary only. No specific experimental details or results which are only reported as degradable. Insuffient experimental details to assess validity of the study. Hexylene glycol is listed in the MITI compilation of Biodegradation and Accumulation Data of Existing Chemicals based on the CSCL Japan, this may be the source of the data reported above. The MITI data are recorded in a separate record.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA) Shell Chemicals Ltd
Reference	:	(20)
12.04.2001		
Type	:	aerobic
Inoculum	:	other
Contact time	:	20 day
Degradation	:	= 90 % after 20 day
Result	:	inherently biodegradable
Deg. Product	:	
Method	:	other:
Year	:	1971
GLP	:	no
Test substance	:	
Method	:	American Public Health Association, New York, 1971 Standard methods for

the examination of water and waste water, 13th Edition

Test condition : The inoculum was an equal volume mixture of two biologically treated petrochemical effluents, settled domestic wastewater, river water from an area receiving industrial and domestic waste water and soil. Acclimation proceeded over 45-60 days.

Reliability : (4) not assignable
Insufficient experimental detail to comment on validity.

Remark : Not a standard procedure % ThOD 55% at 5 days, 85% at 10 days, 88% at 15 days.

Reference : (21)
12.04.2001

Type : aerobic
Inoculum : other: separated domestic waste water
Contact time : 20 day
Degradation : = 63 % after 20 day
Result : readily biodegradable
Deg. Product :
Method : other:
Year : 1971
GLP : no
Test substance : no data

Method : American Public Health Association, New York, 1971 Standard methods for the examination of water and waste water, 13th Edition

Reliability : (4) not assignable
Insufficient experimental detail to comment on validity.

Remark : This test was carried out using non-acclimated inoculum with synthetic seawater in a closed bottle type of test. % ThOD after 5, 10, 15 and 20 days was 0, 7, 9 and 63% respectively. This indicates ready biodegradability in seawater as the pass level of 60% was reached within the 10 day window.

Reference : (21)
12.04.2001

Type : aerobic
Inoculum : other: separated domestic waste water
Contact time : 20 day
Degradation : = 48 % after 20 day
Result : other: not readily biodegradable under these non-adapted conditions
Deg. Product :
Method : other: Standard methods for examination of waste water. 13th edition, APHA
Year : 1971
GLP : no
Test substance : no data

Method : American Public Health Association, New York, 1971 Standard methods for the examination of water and waste water, 13th Edition

Reliability : (4) not assignable
Insufficient experimental detail to comment on validity.

Remark : % THOD at 5, 10, 15 and 20 days respectively 2, 29, 47 and 48%.
Source : Shell Chemicals Ltd
Reference : (21)
12.04.2001

3.6 BOD5, COD or BOD5/COD ratio

BOD5
Method : other
Year :
GLP : no
Concentration : related to
BOD5 : mgO2/l
COD
Method : other: reflux COD
Year :
GLP :
COD : mg/g substance

Result : COD % of theoretical 77.4 by reflux COD; 69.1 by rapid COD
BOD5 using unacclimated seed from settled primary effluent from a treatment plant servicing a high industrial input.
Value <0.004 g/g.

The impact of hexylene glycol on conventional biological treatment systems was assessed in an unacclimated system. HG was subjected to a Warburg analysis at a concentration of 1,040 mg/l concentration ca 10 times greater than the maximum conc. estimated to be in a photoprocessing effluent. TOD was 60 mg/l greater than the control. A COD reduction of 51 mg/l above the control was also measured. The conclusion was drawn that hexylene glycol has no effect on the activity of the biomass and may be biodegradable at a low rate.

Reliability : (2) valid with restrictions
Reference : (22)
10.09.2001

BOD5
Method :
Year : 1971
GLP : no
Concentration : related to
BOD5 : = mgO2/l
COD
Method : other: ASTM D1252-67
Year : 1974
GLP : no
COD : = 2200 mg/g substance
RATIO BOD5 / COD
BOD5/COD : = .009
Reliability : (2) valid with restrictions
Remark : ThOD 2.31 g/g
COD as % of ThOD 95%
Type of test : aerobic - Method : APHA, year 1980 ; BOD5 = 56 % of BODT ; APHA : American Public Heath Association ; Reference BABEU, L. and VAISHNAV, D.D, 1987. Prediction of biodegradability selected organic chemicals. Journal of industrial Microbiology, 2, 107-11.
BOD5 = 0,02 g/g.
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Reference : (23) (24)
14.02.2001

3.7 Bioaccumulation

Remark : No data
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

26.04.1994

3.8 Additional remarks

Memo : Conclusion from biodegradation studies.

Conclusion : Although none of the biodegradation assays carried out are to current standards, the weight of evidence indicates that hexylene glycol is at least inherently biodegradable. There was insufficient experimental detail in terms of determining whether the 10 day window requirement was satisfied to conclude that hexylene glycol is readily biodegradable.

26.02.2001

4.1 Acute/prolonged toxicity to fish

Type	:	flow through
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
LC50	:	= 8690
Method	:	other
Year	:	1980
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Test substance	:	Hexylene glycol was 'reagent grade', supplied by Baker Chemical Co., Phillipsburg NJ. and gave a single chromatographic peak under GC analysis
Method	:	American Public Health Association, Washington, 1980 Standard methods for the examination of water and waste water, 15th Edition
Test condition	:	TEST ORGANISMS - Supplier: Fattig Fish Hatchery, Brady, Nebraska - Weight: mean 0.22g - Feeding: Commercial trout ration twice daily - Pretreatment: Dilute formaldehye for 1 hour against parasites, treatment on arrival and weekly thereafter. - Feeding during test: Not specified assume not STOCK AND TE ST SOLUTION AND THEIR PREPARATION - Dispersion: Toxicant added to flow through tanks using proportional diluters. - Vehicle, solvent: dilution water - Concentration of vehicle/solvent: Not reported - Purity/supplier: Reagent grade from Baker Chemical Co. P hillipsburg, NJ STABILITY OF THE TEST CHEMICAL SOLUTIONS: assume stable DILUTION WATER - Source: ground water spring at the testing facility - Alkalinity: 172 +/-6 mg/l CaCO3 - Hardness: 196 +/-9 mg/l CaCO3 - Conductance: measured but not reported TEST SYSTEM - Test type: flow through - Concentrations: Not reported - Dosing rate: Not reported - Renewal of test solution: water replacement 3-8 hours - Exposure vessel type: 20-60l glass aquaria - Number of replicates, 1 - Fish per replicate: not reported - Test temperature: mean 18.7C - Dissolved oxygen: mean 6.27 mg/l - pH: mean 7.95 - Adjustment of pH: No DURATION OF THE TEST: 96 hours TEST PARAMETER: lethality

MONITORING OF TEST SUBSTANCE CONCENTRATION: Analysed at beginning and end of the test plus on days 2 and/or 3.

Result : RESULTS: EXPOSED
- Nominal/measured concentrations: measured but not reported

LC50 8690 mg/l (95% confidence limits 6400 - 1,800) calculated using trimmed Spearman-Karber method. (Hamilton et al, 1977)

RESULTS: CONTROL
- Number/percentage of animals showing adverse effects: 0%
- Nature of adverse effects: none reported

VALIDITY:
Test temperature (18.7C) lower than OECD recommendation of 21-25C. Although the results of analytical monitoring are not reported any losses from the test system are minimised by use of the flow through technique.

Reliability : (2) valid with restrictions
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Flag : Critical study for SIDS endpoint
Reference : (25)
05.09.2001

Type : flow through
Species : Lepomis macrochirus (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : Yes
LC50 : = 12800
Method : other
Year : 1980
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Test substance : Hexylene glycol was 'reagent grade', supplied by Baker Chemical Co., Phillipsburg NJ. and gave a single chromatographic peak under GC analysis

Method : American Public Health Association, Washington, 1980 Standard methods for the examination of water and waste water, 15th Edition

Test condition : TEST ORGANISMS
- Supplier: Fattig Fish Hatchery, Brady, Nebraska
- Weight: mean for test 0.53g
- Feeding: Commercial trout ration twice daily
- Pretreatment: Dilute formaldehye for 1 hour against parasites, treatment on arrival and weekly thereafter.
- Feeding during test: Not specified assume not

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: Toxicant added to flow through tanks using proportional diluters.
- Vehicle, solvent: dilution water
- Concentration of vehicle/solvent: Not reported
- Purity/supplier: Reagent grade from Baker Chemical Co. Phillipsburg, NJ

STABILITY OF THE TEST CHEMICAL SOLUTIONS: assume stable

DILUTION WATER
- Source: ground water spring at the testing facility
- Alkalinity: 172 +/-6 mg/l CaCO3
- Hardness: 196 +/-9 mg/l CaCO3
- Conductance: measured but not reported

TEST SYSTEM
- Test type: flow through
- Concentrations: Not reported
- Dosing rate: Not reported
- Renewal of test solution: water replacement 3-8 hours
- Exposure vessel type: 20-60l glass aquaria
- Number of replicates: 1
- Fish per replicate: not reported
- Test temperature: mean 17.4C
- Dissolved oxygen: 6.47 mg/l
- pH: mean 8.02
- Adjustment of pH: No

DURATION OF THE TEST: 96 hours

TEST PARAMETER: lethality

MONITORING OF TEST SUBSTANCE CONCENTRATION: Analysed at beginning and end of the test plus on days 2 and/or 3.

Result : RESULTS: EXPOSED
- Nominal/measured concentrations: measured but not reported

LC50 12,800 mg/l (95% confidence limits 11,200 - 14,600)
calculated using trimmed Spearman-Karber method. (Hamilton et al, 1977)

RESULTS: CONTROL
- Number/percentage of animals showing adverse effects: 0%
- Nature of adverse effects: none reported

VALIDITY:
Temperature lower (17.4C) than the OECD recommendation of 21-25C
Although the results of analytical monitoring are not reported any losses from the test system are minimised by use of the flow through technique.

Reliability : (2) valid with restrictions
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Flag : Critical study for SIDS endpoint
Reference : (25)
05.09.2001

Type : flow through
Species : Oncorhynchus mykiss (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : Yes
LC50 : = 9450
Method : other
Year : 1980
GLP : no data

Test substance : as prescribed by 1.1 - 1.4

Test substance : Hexylene glycol was 'reagent grade', supplied by Baker Chemical Co., Phillipsburg NJ. and gave a single chromatographic peak under GC analysis

Method : American Public Health Association, Washington, 1980 Standard methods for the examination of water and waste water, 15th Edition

Test condition : TEST ORGANISMS
- Supplier: Spring Creek Trout Hatchery, Lewistown, Montana and/or US Fish and Wildlife Service Fish Technlogy Centre, Bozeman, Montana.
- Weight: mean 1.33g
- Feeding: Commercial trout ration twice daily
- Pretreatment: None reported
- Feeding during test: Not specified assume not

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: Toxicant added to flow through tanks using proportional diluters.
- Vehicle, solvent: dilution water
- Concentration of vehicle/solvent: Not reported
- Purity/supplier: Reagent grade from Baker Chemical Co. Phillipsburg, NJ

STABILITY OF THE TEST CHEMICAL SOLUTIONS: assume stable

DILUTION WATER
- Source: ground water spring at the testing facility
- Alkalinity: 172 +/-6 mg/l CaCO3
- Hardness: 196 +/-9 mg/l CaCO3
- Conductance: measured but not reported

TEST SYSTEM
- Test type: flow through
- Concentrations: Not reported
- Dosing rate: Not reported
- Renewal of test solution: water replacement 3-8 hours
- Exposure vessel type: 20-60l glass aquaria
- Number of replicates, 1
- Fish per replicate: not reported
- Test temperature: mean 11.4C
- Dissolved oxygen: mean 8.76 mg/l
- pH: mean 7.99
- Adjustment of pH: No

DURATION OF THE TEST: 96 hours

TEST PARAMETER: lethality

MONITORING OF TEST SUBSTANCE CONCENTRATION: Analysed at beginning and end of the test plus on days 2 and/or 3.

Result : RESULTS: EXPOSED
- Nominal/measured concentrations: measured but not reported

LC50 9450 mg/l (95% confidence limits 8820 - 10,100)
calculated using trimmed Spearman-Karber method. (Hamilton et al, 1977)

RESULTS: CONTROL
- Number/percentage of animals showing adverse effects: 0%

- Nature of adverse effects: none reported

VALIDITY:
Test temperature (11.4C) is lower than OECD recommendation of 13-17C
Fish may be rather larger than recommended.
Although the results of analytical monitoring are not reported any losses from the test system are minimised by use of the flow through technique.

Reliability : (2) valid with restrictions
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Flag : Critical study for SIDS endpoint
Reference : (25)
05.09.2001

Type : flow through
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : yes
LC50 : = 10700
Method : other
Year : 1975
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : US EPA committee on methods for toxicity tests with aquatic organisms (1975)

Test condition : Lake Superior water was used for all tests. Hardness and alkalinity 56.3 and 42.2 mg/l CaCO3 respectively. Mean pH 7.5. DOC always 60% of saturation. The LC50 was calculated by the trimmed Spearman-Karber method.

Twenty-five 30 day old fish (weight ca 0.12g) were divided among 12 test tanks (control plus 5 treatments, each in duplicate). Temperature was maintained at 25C +/- 1.

Reliability : (2) valid with restrictions

Remark : Also reported in:

Veith, G.D.; Call, D.J. and Brooke, L.T. 1983
Structure-toxicity relationships for the fathead minnow, Pimephales promelas; narcotic industrial chemicals.
Can. J. Fish Aquatic. Sci. 40(6):743-748

Veith, G.D.; Call, D.J. and Brooke, L.T. 1983
Estimating the acute toxicity of narcotic industrial chemicals to fathead minnows.
Aquatic toxicology and hazard. 6th symposium, Philadelphia
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Flag : Critical study for SIDS endpoint
Reference : (26)
14.03.2001

Type : flow through

Species	:	Carassius auratus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
LC50	:	m = 12000
Method	:	other
Year	:	1980
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Test substance	:	Hexylene glycol was 'reagent grade', supplied by Baker Chemical Co., Phillipsburg NJ. and gave a single chromatographic peak under GC analysis
Method	:	American Public Health Association, Washington, 1980 Standard methods for the examination of water and waste water, 15th Edition
Test condition	:	TEST ORGANISMS - Supplier: supplier in Helena, Montana - Weight: mean for test 1.01g - Feeding: Commercial trout ration twice daily - Pretreatment: Dilute formaldehye for 1 hour against parasites, treatment on arrival and weekly thereafter. - Feeding during test: Not specified, assume not. STOCK AND TEST SOLUTION AND THEIR PREPARATION - Dispersion: Toxicant added to flow through tanks using proportional diluters. - Vehicle, solvent: dilution water - Concentration of vehicle/solvent: Not reported - Purity/supplier: Reagent grade from Baker Chemical Co. Phillipsburg, NJ STABILITY OF THE TEST CHEMICAL SOLUTIONS: assume stable DILUTION WATER - Source: ground water spring at the testing facility - Alkalinity: 172 +/-6 mg/l CaCO3 - Hardness: 196 +/-9 mg/l CaCO3 - Conductance: measured but not reported TEST SYSTEM - Test type: flow through - Concentrations: Not reported - Dosing rate: Not reported - Renewal of test solution: water replacement 3-8 hours - Exposure vessel type: 20-60l glass aquaria - Number of replicates: 1 - Fish per replicate: not reported - Test temperature: 17.6C - Dissolved oxygen: 5.10 mg/l - pH: mean 7.83 - Adjustment of pH: No DURATION OF THE TEST: 96 hours TEST PARAMETER: lethality MONITORING OF TEST SUBSTANCE CONCENTRATION: Analysed at beginning and end of the test plus on days 2 and/or 3.

Result : RESULTS: EXPOSED
- Nominal/measured concentrations: measured but not reported

LC50 12,000 mg/l (95% confidence limits 11,000 - 13,000)
calculated using trimmed Spearman-Karber method. (Hamilton et al, 1977)

RESULTS: CONTROL
- Number/percentage of animals showing adverse effects: 10%
- Nature of adverse effects: death

VALIDITY: Not a recommended OECD test species. Although the results of analytical monitoring are not reported any losses from the test system are minimised by use of the flow through technique.

Reliability : (2) valid with restrictions
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Reference : (25)
05.09.2001

Type : flow through
Species : Gambusia affinis (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : yes
LC50 : = 8510
Method : other
Year : 1980
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Test substance : Hexylene glycol was 'reagent grade', supplied by Baker Chemical Co., Phillipsburg NJ. and gave a single chromatographic peak under GC analysis

Method : American Public Health Association, Washington, 1980 Standard methods for the examination of water and waste water, 15th Edition

Test condition : TEST ORGANISMS
- Supplier: Fattig Fish Hatchery, Brady, Nebraska
- Weight: Mean test 1 - 0.87g; test 2 - 0.23g
- Feeding: Commercial trout ration twice daily
- Pretreatment: Dilute formaldehye for 1 hour against parasites, treatment on arrival and weekly thereafter.
- Feeding during test: Not specified assume not

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: Toxicant added to flow through tanks using proportional diluters.
- Vehicle, solvent: dilution water
- Concentration of vehicle/solvent: Not reported
- Purity/supplier: Reagent grade from Baker Chemical Co. Phillipsburg, NJ

STABILITY OF THE TEST CHEMICAL SOLUTIONS: assume stable

DILUTION WATER
- Source: ground water spring at the testing facility
- Alkalinity: 172 +/-6 mg/l $CaCO_3$
- Hardness: 196 +/-9 mg/l $CaCO_3$

- Conductance: measured but not reported

TEST SYSTEM
- Test type: flow through
- Concentrations: Not reported
- Dosing rate: Not reported
- Renewal of test solution: water replacement 3-8 hours
- Exposure vessel type: 20-60l glass aquaria
- Number of replicates, 2
- Fish per replicate: not reported
- Test temperature: test 1 mean 17.4C; test 2 mean 18.7C;
- Dissolved oxygen: test 1 mean 6.47 mg/l; test 2 mean 6.27 mg/l;
- pH: test 1 mean 8.02; test 2 mean 7.95;
- Adjustment of pH: No

DURATION OF THE TEST: 96 hours

TEST PARAMETER: lethality

MONITORING OF TEST SUBSTANCE CONCENTRATION: Analysed at beginning and end of the test plus on days 2 and/or 3.

Result : RESULTS: EXPOSED
- Nominal/measured concentrations: measured but not reported

LC50 test 1 9910 mg/l (95% confidence limits 8590 - 11,400)
LC50 test 2 8510 (95% confidence limits 6990 - 10,400)
calculated using trimmed Spearman-Karber method. (Hamilton et al, 1977)

RESULTS: CONTROL
- Number/percentage of animals showing adverse effects: 0%
- Nature of adverse effects: none reported

VALIDITY: Not an OECD recommended species. Although the results of analytical monitoring are not reported any losses from the test system are minimised by use of the flow through technique.

Reliability : (2) valid with restrictions
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Reference : (25)
05.09.2001

Type : flow through
Species : Ictalurus punctatus (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : yes
LC50 : = 11200
Method : other: No data
Year : 1980
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Test substance : Hexylene glycol was 'reagent grade', supplied by Baker Chemical Co., Phillipsburg NJ. and gave a single chromatographic peak under GC analysis

Method : American Public Health Association, Washington, 1980 Standard methods

for the examination of water and waste water, 15th Edition

Test condition : TEST ORGANISMS
- Supplier: Fattig Fish Hatchery, Brady, Nebraska
- Weight: mean test 1 - 3.03g; test 2 - 2.61g
- Feeding: Commercial trout ration twice daily
- Pretreatment: Dilute formaldehye for 1 hour against parasites, treatment on arrival and weekly thereafter.
- Feeding during test: Not specified assume not

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: Toxicant added to flow through tanks using proportional diluters.
- Vehicle, solvent: dilution water
- Concentration of vehicle/solvent: Not reported
- Purity/supplier: Reagent grade from Baker Chemical Co. Phillipsburg, NJ

STABILITY OF THE TEST CHEMICAL SOLUTIONS: assume stable
REFERENCE SUBSTANCE:

DILUTION WATER
- Source: ground water spring at the testing facility
- Alkalinity: 172 +/-6 mg/l CaCO3
- Hardness: 196 +/-9 mg/l CaCO3
- Conductance: measured but not reported

TEST SYSTEM
- Test type: flow through
- Concentrations: Not reported
- Dosing rate: Not reported
- Renewal of test solution: water replacement 3-8 hours
- Exposure vessel type: 20-60l glass aquaria
- Number of replicates, 2
- Fish per replicate: not reported
- Test temperature: test 1 mean 17.6C; test 2 mean 16.7C;
- Dissolved oxygen: test 1 mean 5.1 mg/l; test 2 mean 6.2 mg/l;
- pH: test 1 mean 7.83; test 2 mean 8.00;
- Adjustment of pH: No

DURATION OF THE TEST: 96 hours

TEST PARAMETER: lethality

MONITORING OF TEST SUBSTANCE CONCENTRATION: Analysed at beginning and end of the test plus on days 2 and/or 3.

Result : RESULTS: EXPOSED
- Nominal/measured concentrations: measured but not reported

LC50 test 1 11,200 mg/l (95% confidence limits 10,000- 12,600)
LC50 test 2 13,500 (95% confidence limits 12,300 - 14,800)
calculated using trimmed Spearman-Karber method. (Hamilton et al, 1977)

RESULTS: CONTROL
- Number/percentage of animals showing adverse effects: 0%
- Nature of adverse effects: none reported

VALIDITY:
Not OECD recommended species; Feed inappropriate

Reliability	:	(2) valid with restrictions
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) Shell Chemicals Ltd
Reference	:	(25)
05.09.2001		
Type	:	static
Species	:	Alburnus alburnus (Fish, estuary)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	= 8000
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Test substance	:	The supplier of the test substance was Kebo AB, Sweden, purity not specified.
Test condition	:	Static conditions with no renewal. No pH adjustment. No feeding during the test period. 10 fish caught in the Baltic (body length ca 8 cm) were exposed at each test concentration in 70l glass aquaria using natural brackish water pumped directly from the Baltic at a temperature of 10C. Water characteristics were 7% salinity, alkalinity 1.5 meqv./l, pH 7.8. The concentration of dissolved oxygen was measured at the end of the exposure period and 5 mg O2/l was considered a satisfactory minimum level. Light/dark cycle 12/12 hours.
Result	:	96 hour LC50 8000 mg/l (7000-9100) Validity: Supportive data only, unconventional species plus no analysis of test concentrations. Control mortality was not reported.
Reliability	:	(4) not assignable
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) Shell Chemicals Ltd
Reference	:	(27)
05.09.2001		
Type	:	static
Species	:	Carassius auratus (Fish, fresh water)
Exposure period	:	24 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
LC50	:	m > 5000
Method	:	other: APHA
Year	:	1971
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Test condition	:	6 fish/group in glass tanks with 25 litres test solution made with local tap water. 24 hour exposure. Temperature 20C +/-1C. Average length 6.2 +/-0.7cm, average weight 3.3 +/-1.0g. The solutions were aerated throughout the test and for more volatile compounds such as hexylene glycol the test period was limited to 24 hours to ensure that dissolved oxygen did not fall below 4 mg/l.

Reliability	:	(2) valid with restrictions
Remark	:	Supportive data only, non OECD species. As this reference reports results for numerous test materials specific exp erimental details for each product are not given. Target lowest value for dissolved oxygen of 4 mg/l is rather low falling below the recommended 60% of saturation.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA) Shell Chemicals Ltd
Reference 15.08.2001	:	(28)
Type	:	static
Species	:	Lepomis macrochirus (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	> 10000
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Test condition	:	The assay was carried out using fish from a commercial supplier. They were 33-75 mm in length and tested in 1 gallon wide mouth glass jars at 23C. pH of dilution water was 7.6-7.9 with a hardness of 55 mg/l CaCO3. Aeration was used intermittently as required after the first 24 hours of exposure. Number of fish tested was not reported.
Result	:	Test concentrations used were 3200 and 10000 mg/l hexylene glycol. Survival was 100% at both exposure levels. Supportive data only, no analysis of test media, aeration was periodic.
Reliability	:	(4) not assignable
Reference 24.08.2001	:	(29) (30)
Type	:	static
Species	:	Menidia beryllina (Fish, estuary, marine)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	= 10000
Method	:	other
Year	:	1975
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Test condition	:	The assay was carried out using fish caught 14 days prior to testing. They were 40-100 mm in length and tested in glass 5 gallon aquaria with continuous aeration. A synthetic saltwater mix was used to achieve a specific gravity of 1.018. Number of fish tested was not reported.
Result	:	Test concentrations were 5000, 7900 and 10,000 mg/l. All fish survived at 5000 mg/l. After 96 hours % survival at 7900 and 10,000 mg/l was 60 and 50% respectively. 96 hour LC50 is 10000 mg/l

Reliability	:	(4) not assignable
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) Shell Chemicals Ltd
Reference	:	(29) (30)
24.08.2001		

4.2 Acute toxicity to aquatic invertebrates

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no data
EC50	:	= 3200
Method	:	other: ASTM D4229-84
Year	:	1984
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Test substance	:	Reagent grade
Test condition	:	TEST ORGANISMS - Strain: Daphnia magna - Source/supplier: Environmental Research Laboratory, Duluth, Mnnesota - Age: ist instar (<24 hours) - Feeding: suspension of fish food and yeast - Pretreatment: not reported - Feeding during test: not reported - Control group: yes, dilution water STOCK AND TEST SOLUTION AND THEIR PREPARATION Not reported STABILITY OF THE TEST CHEMICAL SOLUTIONS: Not reported REFERENCE SUBSTANCE: Not reported DILUTION WATER - Source: Unchlorinated, carbon filtered well water - Aeration: aerated to saturation before use - Alkalinity: 230 +/-10 mg/l CaCO3 - Hardness: 240 +/-10 mg/l CaCO3 TEST SYSTEM - Test type: static - Concentrations: not reported - Renewal of test solution: no - Exposure vessel type: 250 ml glass beakers containing 200 ml test solution. - Number of replicates, individuals per replicate: 2/treatment, 10/replicate - Test temperature: 23 +/-1C - Dissolved oxygen: measured but not reported - pH: measured but not reported - Adjustment of pH: not reported - Intensity of irradiation: not reported - Photoperiod: 16 hours with 15 minute transition to darkness DURATION OF THE TEST: 48 hours TEST PARAMETER: mortality/immobility MONITORING OF TEST SUBSTANCE CONCENTRATION: Not reported

Result	:	RESULTS: EXPOSED - Nominal/measured concentrations: not reported RESULTS CONTROL: Not reported RESULTS: 48h EC50 3200 mg/l (2700-3700) based on nominal concentrations. Calculated using probit analysis VALIDITY: The test method is similar to OECD 202 deviations being lack of analysis of concentrations and lack of reporting of control mortality.
Reliability	:	(2) valid with restrictions
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA) Shell Chemicals Ltd
Flag	:	Critical study for SIDS endpoint
Reference	:	(31)
06.09.2001		
Type	:	static
Species	:	Daphnia pulex (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no data
EC50	:	= 3300
Method	:	other: ASTM D4229-84
Year	:	1984
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Test substance	:	Reagent grade
Test condition	:	TEST ORGANISMS - Strain: Daphnia pulex - Source/supplier: Environmental Research Laboratory, Duluth, Mnnesota - Age: ist instar (<24 hours) - Feeding: suspension of fish food and yeast - Pretreatment: not reported - Feeding during test: not reported - Control group: yes, dilution water STOCK AND TEST SOLUTION AND THEIR PREPARATION Not reported STABILITY OF THE TEST CHEMICAL SOLUTIONS: Not reported REFERENCE SUBSTANCE: Not reported DILUTION WATER - Source: Unchlorinated, carbon filtered well water - Aeration: aerated to saturation before use - Alkalinity: 230 +/-10 mg/l CaCO3 - Hardness: 240 +/-10 mg/l CaCO3 TEST SYSTEM - Test type: static - Concentrations: not reported - Renewal of test solution: no - Exposure vessel type: 250 ml glass beakers containing 200 ml test solution. - Number of replicates, individuals per replicate: 2/treatment, 10/replicate - Test temperature: 23 +/-1C - Dissolved oxygen: measured but not reported - pH: measured but not reported - Adjustment of pH: not reported

- Intensity of irradiation: not reported
- Photoperiod: 16 hours with 15 minute transition to darkness
DURATION OF THE TEST: 48 hours
TEST PARAMETER: mortality/immobility

MONITORING OF TEST SUBSTANCE CONCENTRATION: Not reported

Result : RESULTS: EXPOSED
- Nominal/measured concentrations: not reported

RESULTS CONTROL: Not reported
RESULTS: 48h EC50 3300 mg/l (2800-4000) based on nominal concentrations. Calculated using probit analysis

VALIDITY: The test method is similar to OECD 202 deviations being lack of analysis of concentrations and lack of reporting of control mortality.

Reliability : (2) valid with restrictions
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Reference : (31)
06.09.2001

Type : Static
Species : Ceriodaphnia sp. (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : no data
EC50 : = 2800
Method : other: ASTM D4229-84
Year : 1984
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Test substance : Reagent grade

Test condition : TEST ORGANISMS
- Strain: Ceriodaphnia reticulata
- Source/supplier: Environmental Research Laboratory, Duluth, Mnnesota
- Age: 1st instar (<24 hours)
- Feeding: yeast suspension
- Pretreatment: not reported
- Feeding during test: not reported
- Control group: yes, dilution water
STOCK AND TEST SOLUTION AND THEIR PREPARATION
Not reported
STABILITY OF THE TEST CHEMICAL SOLUTIONS: Not reported
REFERENCE SUBSTANCE: Not reported
DILUTION WATER
- Source: Unchlorinated, carbon filtered well water
- Aeration: aerated to saturation before use
- Alkalinity: 230 +/-10 mg/l CaCO3
- Hardness: 240 +/-10 mg/l CaCO3

TEST SYSTEM
- Test type: static
- Concentrations: not reported
- Renewal of test solution: no
- Exposure vessel type: 250 ml glass beakers containing 200 ml test

solution.
- Number of replicates, individuals per replicate: 2/treatment, 10/replicate
- Test temperature: 23 +/-1C
- Dissolved oxygen: measured but not reported
- pH: measured but not reported
- Adjustment of pH: not reported
- Intensity of irradiation: not reported
- Photoperiod: 16 hours with 15 minute transition to darkness

DURATION OF THE TEST: 48 hours

TEST PARAMETER: mortality/immobility

MONITORING OF TEST SUBSTANCE CONCENTRATION: Not reported

Result : RESULTS: EXPOSED
- Nominal/measured concentrations: not reported

RESULTS CONTROL: Not reported
RESULTS: 48h EC50 2800 mg/l (2400-3200) based on nominal concentrations. Calculated using probit analysis

VALIDITY: The test method is similar to OECD 202 deviations being lack of analysis of concentrations and lack of reporting of control mortality.

Reliability : (2) valid with restrictions
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Reference : (31)
06.09.2001

Type : Static
Species : Artemia salina (Crustacea)
Exposure period : 24 hour(s)
Unit : mg/l
Analytical monitoring : no data
EC50 : = 5900
Method : other: static
Year :
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Test condition : Shrimp eggs were placed in a hatching device about 48 hours ahead of the time that the shrimps were required for the test. The tests were conducted at 24.5C in 150 ml wide necked bottles containing test material and artifical seawater to a total volume of 100 ml. 1 ml of a brine shrimp suspension was added providing 30-50 shrimp for each bottle. Following incubation the numbers of live and dead shrimp were recorded visually in the bottle with the assistance of a colony counter.

Reliability : (4) not assignable

Remark : This is a non-standard study with no measurement of concentrations of test material. Data can be used as supportive evidence.
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Reference : (21)
27.02.2001

Type	:	Static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	Yes
EC50	:	= 5410
Method	:	other
Year	:	1980
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Test substance	:	Hexylene glycol was 'reagent grade', supplied by Baker Chemical Co., Phillipsburg NJ. and gave a single chromatographic peak under GC analysis
Method	:	American Public Health Association, Washington, 1980 Standard methods for the examination of water and waste water, 15th Edition
Test condition	:	TEST ORGANISMS - Source/supplier: Montana State University - Feeding: slurry of trout feed and Cerophyl. - Pretreatment: none reported - Feeding during test: not reported assume not - Control group: yes STOCK AND TEST SOLUTION AND THEIR PREPARATION - Dispersion: stirring - Vehicle, solvent: dilution water - Concentration of vehicle/ solvent: not reported STABILITY OF THE TEST CHEMICAL SOLUTIONS: assume stable DILUTION WATER - Source: ground water spring at testing facility - Alkalinity: 172 +/-6 mg/l CaCO3 - Hardness: 196 +/-9 mg/l CaCO3 - TOC: - Ca/Mg ratio: 46/9.8 - Na/K ratio: 2/0.5 - TSS: - Conductance: measured but not reported TEST SYSTEM - Test type: Static - Concentrations: Not reported - Renewal of test solution: Not reported - Exposure vessel type: 250 ml hard glass beakers - Number of replicates: 2 - Individuals per replicate: 20 - Test temperature: (a) 23 (b) 22.4C - Dissolved oxygen: (a) 2.8 (b) 5.4 mg/l - pH: (a) 8.17 (b) 8.43 - Adjustment of pH: No DURATION OF THE TEST: 48 hours TEST PARAMETER: Death/Immobility

MONITORING OF TEST SUBSTANCE CONCENTRATION: Measured at beginning and end of exposure.

Result : RESULTS: EXPOSED
- Nominal/measured concentrations: measured but not reported
- Effect data (Immobilisation): LC50 (a) 8700 mg/l (95% confidence limits 7510-10,100) LC50 (b) 5410 mg/l (4540-6440)

RESULTS CONTROL: (a) No effect (b) 10% mortality

VALIDITY:

Not valid, dissolved oxygen too low

Reliability : (2) valid with restrictions
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Reference : (25)
10.09.2001

Type : static
Species : Nitocra spinipes (Crustacea)
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : No
EC50 : c = 7600
Method : other
Year : 1979
GLP : No
Test substance : As prescribed by 1.1 - 1.4

Test substance : The supplier of the test substance was Kebo AB, Sweden, purity not specified.

Test condition : Static conditions with no renewal. No pH adjustment. No feeding during the test period. 2x10 crustacea (cultured) were exposed at each test concentration in 15 ml laboratory test tubes using natural brackish water pumped directly from the Baltic at a temperature of 10C. Water characteristics were 7% salinity, alkalinity 1.5 meqv./l, pH 7.8. The concentration of dissolved oxygen was measured at the end of the exposure period and 5 mg O2/l was considered a satisfactory minimum level. Light/dark cycle 12/12 hours.

Result : 96 hour LC50 7600 mg/l (5800-9900)

Reliability : (4) not assignable
Source : Amway Europe Zaventem
Shell Chemicals Ltd
Reference : (27)
05.09.2001

Type : other
Species : other: Arbacia punctulata
Exposure period : 2 hour(s)
Unit : mg/l
Analytical monitoring :
EC50 : c = 9486
Method : other: screening assay
Year : 1984

GLP : No data
Test substance : As prescribed by 1.1 - 1.4

Reliability : (4) not assignable

Remark : Parameter measured was inhibition of incorporation of tritiated thymidine into the sea urchin embryo over a 2 hour period starting 2 hours after fertilisation which w as correlated with acute toxicity data for Daphnia and Fathead Minnow. A good correlation was found between results of acute toxicity assays and inhibition of thymidine incorporation for a range of organic chmecials including hexylene glycol.

Reference : (32)
14.03.2001

Type : other
Species : other: Arbacia punctulata
Exposure period :
Unit :
Analytical monitoring :

Test condition : Parameter measured was inhibition of incorporation of tritiated thymidine into the sea urchin embryo. Exposures began 1 hour before fertilisation, at the time of fertilisation or 1 hour after fertilisation. All exposures continued to 4 hours after fertilisation.

Result : EC50 8109 mg/l Exposure prefertilisation to 4 hours post fertilistion (total 5 hours)
EC50 8742 mg/l Exposure from fertilisation for 4 hours
EC50 10248 mg/l Exposure from 1 hour post ferilisation for 3 hours.

Reliability : (4) not assignable
Reference : (33)
27.02.2001

Type : flow through
Species : other: Orconnectes immunis
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : yes
EC50 : = 16500
Method : other: flow-through
Year :
GLP : No data
Test substance : As prescribed by 1.1 - 1.4

Test substance : Hexylene glycol was 'reagent grade', supplied by Baker Chemical Co., Phillipsburg NJ. and gave a single chromatographic peak under GC analysis

Test condition : TEST ORGANISMS
- Source/supplier: Fattig Fish Hatchery, Brady, Nebraska
- Feeding: raw groung meat.
- Pretreatment: none reported
- Feeding during test: not reported
- Control group: yes

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: stirring
- Vehicle, solvent: dilution water
- Concentration of vehicle/ solvent: not reported

STABILITY OF THE TEST CHEMICAL SOLUTIONS: assume stable
REFERENCE SUBSTANCE:

DILUTION WATER
- Source: ground water spring at testing facility
- Alkalinity: 172 +/-6 mg/l CaCO3
- Hardness: 196 +/-9 mg/l CaCO3

- TOC:
- Ca/Mg ratio: 46/9.8
- Na/K ratio: 2/0.5
- TSS:
- Conductance: measured but not reported

TEST SYSTEM
- Test type: Flow through
- Concentrations: Not reported
- Renewal of test solution: Not reported
- Exposure vessel type: glass aquaria (20-60l)
- Number of replicates: 2 if replicated
- Individuals per replicate: 20
- Test temperature: (a) 11.6 (b) 17.6C
- pH: (a) 7.95 (b) 8.04
- Adjustment of pH: No

DURATION OF THE TEST: 96 hours

TEST PARAMETER: Death/Immobility

MONITORING OF TEST SUBSTANCE CONCENTRATION: Measured at beginning and end of exposure plus day 2 and/or 3.

Result : RESULTS: EXPOSED
- Nominal/measured concentrations: measured but not reported
- Effect data (Immobilisation): (a) LC50 33,000 mg/l (95% confidence limits 28,900-37,800) (b) LC50 16500 mg/l (14,000-19,600)

RESULTS CONTROL: 0% mortality

VALIDITY: Unconventional species (crayfish), test organism not neonate. Although the results of analytical monitoring are not reported any losses from the test system are minimised by use of the flow through technique.

Reliability : (2) valid with restrictions
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Reference : (25)
10.09.2001

Type : static
Species : other: Tanytarsus dissimilis
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : yes
EC50 : = 4310
Method : static
Year :
GLP : no data

Test substance : as prescribed by 1.1 - 1.4

Test substance : Hexylene glycol was 'reagent grade', supplied by Baker Chemical Co., Phillipsburg NJ. and gave a single chromatographic peak under GC analysis

Test condition : TEST ORGANISMS
- Source/supplier: Montana State University
- Feeding: slurry of trout feed and Cerophyl.
- Pretreatment: none reported
- Feeding during test: not reported
- Control group: yes
- Stage of life cycle: 3rd and 4th larval instar

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: stirring
- Vehicle, solvent: dilution water
- Concentration of vehicle/ solvent: not reported

STABILITY OF THE TEST CHEMICAL SOLUTIONS: assume stable
REFERENCE SUBSTANCE:

DILUTION WATER
- Source: ground water spring at testing facility
- Alkalinity: 172 +/-6 mg/l CaCO3
- Hardness: 196 +/-9 mg/l CaCO3

- TOC:
- Ca/Mg ratio: 46/9.8
- Na/K ratio: 2/0.5
- TSS:
- Conductance: measured but not reported

TEST SYSTEM
- Test type: Static
- Concentrations: Not reported
- Renewal of test solution: Not reported
- Exposure vessel type: 250 ml hard glass beakers
- Number of replicates: 2 if replicated
- Individuals per replicate: 20 controls, test not specified
- Test temperature: 22
- pH: 8.49
- Adjustment of pH: No
- Other: 15 mg sterilised sand was added to the test vessels

DURATION OF THE TEST: 48 hours

TEST PARAMETER: Death/Immobility

MONITORING OF TEST SUBSTANCE CONCENTRATION: Measured at beginning and end of exposure.

Result : RESULTS: EXPOSED
- Nominal/measured concentrations: measured but not reported
- Effect data (Immobilisation): LC504310 mg/l (95% confidence limits 3220 - 6120)

RESULTS CONTROL: 5% mortality

VALIDITY: Unconventional species (insect member of Chironomidae),

neonates not used (3rd-4th larval instar). This species is a sediment dweller but this is not considered a true sediment test. In view of the fact that the substrate was sterilised sand and hexylene glycol has a log Kow of 0.58, little sorbtion is expected. The test results reflect this and are expressed in terms of mg/l rather than mg/kg. There is insufficient information to estimate partitioning and express the result in terms of mg/kg.

Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd

Reference : (25)
10.09.2001

4.3 Toxicity to aquatic plants e.g. algae

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	other: growth rate and biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	m > 429
EC0	:	m > 429
EC10	:	m > 429
EC50	:	m > 429
Method	:	OECD Guide-line 201 "Algae, Growth Inhibition Test"
Year	:	1984
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Test substance	:	Measured purity 99.9% 107-41-5
Test condition	:	TEST ORGANISMS - Strain: Selenastrum capricornutum (now known as Pseudokirchneriella subcapitata) - Source/supplier: Culture Center of Algae and Protzoa - Laboratory culture: Yes - Method of cultivation: - Pretreatment: No - Controls: Yes untreated - Initial cell concentration: 10000 cells/ml STOCK AND TEST SOLUTION AND THEIR PREPARATION - Dispersion: fully water soluble - Vehicle, solvent: water - Concentration of vehicle/ solvent: nominal concentrations of 60-500 mg/l STABILITY OF THE TEST CHEMICAL SOLUTIONS: REFERENCE SUBSTANCE: potassium dichromate DILUTION WATER - Source: Prepared as described in para 1.6.1.2 of EC method C3. - Aeration: No GROWTH/TEST MEDIUM CHEMISTRY - Alkalinity: - Hardness: - Salinity: - TOC: - EDTA: 0.1 mg/l

- TSS:
- pH: 7.36-8.06 control range, test range 7.38-7.94
- Dissolved oxygen: 8.4-10.6 mg/l
TEST SYSTEM
- Test type: static
- Concentrations: Nominal 60, 102, 173, 294, 500
- Renewal of test solution: No
- Exposure vessel type: 100ml ehrlenmeyer flasks stoppered with cotton wool in sterilised gauze and containing 50 ml solution.
- Number of replicates: 3
- Concentrations:
- Test temperature: 22.5C +/- 1.5C
- pH:
- Intensity of irradiation: 6000-7000 lux
- Photoperiod: 16 hours light/8 hours dark
TEST PARAMETER: Growth inhibition
MONITORING OF TEST SUBSTANCE CONCENTRATION: Yes at beginning and end of exposure period.

Result : RESULTS: EXPOSED
- Nominal/measured concentrations:

Nominal 60, 102, 173, 294, 500
Measured no algae
(0 hr) 50.4, 100.2, 157.5, 300.9, 429.2
Measured no algae
(72 hr) 46.5, 75.8, 131.6, 273.1, 531.3
Measured with algae
(72 hr) 48.1, 72.1, 102.2, 234.7, 493.4

- Effect data/Element values:

EC50 and EC10 at 72 hours >429 mg/l for both growth and biomass. Noec >429 mg/l for both growth and biomass.

- Cell density data: Cell density fulfilled test criteria see attached document.

RESULTS: TEST WITH REFERENCE SUBSTANCE
- Results: EC50r at 72 hours 0.90 mg/l; EC50b at 72 hours 0.36 mg/l

STATISTICAL RESULTS: The NOEC corresponded to the highest test concentration, where no significant effect was observed compared to controls determined using the Dunnett test.

Conclusion : The cell concentration in control cultures satisfied the validity requirement of increase by a factor of at least 16 within 3 days. The increase in cell density was actually 163.

There was some loss of hexylene glycol over the exposure period but this was in most cases within the limit of 80% of initial concentration.

EC50 and EC10 at 72 hours >429 mg/l for both growth and biomass. Noec >429 mg/l for both growth and biomass.

Reliability : (1) valid without restriction

Attached doc. : Cell density and growth inhibition.doc
Flag : Critical study for SIDS endpoint
Reference : (34)
11.09.2001

4.4 Toxicity to microorganisms e.g. bacteria

Type	:	
Species	:	Photobacterium phosphoreum (Bacteria)
Exposure period	:	5 minute(s)
Unit	:	mg/l
Analytical monitoring	:	no data
EC50	:	= 3070
Method	:	other:
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable
Remark	:	Bacterial bioluminesence bioassay end point is the 5 minute EC50 (3070 mg/l) for reduction of light output from the bacteria. Study carried out to develop a screen test for prediction of toxicity to fish. The primary source for this data is Curtis et al, 1982. The secondary source is Kaiser et al, 1991 a literature compilation of Microtox results quoted in DOSE. The value for 2-methyl 2,4-pentanediol is misquoted in Kaiser and DOSE. The correct primary source value is reported above.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA) Shell Chemicals Ltd
Reference	:	(35) (36)
24.08.2001		
Type	:	other
Species	:	Pseudomonas aeruginosa (Bacteria)
Exposure period	:	10 day
Unit	:	mg/l
Analytical monitoring	:	no data
EC0	:	ca. 200
Method	:	other: Williams and Bennett
Year	:	1973
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Test substance	:	Industrial grade
Test condition	:	Test medium: Sterile basal salts solution pH 7.0 -7.3 Test concentrations: 0.05-3000 ppm test compound Test suspension contained 50-500 microorganisms/cm2 based on colony count. Test vessel: 250 ml flask containing 100 ml basal salts solution. Procedure: Flasks were agitated in an incubator at 25C for 10 days. Bacterial growth was measured by pour point colony count at 3, 7 and 10 days. Maximum growth culture occured at 10 days after which there was no increase in numbers. 10 day results were therefore reported by the authors.
Result	:	Results: Maximum growth was observed at 200 ppm hexylene glycol. Inhibition of bacterial growth was observed at concentrations greater than 1000 ppm.
Reliability	:	(4) not assignable
Source	:	Shell Chemicals Ltd
Reference	:	(37)

06.09.2001

4.5.1 Chronic toxicity to fish

Remark : No data
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

26.04.1994

4.5.2 Chronic toxicity to aquatic invertebrates

4.6.1 Toxicity to soil dwelling organisms

Remark : No data
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

26.04.1994

4.6.2 Toxicity to terrestrial plants

Remark : No data
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

26.04.1994

4.6.3 Toxicity to other Non-Mamm. terrestrial species

4.7 Biological effects monitoring

Remark : No data
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

26.04.1994

4.8 Biotransformation and kinetics

Remark : No data
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

26.04.1994

4.9 Additional remarks

Memo : Toxicity to Rana catesbiana (tadpoles)

Test substance : Hexylene glycol was 'reagent g rade', supplied by Baker Chemical Co., Phillipsburg NJ. and gave a single chromatographic peak under GC analysis

Method : American Public Health Association, Washington, 1980 Standard methods for the examination of water and waste water, 15th Edition

Test condition : TEST ORGANISMS
- Source/supplier: Carolina Biological Supply
- Feeding: commercial trout ration
- Pretreatment: none reported
- Feeding during test: not reported
- Control group: yes
- Larval stage tested (tadpole) weight 2-5 g

STOCK AND TEST SOLUTION AND THEIR PREPARATION
- Dispersion: stirring
- Vehicle, solvent: dilution water
- Concentration of vehicle/ solvent: not reported

STABILITY OF THE TEST CHEMICAL SOLUTIONS: assume stable
REFERENCE SUBSTANCE:

DILUTION WATER
- Source: ground water spring at testing facility
- Alkalinity: 172 +/-6 mg/l CaCO3
- Hardness: 196 +/-9 mg/l CaCO3
- Conductance: measured but not reported

TEST SYSTEM
- Test type: Flow through
- Concentrations: Not reported
- Exposure vessel type: glass aquaria (20-60l)
- Number of replicates: 1
- Individuals per replicate: not reported
- Test temperature: 19.2C
- Dissolved oxygen: 6.94 mg/l
- pH: 8.04
- Adjustment of pH: No

DURATION OF THE TEST: 96 hours

TEST PARAMETER: Death

MONITORING OF TEST SUBSTANCE CON CENTRATION: Measured at beginning and end of exposure plus day 2 and/or 3.

GLP: No data

Result : RESULTS: EXPOSED
- Nominal/measured concentrations: measured but not reported
Although the results of analytical monitoring are not reported any losses from the test system are minimised by use of the flow through technique.

- Effect data: LC50 11,800 mg/l (95% confidence limits 10,300-13,600)

RESULTS CONTROL: 0% mortality

VALIDITY: This is an unconventional species and there is no test guideline.

However the test has been adequately conducted and provides information on the toxicity to a vertebrate aquatic larval form.

Reliability : (2) valid with restrictions
Source : Shell Chemicals Ltd
Reference : (25)
10.09.2001

5.1.1 Acute oral toxicity

Type	:	LD50
Species	:	rat
Strain	:	other: Sprague-Dawley Crl:CD.BR
Sex	:	male/female
Number of animals	:	10
Vehicle	:	water
Value	:	> 2000 mg/kg bw
Method	:	other: Directive 92/69/EC B1 equivalent to OECD 420 fixed dose procedure
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Test condition	:	TEST ORGANISMS: - Source: Charles River (UK) Margate Kent - Age: 5-7 weeks old - Weight at study initiation: Males 173-191g, Females 145-175g - Number of animals: 5 male + 5 female - Controls: No ADMINISTRATION: - Doses: single dose of 2000 mg/kg - Volume administered or concentration: 10 ml/kg - Post dose observation period: 14 days EXAMINATIONS: Mortality, clinical signs (daily after day 1, frequency on day 1), body weights (weekly). Full macroscopic examination.
Result	:	MORTALITY: No animals died following exposure. CLINICAL SIGNS: Clinical signs in all rats 2-3 hours after dosing included ataxia, decreased activity, muscular flaccidity and palpebral closure. Less common signs were piloerection and voiding of dark faeces (females from 2hour after dosing). Recovery was complete by day 2. BODY WEIGHT: All rats gained in bodyweight over the 14 day observation period. NECROPSY FINDINGS: Isolated macroscopic changes were confined to renal pelvic dilatation in one female and a slightly red and distended caecum in another female. POTENTIAL TARGET ORGANS: Nervous system.
Conclusion	:	Rat oral LD50 > 2000 mg/kg, signs of intoxication suggest an effect on the central nervous system.
Reliability	:	(1) valid without restriction
Source	:	Shell Chemicals Ltd
Flag	:	Critical study for SIDS endpoint
Reference	:	(38)
06.09.2001		

Type	:	LD50
Species	:	rat
Strain	:	Sherman
Sex	:	no data
Number of animals	:	6
Vehicle	:	
Value	:	= 4700 mg/kg bw

Method	:	other: No data
Year	:	1948
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) Shell Chemicals Ltd
Reference	:	(39)
30.08.2001		
Type	:	LD50
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Value	:	= 4 ml/kg bw
Method	:	other
Year	:	1945
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable
Remark	:	LD50 = 3.69 g/kg, signs of intoxication observed within an hour of dosing were loss of muscular coordination, progressing to narcosis which lasted for several hours. Deaths occurred from 1-4 days after dosing.
Source	:	Shell Chemicals Ltd
Reference	:	(40) (41)
12.09.2001		
Type	:	LD50
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	no data
Value	:	= 4470 mg/kg bw
Method	:	other
Year	:	1970
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable
Source	:	Shell Chemicals Ltd
Reference	:	(7) (42) (43)
26.10.2001		
Type	:	LD50
Species	:	rat
Strain	:	Sherman
Sex	:	male
Number of animals	:	10
Vehicle	:	water
Value	:	= 4760 mg/kg bw
Method	:	other
Year	:	1949
GLP	:	no data

Test substance	:	other TS
Test substance	:	Test substance reported as methyl pentane diol
Result	:	Prostration and narcosis occurred within 4 hours of administration. Necropsy did not reveal any treatment related findings. The authors note that the results agreed with an earlier study which reported an LD50 of 4.7 g/kg. LD50 for this study 4.76 g/kg (4.27-5.5)
Reliability	:	(2) valid with restrictions
Source	:	Shell Chemicals Ltd
Reference	:	(44) (45)
26.10.2001		
Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 3700 mg/kg bw
Method	:	other: No data
Year	:	1974
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reference	:	(46)
26.10.2001		
Type	:	LD50
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 3900 mg/kg bw
Method	:	other: No data
Year	:	1976
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(4) not assignable
Remark	:	Reporting data from NIOSH 1981.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) Shell Chemicals Ltd
Reference	:	(47)
12.09.2001		
Type	:	LD50
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	

Vehicle	:	other: assume undiluted
Value	:	= 3.8 ml/kg bw
Method	:	other
Year	:	1946
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions Not to modern standards but probably acceptable as an indication of acute oral toxicity. This value is similar to other reported values for the acute oral toxicity to mice.
Remark	:	Groups of 6-18 mice received single oral doses of hexylene glycol. The LD50 has been reported as 3.8 ml/kg (3500 mg/kg), the hypnotic LD50 was also determined and reported as being 3.2 ml/kg. Signs of intoxication involved an initial stage of exitement followed by anaesthesia with a loss of righting reflex, incoordination and depression. Respiratory failure preceded cardiac failure. The target organ appears to be the central nervous system. Gross pathological changes in animals which died after 48 hours hypnosis were pneumonia, inflammation of large intestine and pale livers. There appeared to be no gross changes in the brain, kidney or heart.
Reference	:	(48) (49)
26.10.2001		

Type	:	LD50
Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 4.5 ml/kg bw
Method	:	other
Year	:	
GLP	:	no
Test substance	:	no data
Reliability	:	(4) not assignable
Remark	:	LD50 = 4.14 g/kg, signs of intoxication observed within an hour of dosing were loss of muscular coordination, progressing to narcosis which lasted for several hours. Deaths occurred from 1-4 days after dosing.
Source	:	Shell Chemicals Ltd
Reference	:	(41)
26.10.2001		

Type	:	LD50
Species	:	rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 3.2 ml/kg bw
Method	:	other: No data
Year	:	1945
GLP	:	no data
Test substance	:	no data
Reliability	:	(4) not assignable

Remark	:	LD50 = 2.94 g/kg, signs of intoxication observed within an hour of dosing were loss of muscular coordination, progressing to narcosis which lasted for several hours. Deaths occurred from 1-4 days after dosing.
Source	:	Shell Chemicals Ltd
Reference	:	(41)
26.10.2001		

Type	:	LD50
Species	:	guinea pig
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 2.8 ml/kg bw
Method	:	other: No data
Year	:	1945
GLP	:	no data
Test substance	:	no data

Reliability	:	(4) not assignable

Remark	:	LD50 = 2.60 g/kg, signs of intoxication observed within an hour of dosing were loss of muscular coordination, progressing to narcosis which lasted for several hours. Deaths occurred from 1-4 days after dosing.
Source	:	Shell Chemicals Ltd
Reference	:	(41)
26.10.2001		

Type	:	LD50
Species	:	mouse
Strain	:	
Sex	:	male
Number of animals	:	
Vehicle	:	
Value	:	= 3097 mg/kg bw
Method	:	other
Year	:	1956
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Reliability	:	(4) not assignable
Reference	:	(50) (51)
26.10.2001		

5.1.2 Acute inhalation toxicity

Type	:	LC50
Species	:	rat
Strain	:	Sherman
Sex	:	no data
Number of animals	:	6
Vehicle	:	
Exposure time	:	8 hour(s)
Method	:	other
Year	:	1949
GLP	:	no
Test substance	:	other TS

Test condition	:	Test substance reported as methyl pentane diol

Result	:	The LC50 is greater than the saturated vapour concentration at room temperature. No other details available.
Reliability	:	(4) not assignable
Source	:	Shell Chemicals Ltd
Reference	:	39) (45)
11.09.2001		
Type	:	LC50
Species	:	rat
Strain	:	no data
Sex	:	no data
Number of animals	:	6
Vehicle	:	
Exposure time	:	8 hour(s)
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	other TS
Test condition	:	Test substance reported as methyl pentane diol
Reliability	:	(4) not assignable
Remark	:	6 rats were exposed for 8 hours to a mist generated by aerating hexylene glycol at 170C. All rats survived, no other details are available. This is a report of unpublished data from the Mellon Institute, 1949 (Union Carbide).
Reference	:	(52) (45)
11.09.2001		
Type	:	LC50
Species	:	rat
Strain	:	no data
Sex	:	
Number of animals	:	
Vehicle	:	
Exposure time	:	1 hour(s)
Value	:	> .31 mg/l
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	no data
Reliability	:	(4) not assignable
Remark	:	Report of unpublished data, Biofax 1970.
Reference	:	(52)
09.04.2001		

5.1.3 Acute dermal toxicity

Type	:	LD50
Species	:	rat
Strain	:	other: Sprague-Dawley Crl:CD.BR
Sex	:	male/female
Number of animals	:	10
Vehicle	:	other: applied undiluted
Value	:	> 2000 mg/kg bw

Method	:	OECD Guide-line 402 "Acute dermal Toxicity"
Year	:	1987
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Test condition	:	TEST ORGANISMS: Rat Sprague-Dawley - Source: Charles River (UK) Ltd, Margate, Kent. - Age: male 6-8 weeks, female 9-10 weeks - Weight at study initiation: Male 260-284 g, Female 229-239g - Number of animals: 5 male + 5 female - Controls: no ADMINISTRATION: - Type of exposure: Single semi-occluded 24 hour exposure - Concentrations: Undiluted EXAMINATIONS: Mortality, clinical signs (daily after day 1, frequencly on day 1) including examination of treated skin, body weights (weekly). Full macroscopic examination.
Result	:	MORTALITY: No animals died. CLINICAL SIGNS: None DERMAL REACTIONS: No signs of irritation at the application site. BODY WEIGHT: The majority of rats gained in bodyweight over the 14 day observation period. One female showed a small weight loss (-11g). NECROPSY FINDINGS: Renal pelvic dilatation in 1 male and 1 female, enlarged spleen in another male. POTENTIAL TARGET ORGANS: None SEX-SPECIFIC DIFFERENCES: None
Conclusion	:	Rat dermal LD50 >2000 mg/kg, no obvious target organs, no effect on the skin at the application site.
Reliability	:	(1) valid without restriction
Source	:	Shell Chemicals Ltd
Flag	:	Critical study for SIDS endpoint
Reference	:	(53)
06.09.2001		
Type	:	LD50
Species	:	rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 13.3 ml/kg bw
Method	:	other: No data
Year	:	1948
GLP	:	no data
Test substance	:	no data
Reliability	:	(4) not assignable
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) Shell Chemicals Ltd

Reference : (39)
30.10.2001

Type : LD50
Species : rabbit
Strain :
Sex :
Number of animals :
Vehicle :
Value : > 5000 mg/kg bw
Method : other: No data
Year : 1976
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
Reference : (40)
22.03.2001

Type : LD50
Species : Rabbit
Strain : no data
Sex :
Number of animals :
Vehicle : other: undiluted
Value : > 1840 mg/kg bw
Method : other
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable

Remark : 24 hour application, no deaths, transitory mild oedema and erythema.
Reference : (49)
11.09.2001

Type : LD50
Species : Rabbit
Strain : no data
Sex : no data
Number of animals : 5
Vehicle : other: undiluted
Value : > 9.4 ml/kg bw
Method : other: cuff method
Year :
GLP : No
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions
Not to modern standards but probably a reasonable indication of the acute dermal toxicity and compatible with other reported values.

Remark : None of the rabbits died following a 24 hour covered application. Signs of intoxication were limited to dyspnoea in 1 rabbit and mild depression in 2 animals. There was no loss of righting reflex. Local effects were slight erythema in 4/5 rabbits and slight oedema in the remaining rabbit were reversible within 24 hours.

LD50 (9.4 ml/kg) 8.68 g/kg

Reference : (48)
11.09.2001

Type : LD50
Species : Rabbit
Strain : New Zealand white
Sex : Male
Number of animals :
Vehicle : no data
Value : = 8.56 ml/kg bw
Method : other
Year : 1949
GLP : No
Test substance : other TS

Test substance : Test substance reported as methyl pentane diol

Reliability : (4) not assignable

Remark : 24 hour occluded exposure. LD50 8.56 ml/kg (5.77-12.71), assuming a density of 0.923 g/cm3, this is equivalent to 7.9 g/kg. Most survivors showed good weight gains by the end of the 14 day observation period. The skin at the application site showed marked erythema. At necrospy some rabbits showed haemorrhagic lungs, mottled or haemorrohagic livers, kidney damage and congestion of the stomach and intestine.

Reference : (45)
11.09.2001

5.1.4 Acute toxicity, other routes

Type : LD50
Species : mouse
Strain : other: Princeton
Sex : male
Number of animals : 5
Vehicle : other: undiluted
Route of admin. : i.p.
Exposure time :
Value : = 1299 mg/kg bw
Method : other
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Reliability : (2) valid with restrictions

Remark : In addition to the ip LD50 reported the hypnotic dose was also reported. HD50 = 2460 mg/kg.
Source : Shell Chemicals Ltd
Reference : (47) (54)
22.03.2001

Type : LD50
Species : mouse
Strain : no data
Sex :
Number of animals :

Vehicle	:	
Route of admin.	:	i.p.
Exposure time	:	
Value	:	= 1.5 ml/kg bw
Method	:	no data
Year	:	
GLP	:	no
Test substance	:	no data
Reliability	:	(4) not assignable
Source	:	Shell Chemicals Ltd
Reference	:	(41)

09.04.2001

Type	:	LC50
Species	:	mouse
Strain	:	no data
Sex	:	no data
Number of animals	:	
Vehicle	:	other: assume undiluted
Route of admin.	:	i.p.
Exposure time	:	
Value	:	= 5 ml/kg bw
Method	:	other
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(2) valid with restrictions Not to modern standards but appears to give a reasonable indication of acute intraperitoneal toxicity although the value obtained is larger than reported by other studies.
Remark	:	Groups of 6-16 mice received single ip injections of hexylene glycol. The LD50 has been reported, the hypnotic LD50 was also determined and reported as being 2.5 ml/kg. Signs of intoxication involved an initial stage of exitement followed by anaesthesia with a loss of righting reflex, incoordination and depression. Respiratory failure preceded cardiac failure. The target organ appears to be the central nervous system. Gross pathological changes in animals which died after 48 hours hypnosis were pneumonia, inflammataion of the large intestine and pale livers. There appeared to be no gross changes in the brain, kidney or heart.
Reference	:	(48)

12.04.2001

Type	:	LD50
Species	:	rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Route of admin.	:	s.c.
Exposure time	:	
Value	:	= 13000 mg/kg bw
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	no data

Reliability	:	(4) not assignable
Remark	:	The summary information reports this value as the subcutaneous LD50 in rabbits and rodents. The data were obtained from the NLM database 1981.
Reference	:	(47)
09.04.2001		

5.2.1 Skin irritation

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Semiocclusive
Exposure time	:	4 hour(s)
Number of animals	:	3
PDII	:	
Result	:	not irritating
EC classification	:	not irritating
Method	:	other: Directive 84/449/EEC, B.4 equivalent to OECD 404
Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Test condition :

TEST ORGANISMS: Rabbit (males) New Zealand White
- Source: Interfauna UK, Huntingdon, Cambs, UK
- Age: 11-12 weeks
- Weight at study initiation: 2.6 to 2.9 kg
- Controls: No

ADMINISTRATION: To shorn dorsal skin
- Doses: single 4 hour application
- Volume administered or concentration: 0.5 ml undiluted
- Post dose observation period: up to 5 days

EXAMINATIONS: 1 hour after removal of test substance and thereafter 24, 48 and 72 hours after exposure up to day 5.

Result :

AVERAGE SCORE (24+48+72 hour mean score)
- Erythema: 0.4
- Edema: 0

Mean scores for erythema at 24, 48 and 72 hours were 0.67, 0.33 and 0.33 respectively. The maximum individual score for erythema was 1, oedema was not observed at any time point.

REVERSIBILITY: All skin sites were normal by the 5th day (96 hours after exposure).

OTHER EFFECTS: None

Conclusion : Hexylene glycol produced slight transient skin erythema at 2/3 test sites. The mean 24+48+72 hour score for erythema was 0.4. On the basis of these results hexylene glycol is not a skin irritant.

Reliability	:	(1) valid without restriction
Source	:	Shell Chemicals Ltd
Flag	:	Critical study for SIDS endpoint
Reference	:	(55)
06.09.2001		

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	23 hour(s)
Number of animals	:	
PDII	:	.25
Result	:	not irritating
EC classification	:	
Method	:	other
Year	:	1973
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : J. Officiel de la du 21/4/1971 et du 5/6/1973. Arrêté du 5/4/1971 et du 16/4/1973 relatif aux méthodes officielles d'analyses des cosmétiques et produits de beauté . Annexe I: determination de l'indice d'irritation primaire.

Conclusion : Conclusion is made that hexylene glycol is not irritating to the skin.

Reliability : (2) valid with restrictions
Insufficient experimental detail given in the reference to make an independent assessment but no reason to believe that this study does not give a reasonable indication of skin irritation. Conducted to a National Cosmetic Testing Standard.

Source : Shell Chemicals Ltd

Reference : (56)
09.04.2001

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Open
Exposure time	:	no data
Number of animals	:	3
PDII	:	
Result	:	
EC classification	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Method : J. Officiel de la Pepublique Francaise du 29/1/1980. Arrete du 18/12/79 relatif a la methode Officielle pour l'appreciation de l'aggressivite superficielle cutanee par applications iteratives pendant 6 semaines d'un produit cosmetique ou d'hygiene corporelle.

2ml of test material was applied undiluted or as a 10% aqueous dilution to the right and left flanks respectively of 3 rabbits daily for 6 weeks. Daily readings of irritancy were expressed as a weekly average. Histological examination was carried out at 6 weeks, there is mention of a recovery period of 1 week after cessation of exposure.

Result : Hexylene glycol was found to be 'relatively well tolerated' when applied undiluted and was 'well tolerated' as a 10% aqueous solution. Mean maximum irritation indices (MMII) of 1.13 and 0.27 respectively were reported.

Conclusion : The data available indicate that hexylene glycol does not cause significant adverse effects when repeatedly applied to open skin over a prolonged

period.

Reliability : (2) valid with restrictions
Not an OECD/EC method but gives an indication of the effects of repeated exposure, conducted to a National Cosmetic Testing Standard.
Source : Shell Chemicals Ltd
Reference : (56)
09.04.2001

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
PDII :
Result : moderately irritating
EC classification : irritating
Method : other: No data
Year :
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Reliability : (4) not assignable

Remark : Application at a level of 1.84 g/kg to the rabbit skin during 24 h caused a mild oedema and erythema
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Reference : (47) (40) (49)
30.08.2001

Species : rabbit
Concentration : undiluted
Exposure : Open
Exposure time :
Number of animals :
PDII :
Result :
EC classification :
Method : other
Year :
GLP : no data
Test substance : no data

Reliability : (4) not assignable

Remark : Minor irritation was reported in this reference to unpublished data from Union Carbide.
Source : Shell Chemicals Ltd
Reference : (5)
12.09.2001

Species : rabbit
Concentration : undiluted
Exposure : Occlusive
Exposure time : 24 hour(s)
Number of animals :
PDII :
Result :

EC classification	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	no data
Reliability	:	(4) not assignable
Remark	:	24 hour occluded exposure to 465 or 500 mg/kg undiluted material is reported to cause moderate skin irritation. Data obtained from the NLM computerised database 1982.
Source	:	Shell Chemicals Ltd
Reference	:	(47)
12.09.2001		
Species	:	rabbit
Concentration	:	undiluted
Exposure	:	Occlusive
Exposure time	:	24 hour(s)
Number of animals	:	
PDII	:	
Result	:	moderately irritating
EC classification	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	no data
Reliability	:	(4) not assignable
Remark	:	A 24 hour occluded application to intact and abraded skin produced moderate irritation. No further details available. This is a reference to an unpublished reort to RIVM by Moreno, 1976.
Source	:	Shell Chemicals Ltd
Reference	:	(40)
12.09.2001		
Species	:	rabbit
Concentration	:	
Exposure	:	no data
Exposure time	:	24 hour(s)
Number of animals	:	5
PDII	:	
Result	:	slightly irritating
EC classification	:	
Method	:	other
Year	:	1949
GLP	:	no
Test substance	:	other TS
Test substance	:	Test substance reported as methyl pentane diol
Reliability	:	(4) not assignable
Remark	:	Application of 0.01 ml to the clipped belly skin resulted in no reaction in 3 rabbits and capillary injection in 2. The same authors applied an unreported volume to the skin for 4 hours in an "insect repellent test" the score was 9 which was described as of the same order as ethyl hexane diol.

Source : Shell Chemicals Ltd
Reference : (45)
12.09.2001

5.2.2 Eye irritation

Species : rabbit
Concentration : undiluted
Dose : .1 ml
Exposure Time : unspecified
Comment : not rinsed
Number of animals : 3
Result : slightly irritating
EC classification : not irritating
Method : OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year : 1987
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Test condition : TEST ANIMALS: Rabbit
- Strain: New Zealand White Crl:NZW/Kbl.BR
- Sex: 2 female, 1 male
- Source: Charles River (UK), Margate, Kent
- Age: 13-16 weeks
- Weight at study initiation: 2.55 to 2.62 kg
- Number of animals: 3
- Controls: None

ADMINISTRATION/EXPOSURE
- Preparation of test substance: Undiluted
- Amount of substance instilled: 0.1 ml
- Postexposure period: up to 8 days post instillation.

EXAMINATIONS
- Scoring system: As in guideline
- Observation period: 8 days
- Tool used to assess score: Either visually or with a pencil-beam torch or similar to illuminate and magnify the eye. Fluorescein staining was used as considered appropriate with a UV lamp.

Result : INDIVIDUAL SCORES

The individual mean 24, 48 and 72 hour scores for each rabbit tested were 1, 0.7, and 0.7 for corneal capacity, 0, 0 and 0 for iritis, 1, 0.7, and 1 for conjunctival erythema, and 1.3, 0.3 and 1 for chemosis

DESCRIPTION OF LESIONS: All animals developed corneal and conjunctival irritation with 1 hour of instillation. This did not exceed diffuse opacity and stippling of the cornea, crimson appearance of the conjunctivae, chemosis sufficient to cause partial eversion of the eye lids and an ocular discharge. One rabbit showed an intensification of the conjunctival reaction such that at 4 hours after exposure the conjunctivae were crimson, chemosis was sufficient to obscure about 1/2 the eye and ocular discharge was marked. Iridial inflammation was also present in this eye at this observation point.

At 24 hours after exposure all rabbits exhibited diffuse corneal opacity and conjunctival redness not exceeding crimson. Chemosis was sufficient to cause partial eversion of the eyelids and and ocular discharge. Corneal

disruption was confirmed with the use of fluorescein.

REVERSIBILITY: From day 2 resolution was progressive and complete by day 4 in 2 rabbits and day 8 in the third.

OTHER EFFECTS: The initial sting response was classed as 'practically none' and scored as 1 on a scale of 4. This response is described as a few blinks only returning to normal within 2 minutes.

Conclusion : Under the conditions of this test hexylene glycol is a slight eye irritant. Effects are reversible within 8 days.

Reliability : (1) valid without restriction
Source : Shell Chemicals Ltd
Flag : Critical study for SIDS endpoint
Reference : (57)
12.09.2001

Species : rabbit
Concentration : undiluted
Dose : .2 ml
Exposure Time : unspecified
Comment : not rinsed
Number of animals : 4
Result : irritating
EC classification :
Method : Draize Test
Year : 1963
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : METHOD: Draize

Result : Group mean 24+48+72 hours scores and 7 day scores (in parentheses) calculated from the Draize results are as follows:

Redness: 1.8 (1.0)
Chemosis: 1.4 (0.8)
Cornea: 1.4 (1.0)
Iris: 0.8 (0.4)

Total Draize scores are as follows:

1-2 hours 31.6
1 day 28.6
2 days 50.1
3 days 38.8
7 days 21.1

Calculation of Draize scores takes into account the area of corneal opacity and conjunctival discharge.

The descriptive category derived from the total Draize scores using Kay and Callandra's technique is severely irritating (grade 6).

Conclusion : Due to experimental and reporting deficiencies this study should not be used for hazard identification purposes.

Reliability : (2) valid with restrictions
This study has certain drawbacks, firstly the test volume was 0.2 ml instead

of the recommended 0.1 ml. The study was terminated at 7 days when effects were still evident although reduced in all parameters. Individual animal data were not reported only the mean values. For these reasons it is considered that this study should not be used for hazard identification especially as there is a more recent GLP study to OECD guideline 405.

Reference : (58)
05.09.2001

Species : rabbit
Concentration : undiluted
Dose : .1 ml
Exposure Time : unspecified
Comment : not rinsed
Number of animals :
Result :
EC classification :
Method : other
Year : 1973
GLP : no data
Test substance : as prescribed by 1.1 - 1.4

Method : J. Officiel de la du 21/4/1971 et du 5/6/1973. Arrêté du 5/4/1971 et du 16/4/1973 relatif aux méthodes officielles d'analyses des cosmétiques et produits de beauté . Annexe I: determination de l'indice d-irritation oculaire.

The test was carried out using both undiluted material and a 10% aqueous dilution.

Result : Results are reported as an acute ocular irritation index (AOII). The Kay and Callandra scale was used to develop this index. A substance is not irritating if the AOII is <15 and there is no corneal opacity. Exactly how this is derived from the Kay and Callandra method, which is based on the highest maximum total score for all parameters over the first 3 days plus the persistance recorded at 7 days, is not clear.

The AOII for undiluted material was 41.33 out of a possible 110. For the 10% dilution the score was 3.83. The authors comment that the effects of hexylene glycol were reversible at 7 days.

Conclusion : Some degree of irritation was observed with the undiluted material that was reversible by day 7. A 10% aqueous solution was not irritating to the rabbit eye. However, the insufficient study details available, which also prevent the degree of irritation being determined, mean no reliable conclusions can be drawn from this study on hazard identification. However, a recent GLP study conducted to OECD guideline 405 is available

Reliability : (4) not assignable
Reference : (56)
05.09.2001

Species : rabbit
Concentration : undiluted
Dose : other: instillation of an excess
Exposure Time : unspecified
Comment :
Number of animals : 2
Result :
EC classification :
Method : other
Year : 1946

GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Not reported but probably early Draize type from the way the results are reported. Too little experimental detail to assign reliability.
Result	:	Scores are reported for 1, 24 and 72 hours after instillation of an excess of undiluted hexylene glycol into the eye. These scores are 17, 35 and 33 respectively (Draize scores?). 50% of the cornea stained with fluorescein after 24 hours observation. A descriptive rating of severely irritant is given.
Conclusion	:	Study not to modern standards.
Reliability	:	(3) invalid
Reference	:	(48) (49)
12.09.2001		
Species	:	rabbit
Concentration	:	25 %
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	
EC classification	:	
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	no data
Reliability	:	(4) not assignable
Remark	:	A 25% aqueous solution of hexylene glycol is reported as non-irritating to the rabbit eye. This is upublished data reported in 1973 to the CFTA. No further details are available.
Reference	:	(47)
22.03.2001		
Species	:	rabbit
Concentration	:	
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	
EC classification	:	
Method	:	other
Year	:	
GLP	:	no
Test substance	:	no data
Reliability	:	(3) invalid Not comparable to modern protocols.
Remark	:	The method used grade concentrations and volumes, a grade of 4 on a scale of 10 was assigned.
Reference	:	(39)
09.04.2001		
Species	:	rabbit

Concentration	:	
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	
EC classification	:	
Method	:	other
Year	:	
GLP	:	
Test substance	:	no data
Reliability	:	(4) not assignable
Remark	:	These reviewers report that undiluted material produced appreciable irritation and corneal injury which was slow to heal. They refer to unpublished data giving 3 references, this particular description is not given in either the Shell data sheet or the Smyth and Carpenter paper so is probably attributable to Union Carbide unpublished data.
Reference	:	(5)

22.03.2001

Species	:	rabbit
Concentration	:	undiluted
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	
EC classification	:	
Method	:	
Year	:	1949
GLP	:	
Test substance	:	other TS
Test substance	:	Test substance reported as methyl pentane diol
Reliability	:	(4) not assignable
Remark	:	Rabbits eyes were reported as severely burned by 0.1 ml amounts of undiluted methyl pentane diol and moderately necrosed by 0.02 amounts. No scores were reported and no other experimental details were provided. It is not possible to assess the validity of this study.
Reference	:	(45)

11.09.2001

5.3 Sensitization

Type	:	Buehler Test
Species	:	guinea pig
Concentration	:	Induction undiluted occlusive epicutaneous Challenge undiluted occlusive epicutaneous Challenge 50 % occlusive epicutaneous
Number of animals	:	20
Vehicle	:	water
Result	:	not sensitizing
Classification	:	not sensitizing
Method	:	other: Directive 84/449/EEC, B.6 equivalent to OECD 406

Year	:	1992
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Test condition	:	TEST ANIMALS: Guinea pig - Strain: Dunkin-Hartley - Sex: female - Source: D. Hall Ltd, Burton on Trent. - Age: 4-6 weeks - Weight at study initiation: 273 to 408 g - Number of animals: 20 - Controls: 10 ADMINISTRATION/EXPOSURE - Study type: Buehler - Preparation of test substance for induction: Undiluted - Induction schedule: Once a week for 3 consecutive weeks. - Concentrations used for induction: Undiluted - Challenge schedule: Single challenge application - Concentrations used for challenge: Undiluted and 50% aqueous. - Rechallenge: No - Positive control: alpha-hexacinnamaldehyde EXAMINATIONS - Pilot study: Yes
Result	:	RESULTS OF PILOT STUDY: Two pilot studies covering 20- 80% aqueous and undiluted test article. No evidence of irritation. RESULTS OF TEST - Sensitisation reaction: No positive reactions at 24 or 48 hours after challenge in either test or control groups. All scores 0. - Clinical signs: None - Rechallenge: None A positive response was obtained with the positive control alpha-hexylcinnamaldehyde.
Conclusion	:	Hexylene glycol is not a skin sensitiser in the Buehler assay.
Reliability	:	(1) valid without restriction
Source	:	Shell Chemicals Ltd
Flag	:	Critical study for SIDS endpoint
Reference 12.09.2001	:	(59)

5.4 Repeated dose toxicity

Species	:	rat
Sex	:	male/female
Strain	:	other: Sprague-Dawley Crl CD (SD) IGS BR
Route of admin.	:	gavage
Exposure period	:	90 days
Frequency of treatment	:	daily (7 days/week)
Post obs. period	:	4 weeks
Doses	:	0, 50, 150 and 450 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL	:	= 450
LOAEL	:	=
Method	:	OECD Guide-line 408 "Subchronic Oral Toxicity - Rodent: 90-day Study"

Year : 1981
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Test condition : TEST ORGANISMS
- Age: 6 weeks approx.
- Weight at study initiation: Males 162-206 mean 190g, Females 135-192 mean 161g.
- Number of animals: 20M+20F at the top dose and control levels, 10M+10F of these were retained at the end of exposure period for a 4 week treatment free period. 10M+10F were dosed at the mid and low dose.

ADMINISTRATION / EXPOSURE
- Duration of test/exposure: 13 weeks
- Type of exposure: gavage
- Post exposure period: 4 weeks top dose and controls only.
- Vehicle: Purified water
- Concentration in vehicle: 10, 30 and 90 mg/l.
- Total volume applied: 5 ml/kg
- Doses: 50, 150 and 450 mg/kg/day

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: daily
- Mortality: twice daily during treatment, once a day in the treatment free periods and at weekend and public holidays.
- Body weight: weekly
- Food consumption: weekly over the 7 day period
- Water consumption: weekly over the 7 day period
- Ophthalmoscopic examination: In control and top dose animals at beginning of treatment and in week 13.
- Haematology: During week 13.
- Biochemistry: During week 13 and at the end of the treatment free period for parameters where an effect was noted in the week 13 analysis.
- Urinalysis: During week 13 (14 hour overnight collection period, without access to food). Also at the end of the treatment free period for males only.

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
-Organ weights: adrenals, brain, epidiymes, heart, kidneys, liver, lungs, ovaries, spleen, testes, thymus, thyroids with parathyroids. In a deviation from the OECD guideline, the uterus was not weighed.
- Macroscopic: Full post mortem examination including external surfaces, all orifices, cranial cavity, external surface of the brain and spinal cord, thoracic, abdominal and pelvic cavities and their organs and tissues, neck and associated organs and tissues.
- Microscopic: Control and high dose: all tissues listed in the protocol (including testes, prostate, seminal vesicles, epididymes, ovaries, vagina and uterus) together with liver, kidneys, stomach and forestomach of males at the end of the treatment free period. Stomach and forestomach of females at the end of the treatment free period.
Low and Mid dose: liver, lungs, stomach and forestomach and all macroscopic lesions.
Premature decedent or early sacrifice: All tissues from any animal which died or was killed prematurely from any group.

ADDITIONAL HISTOLOGY

Subsequent to the main study additional specialised staining of kidney sections was undertaken to identify the acidophilic globules observed in male rat kidneys. The stains used were PAS to identify hyaline droplet

degeneration and Massons Trichrome stain for alpha-2-microglobulins.

Sections from all male rats from the main study (but not the recovery groups) were examined. The results were reported in an addendum to the study report.
OTHER EXAMINATIONS: Functional Observation Battery. Carried out at least 12 hours after dosing on the following study days:

Detailed clinical observation: on before treatment day 1 and in weeks 4, 8 and 12 on the 1st 5 surviving rats of each sex and group.

Reactivity: observation was made before treatment day 1 and in week 12 on the 1st 5 surviving rats of each sex and group.

Motor activity: observation was made over 30 minutes before treatment day 1 and in week 12 on the 1st 5 surviving rats of each sex and group.

STATISTICAL METHODS: A decision sequence for determining appropriate statistical tests was followed using an initial test for normality of distribution (Kolmogorov-Lilliefors' test) and appropriate tests subsequently.

Result : ACTUAL DOSE RECEIVED BY DOSE LEVEL: The achieved dose was within 10% of the nominal dose at all dose levels. The stability of the test material was confirmed over a 9 day period at nominal concentrations of 2 and 200 mg/ml.

TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:

- Mortality and time to death: 1 control female was found dead on day 90. One top dose female was killed prematurely on day 80. The changes seen in this top dose level animal included an oesophageal perforation and were therefore considered accidental (mis-dosing).

- Clinical signs: None attributable to treatment. Soft faeces, regurgitation, areas of hair loss and abnormal growth of teeth were noted at a low incidence, without dose relationship, in both control and treated groups.

- Body weight gain: There were no significant differences between treated and control groups.

- Food consumption: Slight increases in food consumption (up to 12%), occasionally of statistical significance (at weeks, 1, 10, 11 and 12) were observed in males at 450 mg/kg. The overall food consumption was similar between groups and the slight increase in males (maximum 12% at week 11) did not attain statistical significance. There was no corresponding increase in bodyweight.

-Water consumption: Slightly higher weekly mean consumption (up to 28%) was seen in males only at 150 and 450 mg/kg/day. This reached statistical significance at weeks 2, 11 and/or 13 only.

- Ophthalmoscopic examination: No treatment related changes.

- Functional Observational Battery (FOB): Examination of animals in the FOB revealed no treatment related differences between groups.

- Clinical chemistry: Changes in blood biochemistry considered treatment related were increased cholesterol in the high dose groups of both sexes (m +69%, F +26%) and decreased glucose levels in males and females at 150 (m -8%, F-3%) and 450 (m -11%, f -8%) mg/kg. These were considered by

the authors to be related to the adaptive changes observed in the liver.

Other changes which attained marginal statistical significance (1-3% over controls) were higher mean sodium levels in all treated male and female groups, also decreased chloride values in top dose males and higher chloride values in females at all dose levels. Most values were within the performing laboratory's historical control range (sodium) or without a similar trend in both sexes (chloride) and were therefore not considered of toxicological significance.

- Haematology: The only change in haematological parameters considered of significance was a dose related statistically significant increase in mean fibrinogen level in males at 150 (+11%) and 450 (+15%) mg/kg and females at 450 mg/kg (+19%). This increase was considered by the authors to be secondary to the inflammatory reaction seen in the stomach and forestomach.

- Urinalysis: Urinalysis revealed a lower mean urinary pH value (pH 6.2 compared to pH 7.0 in controls) and slightly higher specific gravity (+1.6%) in top dose males only. These observations were considered related to the increased kidney weights in males at 150 and 450 mg/kg and the increased incidence of acidophilic globules in the cortical tubular epithelium of male rat kidneys at these dose levels. A slightly higher incidence of tubular basophilia and peritubular fibrosis were found in these same treatment groups compared to controls (details below). This was considered by the authors to be secondary to the abnormal tubular accumulation of acidophilic globules.

- Organ weights: Increases in liver and kidney weights were associated with microscopic findings in these organs and are therefore considered treatment related.

Liver weights were significantly increased in top dose males and females (absolute m +31%, f +14%; relative m +27%, f +8%). At the end of the recovery period top dose female absolute and relative liver weights and male absolute weights were comparable with controls while male relative liver weights showed partial reversal in recovery animals being (+11%) higher after the recovery period. Increases in females did not attain statistical significance.

Kidney weights were significantly increased in top and mid dose males absolute kidney weights were increased 33% at the top dose while relative weights were +13% and +28% at mid and top doses respectively. Following the 4-week recovery period absolute and relative kidney weights showed recovery the difference from controls being +16% and +15% respectively.

Adrenal weights (absolute) were increased in males at all dose levels (+18%, +16% and +19% at low, mid and high dose respectively) and females at the top dose level(+17%). Relative adrenal weights were increased in top and mid dose males (+20% and +15%) respectively. At the end of the recovery period top dose female adrenal weights and relative male adrenal weights were comparable with controls while male absolute adrenal weights showed partial reversal (+11%). These increases may have been caused by cortical cell hypertrophy which occurred in 2/10 males and 3/10 females at 450 mg/kg/day. As these changes were observed in so few animals without a dose response effect, the change was not considered of toxicological significance and was possibly attributable to stress.

Changes in spleen and thymus weight were not considered of toxicological

significance because they were not related to histopathological change, not dose related and not observed in both sexes.

- Gross pathology: The only changes considered treatment related were a grey/green colouration of the kidney in 2/10 males at 150 mg/kg and 8/10 at 450 mg/kg/day. Enlarged kidneys were noted in 1/10 rats at 150 mg/kg and 5/10 rats at 450 mg/kg/day. These corresponded with microscopic kidney changes observed.

- Histopathology: Treatment related findings were seen in the liver, kidneys, stomach and forestomach.

Hepatocellular hypertrophy in the absence of degenerative or necrotic change was observed in top dose animals of both sexes (m 10/10, f 5/10) and in males at 150 mg/kg (5/10).
These effects reversed over the 4 week recovery period. This is considered an adaptive response to metabolic demand. Similar effects were observed in the range finding study.

Kidney changes and increased kidney weight observed only in male rats were considered, by the authors, to be typical of male rat specific alpha 2-microglobulin nephropathy. The presence of acidophilic globules in the cortical tubular epithelium was recorded in 9/10 males for control groups (main study and recovery controls) and 10/10 males for all treatment groups. Treated recovery males showed an incidence of 5/10. The severity of the findings (based on incidence and grade) was 1.9, 2.7, 3.7 and 4.0 for controls, 50, 150 and 450 mg/kg respectively. Recovery controls were given a severity rating of 1.2 and treated animals a rating of 1.0. In males only at 150 and 450 mg/kg, increased incidences of findings in the kidneys were observed such as basophilic tubules, interstitial monocyte aggregation and dilatated medullary tubules were observed, most notably, peritubular fibrosis in males (at 150 mg/kg 6/10, and at 450 mg/kg, 9/10). These findings were partially reversed in recovery animals (450 mg/kg) with peritubular fibrosis being present in 3/10 males. These male rat specific kidney changes were also observed at both 200 and 1000 mg/kg in the 14 day range finding study. No direct measurement of alpha 2-microglobulin was made at the time these studies were carried out. Subsequently other kidney sections from the 90 day study were stained to confirm that the acidophilic globules were alpha 2-microglobulin (Massons Trichrome stain) and not indicative of hyaline droplet degeneration (PAS) All sections stained negative for PAS and positive for Massons Trichrome indicating that the droplets were alpha 2-microglobulins .
Changes occured in the forestomach and, to a lesser extent, in the stomach of rats of both sexes at 150 and 450 mg/kg, which were considered to reflect local irritation. The stomach and forestomach of rats of both sex administered 1000 mg/kg/day in the 14 day range finding gavage study received microscopic examination. At this time point there were no changes in either stomach or forestomach.

These changes in the forestomach included hyperplasia (males 3/10 at 150 mg/kg, males 8/10 and females 4/10 at 450 mg/kg; after recovery males 3/10, females 2/10) and hyperkeratosis (males 2/10 at 150 mg/kg, males 8/10 and females 4/10 at 450 mg/kg; after recovery males 3/10, females 2/10). Inflammatory cell infiltration and oedema of the mucosa and sub-mucosa was also observed in high dose rats of both sexes some changes were also observed in at 150 mg/kg.

Effects in the stomach were confined to oedema and inflammatory cell infiltration of the submucosa with full recovery over 4 weeks.

In male rats only at 50 mg/kg very minor effects were observed (inflammatory cell infiltration of the stomach 1/10 and forestomach submucosa 2/10), which were considered within normal historical control limits.

There were no treatment related microscopic findings in other organs examined including the ovaries, uterus (horns & cervix), vagina, testes, epididymes, prostate and seminal vesicles.

Conclusion : Changes in the liver (hepatocellular hypertrophy and increased liver weights) are considered a normal physiological adaptive response related to xenobiotic metabolism and are not toxicologically significant.
In the kidney, there was a higher incidence of acidophilic globules in all treated males. At 150 and 450 mg/kg, kidney histopathology and increased kidney weights were confined to male rats. The presence of acidophilic globules together with the male-specific nature of the renal response was indicative of male rat specific alpha-2-microglobulin nephropathy, which is not relevant to human exposure. The identity of the acidophilic globules was subsequently confirmed as alpha-2-microglobulin by an appropriate staining technique (Massons Trichrome stain).
The local changes in the forestomach and to a lesser extent the stomach at 150 mg/kg and above are indicative of a local irritative effect resulting from the oral gavage procedure. Effects in the stomach were reversed after a 4 week treatment free period. There were no adverse effects on other organs including the reproductive organs.

Reliability : (1) valid without restriction

Source : Shell Chemicals Ltd
Flag : Critical study for SIDS endpoint
Reference : (60)
06.09.2001

Species : rat
Sex : male/female
Strain : other: Sprague-Dawley Crl CD (SD) IGS BR
Route of admin. : gavage
Exposure period : 15 days
Frequency of treatment : daily
Post obs. period : No
Doses : 0 (vehicle only) 40, 200, 1000 mg/kg
Control group : yes, concurrent vehicle
Method : OECD Guide-line 407 "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-d Study"
Year : 1981
GLP : yes
Test substance : As prescribed by 1.1 - 1.4

Test condition : TEST ORGANISMS
- Age: 6 weeks old
- Weight at study initiation: males 181-217g females 152-191 g
- Number of animals: 6 male + 6 females/dose level

ADMINISTRATION / EXPOSURE
- Duration of test/exposure: 2 weeks
- Vehicle: Purified water
- Concentration in vehicle: 8, 40, 200 mg/l
- Total volume applied: 5 ml/kg

CLINICAL OBSERVATIONS AND FREQUENCY:

- Haematology: Usual haematology tests
- Biochemistry: Usual blood chemistry

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Organ weights: A limited range of tissues/organs were weighed. For all animals, liver, kidneys, spleen, adrenal glands.
- Macroscopic: Complete post mortem examination for all animals.
- Microscopic: A limited range of tissues/organs were examined. For the first 5 animals selected from each group of 6, all macroscopic lesions at all dose levels plus the liver, kidneys, stomach and forestomach at 1000 mg/kg, liver at 200 mg/kg in both sexes, kidneys from males only at 200 mg/kg, adrenals and spleen from females only at 200 and 1000 mg/kg.

Result : NOAEL (NOEL), LOAEL (LOEL): Range-finding study for 90 day test. Dose levels chosen for the 90 day study were 50, 150 and 450 mg/kg/day. NOAEL for systemic toxicity 1000 mg/kg the only signficant effects were male rat specific nephropathy and adaptive liver change (hepatocellular hypertrophy with no degenerative change)

TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death: There were no mortalities.

- Clinical signs: No notable clinical signs.

- Body weight: Final bodyweights were comparable across the dose levels although there was a slightly higher bodyweight gain (15%) in males only at 1000 mg/kg/day.

- Food consumption: Similar in treated and control groups.

- Clinical chemistry: Small differences from control animals noted in test animals were occasionally statistically significant at $P<0.05$ or $P<0.01$ but were generally within or close to the performing laboratory's historical control ranges. Notably, higher mean cholesterol levels in males at 200 (38%) and 1000 mg/kg (44%), higher mean calcium levels (<5%) in females at 200 mg/kg and in both sexes at 1000 mg/kg, higher mean total protein level (10%) in females at 1000 mg/kg, and lower alkaline phosphatase activity (38%) in males at 1000 mg/kg)."

- Haematology: No treatment related effects.

- Organ weights: Slightly increased higher absolute (males 23%, females 12%) and relative liver weights (males 22%; females 16%) and kidney weights (males only 18-20%) were observed at 1000 mg/kg and considered treatment related as they were associated with histopathological changes. Increased adrenal weights (22-26%) and lower spleen weights (18-19%) in top dose females were not associated with microscopic findings and not considered of toxicological significance.

- Gross pathology: No notable findings.

- Histopathology: Minimal to slight hepatocellular hypertrophy was observed in all top dose animals, there was no evidence of degenerative change. There was an increased incidence of acidophilic globules in the cortical tubules of male rat kidneys at both 200 (4/5; minimal to moderate) and 1000 (5/5; moderate to marked) mg/kg/day. There was a dose relationship in the severity of these findings. These changes were ascribed by the author (but not confirmed by specific assay) to the accumulation of sex-linked alpha-2-microglobulin which occurs in male rats and is not considered relevant to

humans.

There were no histopathological changes in the stomach and forestomach.

Conclusion : In this range-finding study used to determine dose-levels to be used in the 90 day study, increased liver weight and hepatic cell hypertrophy at 1000 mg/kg/day is considered to be a normal physiological response to increased metabolism in the liver and is not toxicologically significant. A dose-related increase in the incidence and severity of acidophilic globules in the kidneys of males seen at 200 mg/kg/day and above may be indicative of the accumulation of sex linked alpha microglobulin, however, in this preliminary assay, differential staining to confirm the identity of the acidophilic globules was not performed.

Reliability : (1) valid without restriction

Source : Shell Chemicals Ltd
Reference : (61)
06.09.2001

Species : rat
Sex : male/female
Strain : other: Sprague-Dawley Crl CD (SD) IGS BR
Route of admin. : gavage
Exposure period : 14 days
Frequency of treatment : daily
Post obs. period : none
Doses : 30, 300, 3000
Control group : yes, concurrent vehicle
NOAEL : = 300 mg/kg bw
LOAEL : = 1000 mg/kg bw
Method : OECD Guide-line 407 "Repeated Dose Oral Toxicity - Rodent: 28-day or 14-d Study"
Year : 1981
GLP : yes
Test substance : As prescribed by 1.1 - 1.4

Test condition : TEST ORGANISMS
- Age: Males 7-9 weeks, Females 9-11 weeks
- Weight at study initiation: males 242.2-293.4, females 241.7-270.9
- Number of animals: 5 male +5 female per treatment group

ADMINISTRATION / EXPOSURE
- Duration of test/exposure: 14 days
- Vehicle: distilled water
- Concentration in vehicle: 6, 60, 200 mg/ml
- Total volume applied: 5 ml/kg
- Doses: 30, 300 and 1000 mg/kg

CLINICAL OBSERVATIONS AND FREQUENCY:
- Clinical signs: daily plus detailed clinical examiniation after 1 week.
- Mortality: Twice daily
- Body weight: Before dosing on day 1 and on days 4, 8 and 12 of treatment.
- Food consumption: Weekly

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC):
- Macroscopic: Full necropsy
- Microscopic: Adrenals*, heart, kidneys*, liver*, spleen*, testes &

epididymes* gross lesions were fixed but not examined. * organ weights measured.

Result : NOAEL (NOEL), LOAEL (LOEL): Range finding study for the developmental toxicity study. NOAEL 300 mg/kg.

ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX not measured

TOXIC RESPONSE/EFFECTS BY DOSE LEVEL:
- Mortality and time to death: all survived
- Clinical signs: none treatment related
- Body weight gain: High dose males gained significantly more weight than controls in the 2nd study week. High dose females showed a slightly higher weight gain but this was not statistically significant.
- Food consumption: Apparent dose related increase in males at all dose levels, slight increase in females a 30 and 300 mg/kg. No statistics carried out.
- Organ weights: Dose related increase in adrenal and kidney weights in both sexes significant at the high dose level. Increased liver weights were apparent in all treated male groups and high dose females, statistical significance was attained in high dose males and females and mid-dose males. Spleen, testes and epididymis weights were unaffected by treatment.
- Gross pathology: Large livers were observed in one male and one female from the high dose group.
- Histopathology: Not carried out

Reliability : (1) valid without restriction

Source : Shell Chemicals Ltd
Reference : (62)
09.04.2001

Species : rat
Sex : male/female
Strain : No data
Route of admin. : drinking water
Exposure period : 8 months
Frequency of treatment :
Post obs. period :
Doses : Average dose males 585 mg/kg/day, females 592 mg/kg/day
Control group :
Method : other
Year : 1955
GLP : No
Test substance : As prescribed by 1.1 - 1.4

Method : 5 male + 5 female rats were exposed at the single dose level and in the control group. The animals were weighed and examined at weekly intervals. Food and water consumption was recorded. Erythrocyte and lecocyte counts were performed monthly on tail blood. Animals were terminated by decapitation. Eye, brain, heart, kidney, spleen, gonad, adrenal and liver tissues may have been studied histologically. (The reference notes that in some cases only liver sections were viewed microscopically). It is not clear whether this was the case for hexylene glycol.

Result : There was no effect on fluid or food consumption and no growth retardation. Blood counts were normal. There were no histopathological changes attributable to treatment.

Conclusion	:	Exposure of rats to approximately 590 mg/kg hexylene glycol/day in the drinking water for 8 months had no adverse effects on the limited parameters examined.
Reliability	:	(4) not assignable
Source	:	Shell Chemicals Ltd
Reference	:	(63)
03.09.2001		
Species	:	rat
Sex	:	male/female
Strain	:	other: Harlan-Wistar derived
Route of admin.	:	inhalation
Exposure period	:	7 hours/day for 9 days
Frequency of treatment	:	9 days exposure in a 14 day period
Post obs. period	:	no
Doses	:	0.7 mg/l as an aerosol
Control group	:	no
Method	:	other
Year	:	1976
GLP	:	no
Test substance	:	As prescribed by 1.1 - 1.4
Method	:	10 rats and one rabbit were exposed to hexylene glycol in aerosol form for 7 hours/day for 9 days in 14. The mean particle size was 1um. Gas chromatographic analysis of the chamber atmosphere indicated a mean hexylene glycol concentration of 0.7 mg/l (140 ppm). The rabbit eyes were examined daily for corneal damage using an aqueous staining technique. Tissues collected at necropsy included the lung, trachea, heart, liver, kidneys, spleen, adrenals, thyroid, parathyroid, oesophagus, bronhci, thymus glands and cervical lymph nodes. Body weight gain, kidney and liver weights were compared using Bartletts test and the Students t-test.
Result	:	There were no overt signs of toxicity and no effects on body weight gain or absolute or relative liver or kidney weights. There were no microscopic lesions in major organs. Histological examination of the windpipe revealed mild lesions of the trachea, comprising tracheal congestion in 2 rats and a single instance of submucosal naemorrhage. Examination of tissues from the rabbit revealed 'mild hyperplasia of tracheal epithelium and tracheal congestion with patchy interstitial pneumonia'. These changes were considered by the authors as the result of a mild insult to the respiratory system which they considered would be reversible.
Reliability	:	(4) not assignable
Source	:	Shell Chemicals Ltd
Reference	:	(52) (64)
03.09.2001		
Species	:	rat
Sex	:	male/female
Strain	:	no data
Route of admin.	:	oral unspecified
Exposure period	:	90 days
Frequency of treatment	:	daily
Post obs. period	:	

Doses	:	43, 78 and 310 mg/kg/day
Control group	:	no data specified
Method	:	other
Year	:	1949
GLP	:	no
Test substance	:	other TS
Test substance	:	Test substance reported as methyl pentane diol
Method	:	Groups of 5M+5F Sherman rats received 0, 0.06, 0.12 or 0.5% in the diet for 90 days (0, 43, 78 and 310 mg/kg/day.
Result	:	There were no mortalities in this study. There were no statistically significant effects on food intake, body weight gain and liver and kidney weights. Cloudy swelling of the liver was reported in 1/5 and 2/5 rats at 43 and 78 mg/kg/day respectively. No liver change was observed at 310 mg/kg/day. No toxicologically significant effects were observed in this study indicating a 90 day NOAEL of > 310 g/kg/day.
Reliability	:	(4) not assignable
Source	:	Shell Chemicals Ltd
Reference 11.09.2001	:	(65) (45)
Species	:	rat
Sex	:	male/female
Strain	:	other: CFE
Route of admin.	:	oral feed
Exposure period	:	89 days
Frequency of treatment	:	daily
Post obs. period	:	none
Doses	:	0, 0.01, 0.05, 0.25 or 1.25% in the diet.
Control group	:	yes
Method	:	other
Year	:	1961
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Groups of 10M+10F rats received the test substance in the diet for 87-89 days. Controls received untreated diet. At the end of the study the animals were killed by exsanguination. Tissue samples were taken from lung, liver, kidney, heart, spleen, pancreas, stomach, duodenum, descending colon, testis or ovary, oesophagus, trachea, thyroid, adrenal and urinary bladder from all test and control animls for macroscopic and microscopic examination. However only the kidney, liver, heart, spleen and testes from 4 male rats at each dose level (except 0.01%) and 4 male controls were actually examined. The animals were selected following the macroscopic examination to reveal the maximum information about the toxic effects of the test substance and were therefore not randomly chosen. The actual dose received in mg/kg/day was for males, 0, 7, 37, 190 and 977 and for females 0, 8, 40, 212 and 1020.
Result	:	There were no deaths during the course of the study. There were no treatment related effects on food consumption. A small but significant reduction in female body weight gain was observed at the highest dose level of 1.25%. At this dose level there was also a significant increase in

liver and kidney weights in both sexes. A decrease in male kidney weight and female liver weight at 0.5% was not considered of toxicological significance in the absence of such effects at the 0.25% level.

At dietary concentrations of 1.25 and 0.25% there was evidence of cloudy swelling in both liver (central cords) and kidneys (proximal tubules). In the kidneys at these dose levels there was evidence of hyaline droplets in the proximal tubules and lipoid deposits in the glomeruli and renal tubules.

The spleen at all dose levels showed indications (haemosiderin deposits) of increased erythrocyte fragmentation.
The incidence was not dose related.

We can conclude that at the dietary concentration of 0.05% (500 ppm or 37 mg/kg/day) the effects in male rats are apparently minimal. At higher dose levels there is some evidence of an effect on the liver and kidney however the interpretation of all this data can only be considered as preliminary in view of the limited numbers of animals examined microscopically.

The results of the gross pathological examination were not reported.

Reliability : (4) not assignable

Source : Shell Chemicals Ltd
Reference : (66) (67)
29.08.2001

Species : rabbit
Sex : male
Strain : no data
Route of admin. : dermal
Exposure period : 15 weeks
Frequency of treatment : 5 days/week for up to 90 applications
Post obs. period : none
Doses : 461, 923 and 1846 mg/kg/day
Control group : other: glycerol
Method : other
Year : 1950
GLP : no
Test substance : as prescribed by 1.1 - 1.4

Method : Repeated uncovered applications, 5 days/week for 90 applications. Groups of 10-12 rabbits were exposed at each dose level. The test material was gently rubbed into the clipped belly of each rabbit for 1 minute in every 15 minutes over a period of 1 hour. At the end of this time excess liquid was blotted off.

The initial dose levels were 1 ml/kg and 2 ml/kg/day. The control animals received glycerol at 2 ml/kg. Due to mortality, unrelated to treatment, a second study was started using hexylene glycol at 1.0 and 0.5 ml/kg/day and glycerol at 1.0 ml/kg/day.

Sections of skin from the treatment site plus liver and kidney were examined microscopically.

Assuming a density of 923 mg/cm3 the actual dose levels applied were 461, 923 and 1846 mg/kg/day.

Result : In the first experiment 2/11 rats receiving 2 ml/kg and 8/10 rats given 1

ml/kg hexylene glycol died due to respiratory infection or diarrhoea. 5 survivors at the higher dose level showed slight cloudy swelling of the liver. The two survivors at 1 ml/kg/day showed no histopathological changes in the liver or kidneys. 8/12 rabbits receiving glycerol also died.

In the second study mortality was also high with 6/10 rabbits at 1 ml/kg and 4/11 at 0.5 ml/kg dying of lung infection. None of the survivors at 1 ml/kg showed any histopathological change in the liver or kidney. One survivor at 0.5 ml/kg showed cloudy swelling of the liver but the kidneys appeared normal.

The effects on the skin were described as 'loss of epithelium and scrappy epidermis' for all treated and control groups. The authors considered this due to friction rather than a toxic effect.

Conclusion : The study gives limited information concerning the effect of repeated inunction due to intercurrent infection amongst the test animals and the method of application. Changes in the skin at all dose levels were not attributed to the test compound.
There were no effects considered treatment related at dose levels of 1 ml/kg/day.

Reliability : (3) invalid
This study is considered invalid due to the high incidence of death due to respiratory infection in all test groups. Also the method of application was unusual and the actual dose level could not be accurately determined. There was potential for ingestion as the site of application was uncovered abdominal skin.

Source : Shell Chemicals Ltd
Reference : (52) (6) (68)
12.09.2001

Species : rat
Sex : no data
Strain : no data
Route of admin. : oral unspecified
Exposure period : 9 days
Frequency of treatment : daily
Post obs. period :
Doses : 1/2 LD 50
Control group : no data specified
Method : other: No data
Year : 1945
GLP : no
Test substance : As prescribed by 1.1 - 1.4

Result : The following microscopic changes were reported following repeated oral exposure to 1/2 LD50 for 9 days. No other details of this study are available.

Liver: slight hyperplasia of hepatic cells with increase in basophilic granules and slight hyaline change in centrolobular cells.

Kidney: Possible excess of proteinaceous material in the renal tubular lumens.

Conclusion : In the absence of further experimental detail no conclusions can be drawn from this study.

Reliability : (3) invalid

Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) Shell Chemicals Ltd
Reference 17.04.2001	:	(40) (41)
Species	:	rat
Sex	:	male
Strain	:	no data
Route of admin.	:	other: oral in milk
Exposure period	:	129 days
Frequency of treatment	:	daily
Post obs. period	:	no
Doses	:	150 and 200 mg/day
Control group	:	yes, concurrent vehicle
Method	:	other: No data
Year	:	1958
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Non-standard method. Groups of 10 male rats received the test material daily administered in 10 ml milk. The rats were offered the milk in deep containers to reduce evaporation. There was evidence of unpalatability of test material solutions. Paired feeding was introduced between the top dose and control groups to adjust for the different intake of milk. Exposure period 129 days.
Result	:	Rats at the 100 mg/day level consumed on average 98 mg hexylene glycol while rats at the 200 mg/day level consumed approx. 150 mg/day. No clinical signs or behavioural changes, no noteworthy changes bodyweight. No histopathological changes in the liver or testes. Minor kidney tubular changes in 3 rats.
Conclusion	:	No conclusions can be drawn from this study.
Reliability	:	(3) invalid
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) Shell Chemicals Ltd
Reference 21.03.2001	:	(4) (69) (40)
Species	:	mouse
Sex	:	male
Strain	:	no data
Route of admin.	:	other: orally in milk
Exposure period	:	57 - 81 days
Frequency of treatment	:	daily
Post obs. period	:	no
Doses	:	5, 10 and 20 mg/day
Control group	:	no
Method	:	other: see methods
Year	:	1954
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Non-standard. Groups of 12 male mice received the test material daily

administered in 2 ml milk. The mice were offered the milk in small well fixed glass funnels. Apparently the mice consumed the milk within a few minutes. 6 mice from each group were killed by coal gas 57-60 days after the beginning of the experiment the remainder were killed on days 77-81.

Result : Initial weight loss not dose related. No significant histopathological findings in the liver or testes top dose animals (lower doses were not examined).

Reliability : (3) invalid

Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd

Reference : (4) (69) (40)
21.03.2001

5.5 Genetic toxicity 'in vitro'

Type : Ames test
System of testing : Salmonella Typhimurium TA 1535 ; TA 1537 ; TA 1538 . TA 98 ; TA 100; Escherichia coli WP2 uvr A pKM 101
Concentration : 31.25 to 4000 microgram/plate
Cycotoxic conc. : >4000 microgram/plate
Metabolic activation : with and without
Result : negative
Method : other: Ames
Year : 1975
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Equivalent to OECD 471 adopted 1997. Deviation lack of statistical analysis.

Test condition : SYSTEM OF TESTING
- Metabolic activation system: rat liver microsomal activation, Arochlor induced.

ADMINISTRATION:
- Dosing: single application
- Number of replicates: Tests were carried out in triplicate with 2 replicate assays carried out on different days.
- Application: Aqueous solutions of test material applied to top agar
- Positive and negative control groups and treatment:
Positive controls 20 microgram/plate benzo(a)pyrene, potassium dichromate and neutral red, 5 m icrgram/plate sodium azide. Solvent control was water.

CRITERIA FOR EVALUATING RESULTS: Reproducible values of 2.5 X control value or greater are considered to indicate a mutagenic response.

Result : GENOTOXIC EFFECTS:
- With and without metabolic activation: no increased incidence in reverse mutation rate.

FREQUENCY OF EFFECTS: Maximum increase in number of reverse mutations for test materials expressed as the ratio mean revertant colonies/treated plate over mean revertant colonies/control plate is 1.4 with and without S9. All postive controls gave increases greater than 2.5 over

controls either with or without metabolic activation.

PRECIPITATION CONCENTRATION: No precipitation

CYTOTOXIC CONCENTRATION: >4000 microgram/plat with and without metabolic activation.

TEST-SPECIFIC CONFOUNDING FACTORS: None

Conclusion : Hexylene glycol does not increase the reverse mutation rate in Salmonella typhimurium strains TA98, 100, 1535, 1537 or 1538 or in Escherichia coli WP2 uvr A pKM 101 in the presence or absence of rat liver metabolic activation fraction at dose levels up to 4000 microgram/plate.

Reliability : (1) valid without restriction
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Flag : Critical study for SIDS endpoint
Reference : (70) (71)
26.07.2001

Type : Mitotic recombination in Saccharomyces cerevisiae
System of testing : Saccharomyces Cerevisiae JD1
Concentration : 0.01 to 5.0 mg/ml
Cycotoxic conc. : > 5.0 mg/ml
Metabolic activation : with and without
Result : Negative
Method : other
Year : 1981
GLP : Yes
Test substance : as prescribed by 1.1 - 1.4

Method : Equivalent to OECD 480 adopted 1997. Deviation was absence of statistical analysis.

Test condition : SYSTEM OF TESTING
- Deficiences/Proficiences: Histidine-4 and tryptophan-5
- Metabolic activation system: Rat liver, Arochlor 1254 induced

ADMINISTRATION:
- Dosing: Single administration
- Number of replicates: 3/4 replicates, 2 assays
- Application: Aqueous solutions of hexylene glycol were added to the liquid suspension culture
- Positive and negative control groups and treatment: positive controls received 4-nitroquinoline-N-oxide 0.00025 mg/ml and cyclophosphamide 1.25 mg/ml, negative controls water.
- Pre-incubation time: None.

CRITERIA FOR EVALUATING RESULTS: Values of greater than twice control values were considered to indicate a mutagenic response.

Result : GENOTOXIC EFFECTS:
- With and without metabolic activation: No increase in mitotic gene conversion rate.

FREQUENCY OF EFFECTS: No increase in prototrophs in excess of twice control levels. Positive controls produced increases in mitotic gene conversion indicative of a mutagneci response.

PRECIPITATION CONCENTRATION: No precipitation.

CYTOTOXIC CONCENTRATION:
- With metabolic activation: >5 mg/l
- Without metabolic activation: >5 mg/l

STATISTICAL RESULTS: No statistical analysis.

Conclusion : Hexylene glycol does not induce mitotic gene conversion in Saccharomyces cerevisiae JDI in the presence or absence of rat liver metabolising fractions at dose levels up to 5 mg/ml.

Reliability : (1) valid without restriction
Source : Atochem Paris la Defense
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Reference : (70) (71)
09.04.2001

Type : Chromosomal aberration test
System of testing : Chinese hamster ovary (CHO) cells
Concentration : 1250, 2500 and 5000 micrograms/ml
Cycotoxic conc. : >5000 mcirograms/ml
Metabolic activation : with and without
Result : negative
Method : other: mam malian chromome aberration assay
Year :
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Method : Equivalent to OECD 473 adopted 1997.

Test condition : SYSTEM OF TESTING
- Species/cell type: Chinese hamster ovary cells
- Metabolic activation system: Rat liver Arochlor 1254 induced.
- No. of metaphases analyzed: 300 for treated and negative controls, 200 for positve controls.

ADMINISTRATION:
- Dosing: Single administration of aqueous solution
- Number of replicates: 3
- Application: Aqueous solutions of test material applied to flask cultures. 5 hour incubation withmetabolic activating fraction, 24 hour incubation without.
- Positive and negative control groups and treatment: Positive controls ethane methane sulphonate 500 microgram/ml; cyclophosphamide 100 micrograms/ml.

CRITERIA FOR EVALUATING RESULTS: Comparison of frequency of aberrations.

Result : GENOTOXIC EFFECTS:
- With and without metabolic activation: no increase in aberration rate

FREQUENCY OF EFFECTS: There was no treatment related increase in the incidence in polyploidy, major malformations, chromatid gaps and chromosome or chromatid aberrations compared to controls. Positive controls confirmed the sensitivity of the assay.

PRECIPITATION CONCENTRATION: No precipitation.

MITOTIC INDEX:
Without activation: 7.2, 6.0, 7.6, 4.2, 2.0 for control, 1250, 2500 and 5000 micrograms/ml hexylene glycol and 500 microgram/ml EMS respectively.
With activation: 7.2, 6.4, 6.0, 4.0, 3.4 for control, 1250, 2500 and 5000 micrograms/ml hexylene glycol and 100 micrograms/ml CP repectively.

CYTOTOXIC CONCENTRATION:
- With and without metabolic activation: 5000 micrograms/ml

STATISTICAL RESULTS: No statistical analysis

Conclusion : Hexylene glycol does not induce chromosome damage in cultured Chinese hamster ovary cells at dose levels up to 5000 micrograms/ml in the presence or absence of rat liver metabolising fraction.

Reliability : (1) valid without restriction
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
Shell Chemicals Ltd
Flag : Critical study for SIDS endpoint
Reference : (70) (71)
17.04.2001

5.6 Genetic toxicity 'in vivo'

5.7 Carcinogenity

Remark : No data
Source : Atochem Paris la Defense
EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
26.04.1994

5.8 Toxicity to reproduction

Type : other: 90 day rat gavage study
Species : rat
Sex : male/female
Strain : other: Sprague-Dawley Crl CD (SD) IGS BR
Route of admin. : gavage
Exposure period : 90 days
Frequency of treatment : daily (7 days/week)
Premating exposure period
Male :
Female :
Duration of test :
Doses : 0, 50, 150, 450 mg/kg/day
Control group : yes, concurrent vehicle
Method : other: OECD Guideline 408 Subchronic oral toxicity - Rodent 90-day study
Year : 1981
GLP : yes

Test substance	:	as prescribed by 1.1 - 1.4
Reliability	:	(1) valid without restriction
Remark	:	No standard reproduction studies are available however in this guideline 90 day study histopathological examination of the reproductive organs [ovaries, uterus (horns and cervix), vagina, testes, epididymes, prostate and seminal vesicles] revealed no treatment related changes.
Reference	:	(60)
26.10.2001		
Type	:	Fertility
Species	:	rat
Sex	:	male
Strain	:	no data
Route of admin.	:	other: oral in milk
Exposure period	:	130 days
Frequency of treatment	:	Daily
Premating exposure period		
Male	:	87 days
Female	:	none
Duration of test	:	
Doses	:	150 mg/day nominal (average daily intake 148-190 mg/day)
Control group	:	yes, concurrent vehicle
Method	:	other: see Methods
Year	:	1958
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Method	:	Non-standard method. Groups of 10 male rats received the test material daily administered in 10 ml milk. The rats were offered the milk in deep containers to reduce evaporation. There was evidence of unpalatability of test material solutions. Paired feeding was introduced between the test and control groups to adjust for the different intake of milk. After 87 days, 6 control and 7 treated males were mated with up to 7 different untreated females over a 47 day period. The animals were paired until pregnancy was confirmed by vaginal smear. Pregnancy was terminated 1-2 days prior to estimated delivery and the numbers of live foetuses counted.
Result	:	In this limited assessment of fertility there were no statistically significant differences between treated and control groups. One treated male appeared infertile showing a lack of interest in mating but there were no histopathological changes in the testes of this male or any others. The females mated with this male were subsequently mated with fertile males but only 2/7 became pregnant.
Conclusion	:	Limited conclusions can be drawn from this study.
Reliability	:	(3) invalid Method not comparable to current guidelines, only one dose level used, invalid method of administration (offered in milk), no statistical analysis.
Source	:	Atochem Paris la Defense EUROPEAN COMMISSION- European Chemicals Bureau Ispra (VA)
Reference	:	(69)
17.04.2001		

5.9 Developmental toxicity/teratogenicity

Species	:	rat
Sex	:	female
Strain	:	other: Sprague-Dawley Crl:CD(SD)IGS BR
Route of admin.	:	gavage
Exposure period	:	Gestation days 6-15
Frequency of treatment	:	Once daily
Duration of test	:	Until day 20 of gestation
Doses	:	30, 300 and 1000 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	= 300 mg/kg bw
NOAEL Teratogen	:	> 1000 mg/kg bw
NOAEL Fetotoxicity	:	= 300 mg/kg bw
Method	:	OECD Guide-line 414 "Teratogenicity"
Year	:	1981
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Test condition :

TEST ORGANISMS: 24 mated females/group aged 9 weeks and weighing between 188.8 and 256.5g at the time of mating.

SELECTION OF DOSE LEVELS
This was based on a range-finding 14 day gavage study in the same strain of rat.

ADMINISTRATION / EXPOSURE
- Vehicle: distilled water
- Concentration in vehicle: 0, 6, 60 and 200 mg/ml
- Total volume applied: 5ml/kg
- Stability: the aqueous solutions prepared were stable over a 7 day period with analytical results within the range 96-105% of nominal.

MATING PROCEDURES: Mating was carried out overnight at the suppliers laboratory and confirmed by the presence of a vaginal plug or sperm in a vaginal smear. The day on which mating was observed was designated day 0 of gestation. Females were received at the test laboratory by day 3 of gestation.

PARAMETERS ASSESSED DURING STUDY:
- Body weight gain
- Food consumption
- Clinical observations
- Examination of uterine content
- Examination of fetuses

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC): Macroscopic observation of dams only.

STATISTICAL METHODS: For each parameter analysed the procedures performed were:

Analysis of variance (ANOVA). Pairwise comparisions were made using Dunnetts test.
Levenes test for equality of variance between groups. Where heterogeneous variances occurred the data were either reanalysed using a log-transformation or non-parametric tests were employed.

Non-parametric tests used were the Kruskal-Wallis ANOVA, Terpstra-

Jonckheere test for dose related trend, Wilcoxon rank sum test for pairwise comparision.

Any statistically significant results obtained only in the ANOVA were not reported.

The Cochran-Armitage test for dose response and the Fischer-Irwin Exact test for pairwise comparisons were also employed. A Bonferroni adjustment was applied to pairwise comparisons where there was no signifcant dose response test.

Result : NOAEL (NOEL), LOAEL (LOEL):

A NOAEL for maternal toxicity of 300 mg/kg bw based on a statistically significant reduction in group mean body weight gain on days 6 to 7 of gestation (no increase in body weight gain was observed) and a statistically significant reduction in food consumption on days 6 to 7 (22%) and days 7 to 8 (8%) at 1000 mg/kg bw. A transient statistically significant ($P<0.01$) reduction in body weight gain was also observed on days 6 to 7 at 300 mg/kg (a mean increase in body weight of 2 g compared to 6 g in controls). No maternal toxicity was observed at 30 mg/kg.

At 1000 mg/kg very marginal decreases (< 7%) in foetal and litter body weight were not statistically significant. There was no significant increase in the overall incidence of defects. However at the top dose level there were more litters where all the foetuses examined showed skeletal variations, 15 litters affected compared to 7 in controls. Marginally higher incidences of some of the foetal variations (skeletal) examined attained statistical significance ($P<0.05$) at 1000 mg/kg as follows:
-occipitals incompletely ossified in 21.6% of foetuses compared to 8.2% of controls
- hyoid arch not ossified in 18% of foetuses compared to 6.1% controls
-extra thoraco-lumbar ribs in 18.7% foetuses compared to 9.5% in controls.

A statistically based dose-response was positive for incomplete ossification of the nasals, frontals, parietals, interparietals and occipitals. These observations are considered related to a delay in normal ossification process probably due to the maternal toxicity (as indicted by reduced maternal body weight gain) observed at this dose level. The NOAEL for foetotoxicity is considered to be 300 mg/kg.

A statistically significant increase in foetuses showing subcutaneous haemorrhage of the trunk and limbs was seen at 1000 mg/kg (12% compared to 3.2% in controls). The author did not consider these very minor defects to be treatment-related as they are known to occur as a result of handling damage at caesarean necropsy. No significant treatment-related developmental toxicity was found in this study and the NOAEL for significant developmental effects is considered to be >1000 mg/kg.

ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX:
Lower than acceptable (= 95-105% nominal) values were initially obtained for the low dose level at week 1 and for the two higher dose levels at week 3. These analyses were repeated and gave satisfactory results.

RANGE-FINDING STUDY
Groups of 5 male and 5 female rats received 0, 30, 300 or 1000 mg/kg/day hexylene glycol for 14 days. There were dose related increases in adrenal, kidney and liver weights which reached statistical significance at the top dose level, liver weights were also increased statistically at the 300 mg/kg level. There were no adverse effects on clinical condition, body weight or

food intake.

MATERNAL TOXIC EFFECTS BY DOSE LEVEL:
- Mortality and day of death: There were no mortalities among treated or control animals. There were no abortions and no significant differences in pregnancy rate.

-Intrauterine effects: The author reports a statistically significant increase in preimplantation loss (22.3% compared to 8.1% in controls) at 1000 mg/kg related to a slightly higher mean number of corpora lutea (12%, not statistically significant) and a slightly lower number of implantations (6%, not statistically significant) compared to the control group. However, as dosing began after implantation was essentially complete, this finding is of questionable biological relevance. No effect was observed on post-implantation loss.

- Body weight/food intake: At 1000 mg/kg, mean body weight gain and food intake were slightly lower than controls during (a few days of) the treatment period and in the intermediate dose group there was a transient reduction in body weight gain. For gestation days 6-7 body weight change was 0 g/rat for top dose animals and 6 g/rat for controls while food intake was 21 g/rat and 27 g/rat respectively.

- Description, severity, time of onset and duration of clinical signs: There were no treatment related clinical signs.

- Gross pathology incidence and severity: At necropsy there was a low incidence of large pale livers in all groups which was marginally higher in the 300 and 1000 mg/kg groups. This was not considered to represent an adverse effect as the observation is reported as common in this strain of rat.

FETAL DATA: There were no statistically signficant effects on litter size and weights, number viable or sex ratio. There was a marginal non-statistical reduction in mean litter weight (41.5 g) and mean foetal weight (3.43 g) at the highest dose level compared to controls (44.5 and 3.62 g respectively).

A marginal increase in the incidence of skeletal variations was apparent at 1000 mg/kg/day. The findings were mainly incomplete ossification and considered indicative of delayed ossification possibly relating to the reduced maternal body weight at this dose level.

There were no treatment related effects on pregnancy or the foetus at 30 or 300 mg/kg/day.

HISTORICAL CONTROL DATA: This was provided in the report for 6 earlier studies (pre international rat) and separately for the one preceding study using the International rat. The laboratory changed to using the 'International' rat immediately prior to the conduct of this study so strictly relevant control data were only available from this one study. However interpretation of the results from this study does not rely significantly on historical control values.

Conclusion : There were no adverse effects on pregnancy or the foetus at 30 or 300 mg/kg/day.

Reliability : (1) valid without restriction

Attached doc. : IUCLID Section 5.9 (1).doc

Source	:	Shell Chemicals Ltd
Flag	:	Critical study for SIDS endpoint
Reference	:	(62) (72)
12.09.2001		
Species	:	rat
Sex	:	female
Strain	:	other: Sprague-Dawley derived CD (SD) BR VAF/Plus strain
Route of admin.	:	gavage
Exposure period	:	gestation days 6 -17
Frequency of treatment	:	daily
Duration of test	:	Until gestation day 20
Doses	:	0, 500, 1200 and 1600 mg/kg/day
Control group	:	yes, concurrent vehicle
NOAEL Maternalt.	:	= 500 mg/kg bw
Method	:	other: FDA Guidelines for Reproduction Studies
Year	:	1966
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4

Test condition :

TEST ORGANISMS
30 mated females/group aged 12.5 weeks and weighing between 228 and 294 grams on gestation day 1.

SELECTION OF DOSE LEVELS
Based on a range finding developmental toxicity study.

ADMINISTRATION / EXPOSURE
- Vehicle: distilled water
- Concentration in vehicle: 0, 50, 120 and 160 mg/ml
- Total volume applied: 10 ml/kg
- Stability: the aqueous solutions prepared were stable over a 10 day period with recovery on day 10 being within 94-101% of the level measured at day 0.

MATING PROCEDURES: Mated one to one with control males, evidence of mating was determined by evidence of a vaginal plug. Day of evidence of mating was considered as gestation day 0.

PARAMETERS ASSESSED DURING STUDY:
- Body weight gain
- Food consumption
- Clinical observations
- Examination of uterine content
- Examination of fetuses

ORGANS EXAMINED AT NECROPSY: Only macroscopic examinations were conducted on dams. No histopathological examination was conducted on foetuses.

STATISTICAL ANALYSIS: One way analysis of variance (ANOVA) was used and if this was significant pairwise comparisons to controls were carried out using Dunnetts test. If ANOVA was not significant no further tests were carried out.

A non-parametric test (Kruskal-Wallis) was used where appropriate and where this was significant pairwise comparisons to control were performed using a Mann-Whitney U test.

A PEARSON chi-square test was also used and where significant pairwise

comparisons were made using a Fischers exact test. If chi-square was not significant no further tests were carried out.

Result : NOAEL (NOEL), LOAEL (LOEL): NOAEL for maternal toxicity 500 mg/kg/day based on observations at 1200 and 1600 mg/kg of overt clinical signs, reduced weight gain and reduced food consumption. Compared to controls, a statistically significant decrease in body weight gain was seen on gestational days 6 to 9 and 18 to 20 at 1200 (83 and 19%, respectively) and 1600 mg/kg (a 2 % reduction in body weight and 27% reduction in body weight gain, respectively). Statistically significant reductions in food consumption were observed at 1200 mg/kg between gestation days 6 to 9 (22%) and at 1600 mg/kg between days 6 to 9 (34%) and 9 to 1 2 (11%).

NOAEL for developmental toxicity 500 mg/kg based on statistically significant reductions in foetal weight at the higher dose levels (5% at 1200 mg/kg and 10% at 1600 mg/kg). There was no statistically signficant increase in total external, visceral and skeletal malformations or variations. However there were sporadic, low occurences of developmental abnormalities at 1200 and 1600 mg/kg. There was an increased incidence of skeletal variations (delayed ossification, extra ribs) at 1600 mg/kg when analysed on a foetal basis. For % affected fetuses/litter the increase was only statistically significant for unossified sternebra (37.57 compared to 15.04 in controls) and rudimentary ribs (41.65 compared to 27 in controls). As foetuses were not examined at the lower dose levels no clear NOEL can be ascribed from this study.

ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX: The overall mean percent of nominal concentrations found in the test preparations were 105, 105 and 99% respectively for the 50, 120 and 160 mg/ml dose solutions.

MATERNAL TOXIC EFFECTS BY DOSE LEVEL:

- Mortality and day of death: No treatment related deaths.

- Number aborting: One animal aborted at gd 19 at the highest dose level. At necropsy there was evidence of perforation of the oesophagus and associated systemic infection. This abortion was therefore considered due to gavage damage and not treatment related.

-Intrauterine parameters: There were no statistically significant differences in numbers of live foetuses between treated and control groups. An increase in late resorptions, which was not statistically significant and did not show a dose response, was observed in the 500 and 1600 mg/kg groups (0.08 and 0.15 per animal respectively, compared to 0 in controls) but the total post-implantation losses in the treated groups were comparable with the control groups and considered within historical control limits (mean postimplantational loss/dam for 32 studies over the period 1982-1994 was 1.0). There were no other significant differences between treated and control groups.

- Duration of Pregnancy: At 500 mg/kg one animal delivered early and was necropsied on gd20. There were no other early deliveries.

- Body weight: Maternal body weight gain was significantly reduced over the period of the study at 1200 and 1600 mg/kg.

- Food consumption: this was significantly reduced at 1600 mg/kg over the entire period of the study and for some time intervals at 1200 mg/kg.

- Description, severity, time of onset and duration of clinical signs: Treament

related signs seen in treated animals only included dehydration, impaired limb function, ataxia, decreased activity, lethargy, decreased defecation, body surface staining, rales, laboured breathing, staining around the mouth and material around the eye. There was overt evidence of maternal toxicity at 1200 and 1600 mg/kg which continued through the dosing period, by the time of sacrifice (3 days after cessation of dosing) most animals were reported as appearing normal.

- Gross pathology incidence and severity: There were gross pathological changes due to the gavage procedure but other than this there were few macroscopic changes. Pitted kidneys were noted in 1 rat at 1200 and 2 at 1600 mg/kg. The only other observations were a subcutaneous axillary mass in one rat at 1200 mg/kg/day and a cystic ovary in one rat at 1600 mg/kg.

FETAL DATA:
- Litter size and weights: Litter size was not statistically significantly affected by treatment. A statistically significant decrease in mean foetal body weight was seen at 1200 and 1600 mg/kg. Mean gravid uterine weight was also reduced at 1200 and 1600 mg/kg but the differences were not of statistical significance.

- Number viable: There was no statistically significant difference in numbers of live foetuses.

-·Sex ratio: Not affected by treatment.

- External abnormalities: At 1200 mg/kg ethmocephaly was observed in one foetus and a threadlike tail in another both from different litters. At 1600 mg/kg two foetuses from different litters showed mandibular micrognathia, one of these foetuses also exhibited aglossia and microphthalmia. Also observed at 1600 mg/kg were one foetus with mandibular agnathia and another with omphalocoele. However there was no statistical difference between treated and control groups in the incidence of external malformations.

- Soft tissue abnormalities: None other than the single case of omphalocoele at 1600 mg/kg. This abnormality was observed at a low incidence in historical controls (3 foetuses in 3 litters from 760 litters examined. Only top dose and control groups were examined.

- Skeletal abnormalities: At 1600 mg/kg there was a statistically significant increase in the foetal incidence of unossified hyoid and sternebrae, rudimentary rib, extra pair of ribs and 7th cervical rib. Other skeletal variations also occurred at a greater frequency at this dose level but the increase did not reach statistical significance. Only the top dose group and control groups were examined.

HISTORICAL CONTROL DATA
This was provided for 32 studies over the period 1982-1994.

Conclusion : Given the high maternal toxicity and lack of full foetal examinations limited conclusion can be drawn.

Reliability : (2) valid with restrictions
Although apparently a reasonably designed study, serious questions have been raised concerning its validity. Shell have received correspondence from The Procter and Gamble Co. (P&G), the sponsors, concerning interpretation of this study which was commissioned unbeknown to either party at a similar time to the Shell sponsored study (Clode, 1997). P&G

decided to investigate internally the aetiology of the maternal toxicity which they hypothesised was due to metabolic acidosis in the dam with consequent effects on the litter.

P&G have notified Shell that they have attempted to repeat the findings at 1200 and 1600 mg/kg but were unsuccessful (personal communication to Shell). P&G were also unable to raise the matter with the original contract laboratory as they no longer exist.

Source : Shell Chemicals Ltd
Reference : (73) (74)
12.09.2001

Species : rat
Sex : female
Strain : other: Sprague-Dawley derived Crl:CD VAF/plus SD derived
Route of admin. : gavage
Exposure period : Gestation days 6-17 for dose levels up to 1000 mg/kg, 7-17 for 2000 mg/kg
Frequency of treatment : daily

Duration of test : Until gestation day 20
Doses : 0, 5, 50, 500, 1000 and 2000 mg/kg/day
Control group : yes, concurrent vehicle
NOAEL Maternalt. : = 1000 mg/kg bw
NOAEL Teratogen : = 1000 mg/kg bw
Method : other: Range-finding study
Year : 1966
GLP : yes
Test substance : as prescribed by 1.1 - 1.4

Test condition : TEST ORGANISMS: 5 mated females/group

ADMINISTRATION / EXPOSURE
- Type of exposure: gavage
- Duration of test/exposure: Gestation days 6-17 however the original top dose level of 3000 mg/kg/day proved excessively toxic and dosing was terminated and the animals sacrificed on GD9. This group was replaced by a top dose level of 2000 mg/kg/day, dosing of this group covered gd7-17.
- Vehicle: distilled water
- Total volume applied: 10 ml/kg except 2000 mg/kg level which received 6.7 ml/kg

PARAMETERS ASSESSED DURING STUDY:
- Body weight
- Clinical observations
- Examination of uterine content

ORGANS EXAMINED AT NECROPSY (MACROSCOPIC AND MICROSCOPIC): Only macroscopic examinations were conducted on dams.

STATISTICAL METHODS: None

Result : NOAEL (NOEL), LOAEL (LOEL): 1000 mg/kg for maternal and development effects.

ACTUAL DOSE RECEIVED BY DOSE LEVEL BY SEX: Not measured.

MATERNAL TOXIC EFFECTS BY DOSE LEVEL:

- Mortality and day of death: No deaths other than animals sacrificed on

gestation day 9 at the 3000 mg/kg/day level
- Number pregnant per dose level: 5/5 for all dose levels except 1000 mg/kg and controls (4/5).
- Number aborting: None
- Number of resorptions(post-implantation loss): Early+late mean % of implants/animal 11.79, 6.4, 3.68, 4.81, 5.61, 52.0 at 0, 5, 50, 500, 1000 and 2000 mg/kg/day respectively.
- Number of implantations: Mean number of implantation sites/animal 14.74, 13.6, 16.6, 16.4, 17.25, 18.2 at 0, 5, 50, 500, 1000 and 2000 mg/kg/day respectively.
- Pre implantation loss: No treatment related effect.
- Number of corpora lutea: No treatment related effect.
- Duration of Pregnancy:
- Body weight: There was a significant reduction in bodyweight gain in dams at 2000 mg/kg over gestation days 6-18 (41%), mainly due to a loss in body weight in these animals between days 6-9.
- Description of clinical signs: No treatment related signs at dose levels up to and including 1000 mg/kg. At 2000 (and 3000) mg/kg clinical signs included ataxia, lethargy and reduced defecation in all animals other signs observed in 1 or 2 rats included vaginal discharge, reddish fluid in cage tray, laboured breathing, loss of righting reflex.

FOETAL DATA:
- Number viable: Live foetuses %/animal(mean) 88.21, 93.6, 96.32, 95.19, 94.39, 48.0 at 0, 5, 50, 500, 1000 and 2000 mg/kg/day respectively.
-·Sex ratio: Not reported

Foetal bodyweights were not recorded and the foetuses were not examined for malformations or anomalies.

STATISTICAL RESULTS: not carried out.

VALIDITY: not a guideline study, used only as a range-finder, lack of statistical analysis was due to the small numbers of pregnant animals used.

Conclusion : NOAEL for maternal and developmental toxicity in this range finding study was 1000 mg/kg/day. At the higher dose level of 2000 mg/kg/day there was evidence of maternal toxicity (reduced weight gain and clinical signs) and developmental toxicity (increased post-implantational loss).

Reliability : (2) valid with restrictions
Source : Shell Chemicals Ltd
Reference : (75)
06.09.2001

Species : other: Hydra attenuata
Sex :
Strain : other
Route of admin. :
Exposure period :
Frequency of treatment :
Duration of test :
Doses :
Control group :
Method : other: in vitro screening assay
Year :
GLP :
Test substance : as prescribed by 1.1 - 1.4

Conclusion : None of the glycols tested was using this in vitro procedure was considered

as having a high potential for disrupting embryonic develpment.

Reliability : (4) not assignable

Remark : This in vitro study utilized Hydra attenuata to evaluate developmental toxicity and structure activity correlates of glycols and glycol ethers. An A/D ratio (ratio of adult minimum effect concentration to developmental minimum effect concentration) of 3.3 was reported for HG. The A/D ratio is considered as a developmental toxicity hazard index whose increasing size is directly proportional to a chemical's ability to injure embryos in the absence of adult toxicity. The authors concluded from this study that the hydra assay is predictive of the likely adult/developmental toxicity relationship in laboratory animals. The relevance of this assay, however, to mammals/humans has not been established.

Source : Shell Chemicals Ltd

Reference : (76)

09.04.2001

5.10 Other relevant information

Type : Metabolism

Method : One rabbit received a single oral dose of 1.0 ml/kg 2-methyl-2,4-pentanediol. Levels of glucuronate were measured in the plasma and urine over a 24 hour period.

Reliability : (4) not assignable

Remark : An increase in the levels of glucuronates was observed in the plasma and urine of rats and rabbits following one oral dose of hexylene glycol. There was no change in the glucuronic acid values in blood cells. Plasma levels of hexuronates increased significantly and in direct relation to the quantities of hexuronates excreted in the urine.

Reference : (77)

13.09.2001

Type : Metabolism

Reliability : (4) not assignable

Remark : Excretion of glucuronate in the urine of 3 rabbits administered about 118 mg/kg hexylene glycol by stomach tube was reported. 67% of the dose was recovered from the urine in conjugated form. None of the glucuronides was isolated in a crystalline form. No further information is available from this reference.

Reference : (78)

13.09.2001

Type : Metabolism

Method : The excretion of free and bound hexylene glycol was determined in the 24 hour pooled urine of groups of 6 male rats following acute and repeated exposure to hexylene glycol.

The rats receiving a single dose received 400 mg hexylene glycol in aqueous solution by stomach tube.

Repeated doses were administered in milk at nominal concentrations of 100

mg/kg/day for 62-98 days or 200 mg/kg/day for 60-131 days.

Reliability : (4) not assignable

Remark : Rats receiving 200 mg/kg/day hexylene glycol/day excreted 40% of the amount consumed in the urine. Only 4% of the excreted quantity was in the form of free glycol.

Rats receiving 100 mg/kg/day hexylene glycol excreted 51% in the urine of which about 7% was in the form of free glycol.

Rat receiving a single dose of 400 mg/kg excreted 49% in the urine of which about 14% was in the form of free glycol.

Reference : (69)
13.09.2001

Type : Biochemical or cellular interactions

Reliability : (4) not assignable

Remark : Hexylene glycol inhibited communication between hamster lung cells (V79) in culture in the 'metabolic cooperation assay'. The authors were attempting to develop an in vitro screening assay for potential teratogens, tumour promoters and reproductive toxicants. The authors state that the correlation of the in vitro results obtained in the assay with in vivo data "was not rigourously possible".

In the case of hexylene glycol a guideline rat developmental toxicity at dose levels up to 1000 mg/kg/day by oral gavage produced no evidence of a teratogenic effect. Additionally in a good quality 90 day repeat dose toxicity study in which rats were administered hexylene glycol at doses up to 450 mg/kg/day by oral gavage, no effects on the gonads were observed.

Reference : (79)
13.09.2001

Type : Biochemical or cellular interactions

Method : Whole blood (heparinised) was obtained from 16 human volunteers. Sodium oxalate was added as an inducer of radial segmentation in the nuclei. Hexylene glycol was then added to provide concentrations of 0.1 or 0.5%. The pH of the test samples was not affected by addition of hexylene glycol. There was no evaluation of the potential cytotoxicity of hexylene glycol to the blood cells. After 6 hours incubation smears were prepared and 500 mono-nuleated cells counted and the number of radially segmented nuclei counted.

Conclusion : This study using an experimental system for induction of mitotic radial segmentation does not provide information relevant for an assessment of the possible mutagenic hazards of hexylene glycol. Test concentrations used were in excess of those found to be cytotoxic in a negative CHO chromosome aberration study carried out to OECD guideline 473.

Reliability : (4) not assignable

Remark : The induced radial segmentation (by sodium oxalate) of the mitotic apparatus in the nuclei of human monocytes in vitro was inhibited by hexylene glycol (0.5 and 0.1% aqueous).

Reference : (80)
13.09.2001

Type : Biochemical or cellular interactions

Reliability : (4) not assignable

Remark : Hexylene glycol was reported to decrease the secretion of insulin from isolated pancreatic cells following exposure to high glucose concentration. It was suggested that that this might be due to an effect on the integrity of the microtubular-microfilamentous system required for glucose to exert its normal stimulant action on insulin secretion.

Reference : (81)
12.09.2001

Type : Biochemical or cellular interactions

Reliability : (4) not assignable

Remark : Hexylene glycol has been shown to inhibit migration of human monocytes. The suggested mechanism is by stabilising cytoplamsic microtubules.

Reference : (82)
21.03.2001

Type : Biochemical or cellular interactions

Reliability : (4) not assignable

Remark : Hexylene glycol, which stabilises microtubule formations in mitosis, has been shown to inhibit thyroid secretion in isolated thyroid lobes.

Reference : (83)
21.03.2001

Type : Biochemical or cellular interactions

Reliability : (4) not assignable

Remark : Using isolated pancreatic lobules hexlene glycol was found to inhibit protein synthesis but it did not affect the secretory process.

Reference : (84)
13.09.2001

Type : other: Comedogenic activity

Reliability : (4) not assignable

Remark : Neat hexylene glycol was applied to the rabbit inner ear 5 days/week for 2 weeks to evaluate the comedogenic effects of HG. This gave rise to acne-like eruptions and hexylene glycol was considered a moderate comedogen in this study (grade 3 on a scale of 1-5).

Reference : (85)
13.09.2001

Type : other: Pharmacology
Reliability : (4) not assignable

Remark : Hexylene glycol given orally raised the cortical threshold of the rat brain to electric shock and also exhibited some anti-convulsant activity. The dose which eliminated the tonic-extensor phase of maximal seizures by 50% (ED50) was 465 mg/kg while the TD50, the dose which caused ataxia in 50% of animals was 700 mg/kg.

Reference : (63)
13.09.2001

5.11 Experience with human exposure

Memo	:	Metabolism
Test condition	:	Five male volunteers aged 50-60 were given single and repeated oral daily doses of 1 -5 g hexylene glycol using various dosing regimes.
Reliability	:	(4) not assignable
Remark	:	Both free and conjugated HG were recovered from the urine, about 20-35% of ingested dose being excreted in the conjugated form. Elimination continued for 5-10 days after cessation of exposure.
Reference 13.09.2001	:	(86)
Memo	:	Skin reactions
Conclusion	:	Damaged human skin may be more susceptible to the possible irritant effect of hexylene glycol than undamaged skin.
Reliability	:	(4) not assignable
Remark	:	823 eczema patients were patch tested (48 hour occluded) with 30 or 50% hexylene glycol, 2.8% showed erythema and oedema. Erythema only was reported in 5.7% of patients patch tested with hexylene glycol. 7 patients with a positive patch test to hexylene glycol were tested by ROAT (Repeated Open Application Test) a postive response was obtained in 1 patient. The authors hypothesized the reaction in this patient may be due to cross-sensitivity with the contact allergen propylene glycol.
Source	:	Shell Chemicals Ltd
Reference 13.09.2001	:	(87)
Memo	:	Skin reactions
Reliability	:	(4) not assignable
Remark	:	Hexylene glycol (10% aqueous) was used as a standard patch test in a group of 230 patients exposed to cutting oils who had been diagnosed with occupational dermatitis. 9 patients gave a positive response to challenge with hexylene glycol, 3.9% of the total number tested.
Source	:	Shell Chemicals Ltd
Reference 13.09.2001	:	(88)
Memo	:	Skin reactions
Reliability	:	(4) not assignable
Remark	:	Hexylene glycol is negative for skin sensitisation on normal healthy skin. A maximization test carried out on 33 human volunteers (with assumed healthy skin) found that hexylene glycol tested at a concentration of 20% in petrolatum produced no skin sensitisation reactions (Epstein, 1976 unpublished report to RIFM).
Reference 13.09.2001	:	(40)
Memo	:	Skin reactions

Conclusion : Hexylene glycol was not irrant to human skin under the conditions of this study.

Reliability : (4) not assignable

Remark : Undiluted hexylene glycol was applied to the forearm under occluded (37 volunteers) and semi-occluded patches (39 volunteers). Exposure was for 24 hours. Irritation was minimal under both occlusive and semiocclusive patches. PIIs of 0.11 for occluded and 0.02 for semi-occluded were reported (max. score 4).

Unpublished data CFTA, 1973 reported in summary.

Source : Shell Chemicals Ltd

Reference : (47)
13.09.2001

Memo : Sensory response to vapours

Method : Agroup of human volunteers (number unspecified) were studied for sensory irritation effects following exposure to hexylene glycol vapour for 15 minutes. There was no measurement of vapour concentrations.

The literature report (Silverman et al, 1946) refers the reader to an earlier reference for further details of the test procedure. This report (Nelson et al, 1943) indicates that an unspecified number of volunteers were exposed at different times to more than one solvent at different concentrations. They did not know to which solvent or at which concentration they were exposed. Exposures took place in a 1200 cubic ft gas cabinet. Immediately following the exposure each individual classified the effect on the eyes, nose and throat following exposure on a scale of no reaction, slightly irritating and very irritating. There was no independent clinical assessment of the reported effects. The volunteers were also asked if they could work in the atmosphere for an 8 hour day.

Nelson, K.W. et al, 1943 Sensory response to certain industrial solvent vapours. J. Ind. Hyg. Toxicol. 25(7):282-285, 1943

Reliability : (3) invalid
Interpretation of this study is complicated due to possible bias associated with odor and subjective (self) reporting. There was no independent clinical assessment of effects.

Remark : A group of human volunteers were studied for sensory irritation effects following exposure to hexylene glycol vapour for 15 minutes. The majority of the subjects reported 50 ppm (approximate saturation concentration at room temperature, 25°C) hexylene glycol vapour to be slightly irritating to the eyes. At concentrations > 50 ppm (not specified), irritation effects included the nose and throat. The majority of volunteers estimated that 50 ppm was the highest concentration which would be satisfactory for an 8 hour exposure suggesting that the responses noted were minimal.

Reference : (89)
13.09.2001

Memo : Sensory response to vapours

Method : 7 human volunteers were exposed to vapours of hexylene glycol at a level of 100 ppm. The exposure was whole body in an inhalation chamber to a static atmosphere generated by vapourising a predetermined quantity of the test solvent from a hot surface. 5 minutes were allowed for vapourisation and equilibration and the volunteers were then exposed to the vapour

generated for 5 minutes. There was no measurement of vapour concentrations.

Visual inspection of the eyes and physical examination of the chest was carried out after each exposure.

Result : The effects and frequency reported are as follows: olfactory recognition 5/7; slight eye irritation 1/7; slight nasal irritation 4/7; slight pulmonary discomfort 1/7; CNS effects 0/7.

Reliability : (4) not assignable
Reference : (90)
13.09.2001

Memo : Toxic effects in burn patients.

Reliability : (4) not assignable

Remark : The author reports several cases of coma and death in children treated with hexylene glycol impregnated burn dressings. Effects described include narcosis, renal impairment and possible hepatocellular damage.
Source : Shell Chemicals Ltd
Reference : (91)
13.09.2001

Memo : Toxic effects in burn patients.

Reliability : (4) not assignable

Remark : This is a case study of an adult in whom delerium and ataxia developed progressively following application of a hexylene glycol impregnated burns dressing. Within 12 hours of removal of the dressing recovery was complete.
Source : Shell Chemicals Ltd
Reference : (92)
13.09.2001

(1) UK HSE, Occupational Exposure Limits 2000, EH40/2000

(2) ACGIH 2001 Threshold limit values for chemical substances and physical agents and biological expousre indices.

(3) INRS, Valeurs limites d'exposition professionnelle aux agents chimiques en France, Cah. Notes Doc. 1993, 153, 557-574

(4) Cosmetic Ingredient Review (CIR) (1985) Final Report of the safety assessment of Butylene Glycol, Hexylene Glycol, Ethoxydiglycol and Dipropylene Glycol. J. Amer. College Toxicol., 4(5):223-248.

(5) Cavender, F.L.; Sowinski, E.J. (1994) Glycol. Chapter 49 in Patty's Industrial Hygiene and Toxicology, 4th edition Editors Clayton, G.D. & F.E., Wiley-Intersciene.

(6) Rowe VK and Wolf MA. (1981). Chapter Fifty. Glycols. In: Patty's Industrial Hygiene and Toxicology. Third Revised Edition. Clayton GD and Florence FE (Eds). John Wiley & Sons, New York.

(7) British Industrial Biological Research Association (BIBRA) Toxicity profile Hexylene glycol. 1991

(8) Opdyke, D. (1978) Fragance Raw Material Monographs : Hexylene Glycol. Food & Cosmet. Tox., 16(1):777-778.

(9) Kirk-Othmer, Encyclopedia of Chemical Technology 4th Edition Vol. 22 p547, 1997

(10) Safety Data Sheet ELF ATOCHEM December 1992

(11) Sax's Dangerous Properties of Industrial Materials, (9th Edition)

(12) Shell Chemicals Data Sheet IS 1.1.2 revised August 1994

(13) Hawley's Condens ed Chemical Dictionary, 12th edition.

(14) Riddick, J.A. et al. Techniques of Chemistry Vol. II Organic Solvents Physical Properties and Methods of Purification, 4th Edition, Editor: Arnold Weissberger, Wiley-Interscience 1986

(15) Syracuse KOWWIN v1.57 estimate

(16) Hansch, C.; Leo, A.J.,1985. Medchem project. Claremont, CA : Pomona College. Issue = 19.

(17) Howard, P.H. (Editor) (1993) Handbook of environmental fate and exposure data for organic chemicals. Lewis publishers

(18) Blok, J.; de Morsier, A.; Gerike, P.; Reynolds, L.; Wellens, H. Harmonisation of ready biodegradability tests. Chemosphere 14(11/12): 1805-1820, 1985

(19) MITI, Japan. Biodegradation and bioaccumulation data of existing chemicals based on CSCL, Japan. Edited by Chemicals Inspection and Testing Institute, Japan. Also reported on the CERI (Chemicals Evaluation and Research Institute) web site, Japan 1999

(20) Kawasaki, M., 1980. Experiences with the test scheme under the chemic control law of Japan : an approach to structure-activity correlations. Ecotoxicol. Environ. Saf., 4, 444-454.

(21) Price, K.S., Waggy, G.T. and Conway, R.A., 1974. Brine shrimp bioassay and seawater BOD of petrochemicals. J Water Pollut. Control Fed., 46(1) 63-77.

(22) National Association of P hotographic Manufacturers Inc. (1974) Environmental effect of photoprocessing chemicals. Vols 1 and 11. EPA/OTS 40-8469216 (NTIS/OTS -0507473)

(23) Bridie A.L., Wolff,C.J.M. and Winter, M., 1979. BOD and COD of some petrochemicals. Water Research, 13, 627-30.

(24) Bridie, A.L.; Winter, M.; Wolff, C.J.M. 1974 Determination of the chemical oxygen demand of Shell Chemicals. Shell Research BV Report No. AMGR.0184.74

(25) Thurston, R.V., Gilfoil, T.A., Meyn, E.L., Zajdel, R.K., Aoki, T.I. and Veith, G.D., 1985. Comparative toxicity of ten organic chemicals to common aquatic species. Water Research, 19(9), 1145/1155.

(26) Brooke, L.T., Call, D.J., Geiger, D.L. and Northcott,C.E. (Editors) 1984. Acute toxicities of organic chemicals to fathead minnows (Pimephales promelas), Vol.1. Center for lake Superior Environmental Studies, University of Wisconsin-Superior: p181.

(27) Linden, E., Bengtsson, B.E., Svanberg, O. and Sundstrom, G., 1979. The acute toxicity of 78 chemicals and pesticides formulations againsttwo brackish water organisms, ... Chemosphere, 8(11/12), 843/851.

(28) Bridie A.L., Wolff, C.J.M. and Winter, M, 1979. The acute toxicity some petrochemicals to goldfish. Water Research, 13(7), 623/626.

(29) Dawson, G.W., Jennings, A.L., Drozdowski, D . and Didier, (1975/1977). The acute toxicity of 47 industrial chemicals to fresh saltwater fishes. J. Hazardous Materials, 1(4), 303/318.

(30) Verschueren, K. Handbook of Environmental Data on Organic Chemicals. Third Edition 1996

(31) Elnabarawy, M.T., Welter, A.N. and Robideau, R.R., 1986. Relative sensitivity of three daphnid species to selected organic and inorganic chemicals. Environ. Toxicol. Chem., 5(4), 393/398.

(32) Jackim, E.; Nacci, D. (1984) A rapid aquatic assay utilizing labelled thymidine incorporation in sea urchin embryos. Env. Toxicol. Chem. 3:631-636

(33) Nacci, D.E.; Jackim, E. (1985) Rapid aquatic toxicity assay using incorporation of tritiated-thymidine into sea urchin Arbacia puntulata embryo: Evaluation of toxicant exposure procedures. Aquatic Toxicology and Hazard Assessment 8th Symposium ASTM STP 891, BAhner, R.C. & Hansen, D.J. Eds. ASTM pp382-394

(34) Thiebaud, H.; Chedaille, D. 1999 Hexylene glycol inhibition de la croissance des algues. Elf Atochem S.A. Centre d'application de Levallois Study no. 4116/97/A

(35) Curtis, C., Lima, A., Lozano, S.J. and Veith, G.D., 1982. Evaluation of a bacterial bioluminescence bioassay as a method for predicting acute toxicity of organic chemicals to fish. Aquatic toxicology and hazard assessment : 5th Annual Symposium on Aquatic Toxicity, ASTM STP 766:170/178.

(36) Kaiser, L.E. ; Palabrica, V.W. Photpbacterium phosphoreum Toxicity Data Index. Water Poll. Res. J. Canada 26(3):361-431, 1991

(37) Daugherty, L.C., 1980. The growth of Pseudomonas aeruginosa on glycol of industrial importance. Lubrication Engin., 36, 718-723.

(38) Gardner, J.R. (1996) Hexylene glycol: Acute oral toxicity study in the rat. Report No. 1439/15-1032 from Corning Hazelton (Europe) to Shell Chemicals Europe Ltd October 1996 Shell Toxicology Report No. 96.1248

(39) Smyth, H.F.; Carpenter, C.P. (1948) Further experience with the range-finding test in the industrial laboratory. J. Ind. Hyg. Tox. 30(1): 63-68

(40) Opdyke, D. (1978) Fragance Raw Material Monographs : Hexylene Glycol. Food & Cosmet. Tox., 16(1):777-778.

(41) Woodard, G.; Johnson, V.D.; Nelson, A.A. (1945) Acute toxicity of 2-methyl-2,4-pentanediol. Fedn Proc Fedn Am Soc Exp Biol 4:142-143.

(42) German MAK Commission (1997) Hexylene glycol

(43) Industrial Biotest Laboratories (1970) Data sheets 12-4/1970. BIOFAX unpublished data.

(44) British Industrial Biological Research Association (BIBRA) Toxicity profile Hexylene glycol. 1991 Reporting unpublished data from the Mellon Institute (Union Carbide) 1946

(45) Union Carbide (1949) The acute and subacute toxicity of methyl pentane diol. Mellon Institute of Industrial Research, Special report 12-54,

(46) R.T.E.C.S. on line October 1991

(47) Final Report of the safety assessment of Butylene Glycol, Hexylene Glycol, Ethoxydiglycol and Dipropylene Glycol J. Amer. College Toxicol., 4(5), pp. 223/248, 1985.

(48) Anderson, H.H. and McOmie, W.A. (1946). Hexylene glycol. Report UC 86, University of California Medical School.

(49) SCC (Shell Chemical Corporation). (1958). Industrial Hygiene Bulletins. Hexylene Glycol, SC:57-101 and SC:57-102.

(50) RTECS on line 2001

(51) Wenzel, D.G.; Koff, G.Y. (1956) Anticonvulsant properties of some alkyldiols, alkyldiones and related compounds. J. Am. Pharm. Assoc. 45:669-672

(52) British Industrial Biological Research Association (BIBRA) Toxicity profile Hexylene glycol. 1991 Reporting unpublished data from the Mellon Institute (Union Carbide)

(53) Gardner, J.R. (1996) Hexylene glycol: Acute dermal toxicity study in the rat. Report No. 1439/16-1032 from Corning Hazelton (Europe) to Shell Chemicals Europe Ltd, October 1996 Shell Toxicology Report No. 96.1249

(54) Hine CH, Anderson HH and Evans E. (1956). Toxicity studies on a series of organic solvents. Report UC 259, University of California Medical School.

(55) Parcell, B.I. (1995) Hexylene glycol: Skin irritation in the rabbit. Report No. SLL 302/950034/SE from Huntingdon Research Centre to SIPM B.V.

(56) Guillot JP et al. (1982) Safety evaluation of some humectants and moisturizers used in cosmetic formulations. Int. J. Cos. Sc. 4:67-80.

(57) Gardner, J.R. (1996) Hexylene glycol eye irritation study in the rabbit. Report no. 1439/17-1032 from Corning Hazelton to Shell Chemicals Europe Ltd, Toxicology report No. 96.1250

(58) Coombs, A.D. (1978) Toxicity of solvents: Eye irritation study on hexylene glycol. Shell Research Ltd, Sittingbourne Research Centre, Report No. TLGR.0035.78

(59) Gardner, J.R. (1996) Hexylene glycol: Skin sensitisation study in the guinea pig (Buehler method) Report no. 1439/018-1032 from Corning Hazelton to Shell Chemicals Europe Ltd, Toxicology report No. 96.1251

(60) Fabreguettes, C. (1999b) Hexylene glycol: 13-week study by oral administration (gavage) to rats followed by a four-week treatment-free period. Report from CIT study number 15837 TSR and addendum to Elf Atochem SA, France, Sponsor.

(61) Fabreguettes, C. (1999a) Hexylene glycol: Two-week range-finding toxicity study by oral administration (gavage) in rats. Report from CIT study number 15836 TSR to Elf Atochem SA, France, Sponsor.

(62) Clode SA. (1997). Hexylene glycol: 14 day Oral (gavage administration) toxicity study in the rat. Covance Laboratories, Ltd, North Yorkshire England, Report No. CHE121/28. Study sponsored by Shell Chemicals Europe Ltd (Toxicology Report No. 97.1195).

(63) Brown B, Schaffarzick RW and Dreisbach RH. (1955). Anticonvulsant properties of certain secondary and tertiary alcohols. J. Pharmacol. Exp. Ther. 115:230-239.

(64) Union Carbide Corporation (1976) Hexylene Glycol 9-day repeated aerosol inhalation by rats. Carnegie-Mellon Institute of Research Special Report 39-42, April 7, 1976

(65) British Industrial Biological Research Association (BIBRA) Toxicity profile Hexylene glycol. 1991 Reporting unpublished data from the Mellon Institute (Union Carbide) 1949

(66) British Industrial Biological Research Association (BIBRA) Toxicity profile Hexylene glycol. 1991 Reporting unpublished data from the Mellon Institute (Union Carbide)1961

(67) Union Carbide Corporation (1961) Results of three months of inclusion of hexylene glycol in the diet of rats. Mellon Institute of Industrial Research, Report 24-31, April 24th, 1961.

(68) Union Carbide (1950) Repeated inunction of rabbits with methyl pentane diol. Mellon Institute of Industrial Research, Special report no. 13-71 dated 24th August 1950.

(69) Larsen V. (1958). The toxicity of 2-methyl-pentan-2,4-diol (Hexylene glycol) by chronic oral administration to rats and mice. Acta Pharmacol et Toxicol, 14:341-349.

(70) Brooks, T.M. et al., (1988) The genetic toxicology of some hydrocarbon and oxygenated solvents. Mutagenesis, 3(3): 227-232

(71) Meyer, A.L; Brooks, T.M; Wiggins, D.E. (1985) Genotoxicity studies with hexylene glycol. Shell Research Ltd, Sittingbourne Research Centre Report No. SBGR.85.253.

(72) Clode SA. (1997). Hexylene glycol: Oral (gavage) study of embryo-foetal development in the rat. Covance Laboratories, Ltd, North Yorkshire England report No. 121/27. Study sponsored by Shell Chemicals Europe Ltd (Toxicology Report No. 97.1195).

(73) Daston, G. Letter dated June 23rd 1999 from G. Daston, Procter and Gamble Co. to M.Banton, Shell Chemical Co.

(74) Denny, K.H (1996) Developmental toxicity study in rats. Test article: D1748.01 (hexylene glycol). Report from MPI Research formerly International Research and Development Corporation, Mattawan, MI, USA. Study no. 191-1606 to The Procter & Gamble Co (sponsors).

(75) Satala, B.S. (1995) Range-finding developmental toxicity study in rats. Test article: D1748.01 (hexylene glycol). Report from International Research and Development Corporation, Mattawan, MI, USA. Study no. 191-1605 to the Procter & Gamble Co (sponsors).

(76) Johnson EM, Gabel BEG and Larsen J. (1984). Developmental toxicity and structure/activity correlates of glycols and glycol ethers. Env Health Persp, 57:135-139.

(77) Diechmann WB and Dierker M. (1946). The spectrophotometric estimation of hexuronates (expressed as glucuronic acid) in plasma or serum. J. Biol. Chem. 163:753

(78) Gessner P.K.; Parke, D.V.; Williams, R.T. (1960)Studies in detoxification 80. The metabolism of glycols. . Biochem. J. 74:1-5

(79) Chen, TH et al. (1984) Inhibition of metabolic cooperation in Chinese hamster V79 cells by various organic solvents and simple compounds. Cell Biol. Toxicol. 1:155-171

(80) Norberg B. (1979). Cytoplasmic microtubules and radial-segmented nuclei (reider cells). Effects of osmolality, ionic strength, pH, penetrating non-electrolytes, griseofulvin, and a podo-philline derivative. Scand J Haemat, 7:349-356.

(81) Malaisse WJ, Malaisse-Lagae F, Walker MO and Lacy PE. (1971). The stimulus-secretion coupling of glucose-induced insulin release. V. The participation of a microtubular-microfilamentous system. Diabetes, 20(5):257-265.

(82) Crispe N. (1976). The effect of vinblastin, colchicine and hexylene glycol on migration of human monocytes. Exp Cell Res Vol, 100(2):443-447.

(83) Williams JA and Wolff J. (1972). Colchicine-binding protein and the secretion of thyroid hormone. J Cell Biol, 54(1):157-165.

(84) Seybold J, Bieger W and Kern HF. (1975). Studies on intracellular transport of secretory proteins in the rat exocrine pancreas. II. Inhibition by antimicrotubular agents. Virchows Arch A Path Anat Hist, 368:309-327.

(85) Fulton, J.E. (1976) Non-comedogenic cosmetics. Cutis 17:344-351.

(86) Jacobson E. (1958). The excretion of hexylene glycol (2-methyl-2,4-pentane diol) in man. Acta Pharmacol et Toxicol, 14:207-213.

(87) Kinnunen T and Hannuksela M. (1989). Skin reactions to hexylene glycol. Contact Dermatitis, 21:154-158.

(88) Alomar, A. et al (1985). Occupational dermatoses from cutting oils. Contact Dermatitis 12:129-138.

(89) Silverman L, Schulte HF, and First MW. (1946). Further studies on sensory response to certain industrial solvent vapors. J Ind Hyg Toxicol. 28:262-266.

(90) Hine CH, Anderson HH and Kodama, JK (1955). Sensory thresholds with certain Shell organic solvents. Report UC 247, University of California Medical School.

(91) Procter, D.S.C. et al (1966). Coma in burns the cause traced to dressings. S.A. Medical Journal 40:1116-1120.

(92) Fischer, A.J. G. et al. (1968). Burn coma due to dressings impregnated with hexylene glycol. S.A. Medical Journal :975-976