FOREWORD INTRODUCTION

Monoethylene Glycol Ethers Category

CAS N°:

2807-30-9
111-76-2
112-07-2
112-25-4

SIDS Initial Assessment Report

For

SIAM 19

Berlin, Germany, 19-22 October 2004

1.	**Chemical Name:**	Monoethylene Glycol Ethers Category
2.	**CAS Number:**	2807-30-9, 111-76-2, 112-07-2, 112-25-4
3.	**Sponsor Country:**	USA U.S. Environmental Protection Agency Mr. Oscar Hernandez, Director Risk Assessment Division (7403M) 1200 Pennsylvania Ave., NW Washington, DC 20460 Phone: 202-564-7641
4.	**Shared Partnership with:**	No partner, single sponsor
5.	**Roles/Responsibilities of the Partners:**	Not Applicable
•	Name of industry sponsor /consortium	ACC Ethylene and Propylene Glycol Ethers Panel CEFIC Oxygenated Solvents Producers Association
•	Process used	The industry sponsor conducted a comprehensive literature search, including all generally accepted databases, reference books, unpublished studies and data in company files. This information formed the basis for compilation of the IUCLID dossier
6.	**Sponsorship History**	
•	How was the chemical or category brought into the OECD HPV Chemicals Programme?	The Ethylene Glycol Ethers and Propylene Glycol Ethers Panels of the American Chemistry Council notified the Environmental Protection Agency that they wished to volunteer to sponsor a number of ethylene glycol ethers in SIDS program, including mono ethylene glycol ethers. Originally these chemicals were to be part of a category of low boiling ethylene glycol ethers, but the EPA and the sponsors later agreed that the mono ethylene glycol ethers should be sponsored as a separate category from the diethylene glycol ethers, which will be presented as a separate, subsequent category.
7.	**Review Process Prior to the SIAM:**	SIDS Dossiers and Testing Plan were reviewed by the US EPA and the following SIDS Testing Plan was recommended: no testing (X)
8.	**Quality check process:**	On completing the literature search and data collection, important and significant studies were identified for all endpoints. These studies were reviewed and summarized

following current guidelines for robust summaries. Reliability ratings were assigned following the Klimisch rating system. Studies assigned ratings of 1 or 2 were considered to be acceptable. The key studies were identified based on completeness, protocol and GLP use and other quality factors. These were flagged as critical studies. The summaries were compiled using the IUCLID program.

9. Date of Submission: May 18,2004

10. Date of last Update: July 23,2004

11. Comments: Data on Ethylene glycol butyl ether (EGBE) are contained within this submission. 2-butoxyethanol (EGBE) was previously reviewed at SIAM 6 and reviewed again at SIAM 23 due to new data available. The reader should look for the SIAP agreed at SIAM 23.

SIDS INITIAL ASSESSMENT PROFILE

CAS No.	2807-30-9, 111-76-2(surrogate only), 112-07-2, 112-25-4
Chemical Name	Monoethylene glycol ethers category (Mono EGEs)
Structural Formula	$HOCH_2\ CH_2OCH_2CH_2CH_3$ Ethylene glycol propyl ether (EGPE, CAS No. 2807-30-9), $HOCH_2\ CH_2O\ CH_2\ CH_2CH_2\ CH_3$ Ethylene glycol butyl ether (EGBE, CAS No. 111-76-2), $CH_3C(=O)OCH_2\ CH_2O\ CH_2CH_2CH_2CH_3$ Ethylene glycol butyl ether acetate (EGBEA, CAS No. 112-07-2), $HOCH_2\ CH_2OCH_2CH_2\ CH_2CH_2\ CH_2CH_3$ Ethylene glycol hexyl ether (EGHE, CAS No. 112-25-4)

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

The four substances of this category all have similar molecular structures, functionality and metabolic pathways. The category members demonstrate similar physicochemical properties and mammalian toxicity. EGBE is included in the category only to fill data gaps for mammalian toxicity. A separate dossier on EGBE is not included as this chemical's data set was previously agreed to at SIAM 6. The reader should refer to the existing SIDS dossier for additional information on EGBE. The acetylated glycol ether, EGBEA, although rapidly metabolized *in vivo* to its corresponding glycol ether, is not expected to hydrolyze rapidly to EGBE in the aqueous environment. Therefore, EGBEA aquatic toxicity data are not extrapolated to the other category members.

Toxicokinetics

EGPE, EGBE and EGHE are substrates for alcohol dehydrogenase isozyme ADH-3, which catalyzes the conversion of their terminal alcohols to aldehydes (which are transient metabolites). Further, rapid conversion of the aldehydes by aldehyde dehydrogenase produces alkoxyacetic acids, which are the predominant urinary metabolites of mono substituted glycol ethers; for example, 2-propoxy acetic acid (PAA) is a metabolite of EGPE and butoxy acetic acid (BAA) is a metabolite of EGBE. At equivalent concentrations, metabolism of EGPE is less rapid than EGBE and more rapid than EGHE.

Human Health

Oral LD_{50} values in rats for all category members range from 739 (EGHE) to 3089 mg/kg bw (EGPE), with values increasing with decreasing molecular weight. Four to six hour acute inhalation toxicity studies were conducted for these chemicals in rats at the highest vapour concentrations practically achievable. Values range from LC_0 > 85 ppm (508 mg/m^3) for EGHE, LC_{50} > 400ppm (2620 mg/m^3) for EGBEA to LC_{50} > 2132 ppm (9061 mg/m^3) for EGPE. No lethality was observed for any of these materials under these conditions.Dermal LD_{50} values in rabbits range from 435 mg/kg bw (EGBE) to 1500 mg/kg bw (EGBEA). Overall these category members can be considered to be of low to moderate acute toxicity. All category members cause reversible irritation to skin and eyes, with EGBEA less irritating and EGHE more irritating than the other category members. EGPE and EGBE are not sensitizers in experimental animals or humans.

Signs of acute toxicity in rats, mice and rabbits are consistent with hemolysis (with the exception of EGHE) and non-specific CNS depression typical of organic solvents in general. Alkoxyacetic acid metabolites, PAA and BAA,

are responsible for the red blood cell hemolysis. Signs of toxicity in humans deliberately ingesting cleaning fluids containing 9-22% EGBE are similar to those of rats, with the exception of hemolysis. Although decreased blood hemoglobin and/or hemoglobinuria were observed in some of the human cases, it is not clear if this was due to hemolysis or hemodilution as a result of administration of large volumes of fluid. Red blood cells of humans are many-fold more resistant to toxicity from EGPE and EGBE *in vitro* than those of rats. Accepted PBPK models are available for rats and humans which predict the distribution and metabolism of EGBE. These demonstrate that even at saturated vapor concentrations of EGBE, it is not possible to reach haemolytic blood concentrations of BAA in humans by the inhalation route of exposure.

Evaluation of hemolysis and its associated effects in the liver, spleen, and kidney of rodents and rabbits was done by repeatedly exposing rats via inhalation to 100, 200, or 400 ppm EGPE (425, 850, or 1700 mg/m^3) 6h/day, 5d/week for 14 weeks or to EGBE (rats and mice) at 31, 62.5, 125, 250, 500 ppm (150, 302, 603, 1207 or 2415 mg/m^3) and to EGHE (rats) at 20, 41 or 71 ppm (120, 245 or 425 mg/m^3). The NOAEL for EGPE in rats was 100 ppm and those for EGBE were less than 31 ppm (150 mg/m^3) in rats and 62.5 ppm (302 mg/m^3) in mice, respectively. For EGHE the NOAEL was 41 ppm (245 mg/m^3). Orally administered EGPE to rats at gavage doses of 195, 390, 780, or 1560 mg/kg bw/day for 6 weeks, generated a NOAEL of 195 mg/kg bw/day. Hemolysis and histopathological changes in the liver and kidney were not seen in rats exposed for 14 weeks with up to 71 ppm (425 mg/m^3) EGHE by inhalation, suggesting that this material is not as potent a hemolytic agent as EGBE. In the case of EGBE and EGPE, the hemolytically active agents have been shown to be the acid metabolites, BAA and PAA, respectively.

The fact that the NOAEL for repeated dose toxicity of EGBE is less than that of EGPE is consistent with red blood cells being more sensitive to EGBE than EGPE. Blood from mice, rats, hamsters, rabbits and baboons were sensitive to the effects of BAA *in vitro* and displayed similar responses, which included erythrocyte swelling (increased hematocrit and mean corpuscular hemoglobin), followed by hemolysis. Blood from humans, pigs, dogs, cats, and guinea pigs was less sensitive to hemolysis by BAA *in vitro*.

In the absence and presence of metabolic activation, EGBE tested negative for mutagenicity in Ames tests conducted in *S. typhimurium* strains TA97, TA98, TA100, TA1535 and TA1537 and EGHE tested negative in strains TA98, TA100, TA1535, TA1537 and TA1538. *In vitro* cytogenicity and sister chromatid exchange assays with EGBE and EGHE in Chinese Hamster Ovary Cells with and without metabolic activation and in vivo micronucleus tests with EGBE in rats and mice were negative, indicating that these glycol ethers are not genotoxic.

The US National Toxicology Program (NTP) conducted a 2-year inhalation chronic toxicity and carcinogenicity study with EGBE in rats and mice. A significant increase in the incidence of liver hemangiosarcomas was seen in male mice and forestomach tumours in female mice. The data were evaluated by IARC in June 2004 and EGBE was classified as IARC Group 3 (inadequate evidence of carcinogenicity in humans and limited evidence of carcinogenicity in animals). In 2000, the EU classification of EGBE was reviewed under the European Commission process for the classification and labeling of dangerous substances. It was decided that based on the mode of action data available, there was no significant hazard for human carcinogenicity and there was no support for a category 3 (carcinogen) classification. This decision was reconfirmed in 2004.

The results of reproductive and developmental toxicity studies indicate that the glycol ethers in this category are not selectively toxic to the reproductive system or developing fetus, developmental toxicity is secondary to maternal toxicity. Results of the 2-generation, continuous breeding study in CD1-mice exposed by drinking water to 700, 1,300, or 2,100 mg/kg bw/day EGBE show that parental toxicity was observed at all doses tested (significantly reduced liver and kidney weights at the lowest dose, severe toxicity, including death at the mid and higher doses) and fertility was affected at the two highest doses. Although there was no effect of 700 mg/kg bw/day on fertility, live pup weights from animals in this group were slightly but statistically significantly reduced. The parental and offspring LOAELs were 700 mg/kg bw/day but the NOAEL can be considered close to this value. The repeated dose toxicity studies in which reproductive organs were examined indicate that the members of this category are not associated with toxicity to reproductive organs (including the testes).

Results of the developmental toxicity studies conducted via inhalation exposures during gestation periods on category members EGPE (rabbits -125, 250, 500 ppm or 531, 1062, or 2125 mg/m^3 and rats - 100, 200, 300, 400 ppm or 425, 850, 1275, or 1700 mg/m^3), EGBE (rat and rabbit - 25, 50, 100, 200 ppm or 121, 241, 483, or 966 mg/m^3), and EGHE (rat and rabbit - 20.8, 41.4, 79.2 ppm or 124, 248, or 474 mg/m^3) indicate that the members of the category are not teratogenic.

Inhalation of a maternally toxic concentration of EGBE [100 ppm (or 483 mg/m^3) in the rat and 200 ppm (or 966 mg/m^3) in the rabbit] throughout gestation was associated with embryotoxicity, as evidenced by an increased

number of resorptions, and a decreased number of implantations. An increase in the number of fetuses with skeletal variations was noted in offspring of rats exposed to maternally toxic concentrations of EGPE by inhalation (≥ 200 ppm or 966 mg/m^3). In rats exposed to EGHE and rabbits exposed to EGHE or EGPE by inhalation, no effects on the fetus were noted (even at concentrations that produced maternal toxicity).

The NOAELs for developmental toxicity are greater than 500 ppm or 2125 mg/m^3 (rabbit-EGPE), 100 ppm or 425 mg/m^3 (rat-EGPE), 50 ppm or 241 mg/m^3 (rat EGBE) and 100 ppm or 483 mg/m^3 (rabbit EGBE) and greater than 79.2 ppm or 474 mg/m^3 (rat and rabbit-EGHE). Based on the structural similarities between the members, developmental toxicity data for the tested glycol ethers are expected to be predictive of data for EGBEA.

Environment

Members of the category are high boiling liquids (boiling points in the 150-208ºC range), with low melting points (-70 to -50°C). Vapor pressures are in the range of 0.067-1.3 hPa at room temperature. Water solubility values range from soluble (EGHE 9.9 g/L, EGBEA 15 g/L) to miscible (EGPE and EGBE). Octanol-water partition coefficients range from 0.79 to 1.97. Henry's Law Constants range from $7.38x10^{-8}$ to $6.38x10^{-6}$ atm-m^3/mole. Hydroxyl radical induced photodegradation half-lives range from 4.9 – 6.0 hours.

EGPE and EGHE, like other simple glycol ethers, possess no functional groups in their molecular structures that are readily subject to hydrolysis in the presence of water. EGBEA, however, possesses an ester group that is estimated to have a half-life of about 30 days in neutral ambient water under abiotic conditions. Level III fugacity modeling indicates that category members, when released to air and water, will partition predominately to water and, to a lesser extent, to air and soil. Estimates of soil and sediment partition coefficients (Kocs ranging from 1 – 10) suggest that category members would exhibit high soil mobility. Estimated bioconcentration factors (log BCF) range from 0.463 to 0.732. Biodegradation studies indicate that all category members are readily biodegradable. The physical chemistry and environmental fate properties indicate that category members will not persist or bioconcentrate in the environment.

The aquatic toxicity data for ethylene glycol ether acetate (EGBEA) and the glycol ethers (EGPE, EGBE and EGHE) are considered separately because glycol ether acetates do not hydrolyze rapidly into their corresponding glycol ethers in water under environmental conditions. The LC_{50} or EC_{50} values for EGHE (which has the longest chain length and highest log Kow value) are lower than those for EGPE and EGBE (which have shorter chain lengths and lower log Kow values). Overall, the LC_{50} values for the glycol ethers in aquatic species range from 94 to > 5000 mg/L. For EGHE, the 96-hour LC_{50} for *Brachydanio rerio* (zebra fish) is between 94 and215 mg/L, the 48-hour EC_{50} for *Daphnia magna* was 145 mg/L and the 72-hour EC_{50} values for biomass and growth rate of algae (*Scenedesmus subspicatus*) were 98 and 198 mg/L, respectively. LC_{50}/EC_{50} values for EGPE and EGBE in aquatic species are 835 mg/l or greater.

Aquatic toxicity data for EGBEA show a 96-hour LC_{50} of 28.3 mg/L for rainbow trout (*Oncorhynchus mykiss)*, a 48-hour LC_{50} of 37-143 mg/L for *Daphnia magna*, a 72-hour EC_{50} of greater than 500 mg/L for biomass or growth rate of algae (*Scenedesmus subspicatus* and *Pseudokirchneriella subcapitata*, respectively), and a 7-day EC_{10} of 30.4 mg/L and a NOEC of 16.4 mg/L for reproduction in *Ceriodaphnia dubia*.

Exposure

Annual U.S. production volumes for EGPE and EGBEA are each in the range of 4,540 – 22,700 metric tons. The production volume for EGHE is 450 – 4,500 metric tons. The use patterns for these materials are similar, with qualitative differences. All are used predominately as solvents or coalescing aids for surface coatings, printing inks, metal cleaners, detergents, fire foams, oil field chemicals, pharmaceutical manufacture, agricultural chemicals, leather manufacture and finishing cleaners and adhesives. They are also used as chemical intermediates and in hair dyes. Most applications are industrial, but these materials may also be present at the 1-10% range in some consumer products.

Human exposures to category members occur primarily via inhalation and dermal contact. Exposures occur to some extent during manufacture and formulation into products, but are more likely to be associated with the widespread uses given above. Exposure during manufacture is limited by the predominately closed, continuous nature of the process and equipment. Some releases to the atmosphere and water may occur during manufacture through venting and aqueous streams. Aqueous waste streams are routinely biologically treated. Although engineering controls and work practices may limit exposures during industrial use, solvent application conditions may vary widely, and atmospheric releases are expected through solvent evaporation.

Consumers may be exposed through use of products containing category members and also from environmental concentrations. Because category members degrade readily in the environment, environmental exposure should not be a major concern. Exposure monitoring information is not readily available.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK

These chemicals are currently of low priority for further work.

Human Health: The substances in the category possess properties indicating a hazard for human health (reversible eye and skin irritation, reversible CNS depression). These hazards do not warrant further work. However, they should nevertheless be noted by chemical safety professionals and users. Hemolysis and associated organ toxicity are noted in rats, mice and rabbits exposed to EGPE and EGBE. Humans are many-fold less sensitive to these effects and associated organ toxicity. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: EGPE, EGBE, and EGHE are of low priority for further work because of their low hazard profile. EGBEA possesses properties indicating a hazard for the environment. These hazards do not warrant further work as they are related to acute toxicity which may become evident only at high exposure level and the substance is readily biodegradable. However, they should be noted by chemical safety professionals and users.

SIDS Initial Assessment Report

1 IDENTITY

1.1 Identification of the Substance

CAS Number: 2807-30-9
111-76-2
112-07-2
112-25-4

IUPAC Name: 2807-30-9: Ethylene glycol propyl ether
111-76-2: Ethylene glycol butyl ether
112-07-2: Ethylene glycol butyl ether acetate
112-25-4: Ethylene glycol n-hexyl ether

Molecular Formula: 2807-30-9: $C_5H_{12}O_2$
111-76-2: $C_6H_{14}O_2$
112-07-2: $C_7H_{16}O_3$
112-25-4: $C_8H_{18}O_2$

Structural Formula: 2807-30-9: $HOCH_2\ CH_2OCH_2CH_2CH_3$
111-76-2: $HOCH_2\ CH_2O\ CH_2\ CH_2CH_2\ CH_3$
112-07-2: $CH_3C(=O)OCH_2\ CH_2O\ CH_2CH_2CH_2CH_3$
112-25-4: $HOCH_2\ CH_2OCH_2CH_2\ CH_2CH_2\ CH_2CH_3$

Molecular Weight: 2807-30-9: 104.15
111-76-2: 118.18
112-07-2: 160.21
112-25-4: 146.23

Synonyms:

Ethylene glycol propyl ether (IUPAC Name):
2-propoxyethanol; Eastman EP ®solvent; EGPE; EP; ethylene glycol monopropyl ether; n-Propyl Oxitol® Glycol; Propyl Cellosolve®; propyl glycol

Ethylene glycol butyl ether (IUPAC Name):
BGE; beta-butoxyethanol; 2-butoxy-1-ethanol; 2-butoxyethanol; butoxyethanol; Butyl Cellosolve®; butyl glycol; butyl glycol ether; butylglycol; butylglykol; Butyl Oxitol® Glycol; Dowanol® EB; Eastman® EB Solvent; EB; EGBE; ethanol, 2-butoxy-; ethylene glycol n-butyl ether; ethylene glycol, monobutyl ether; ethylenglycolmonobutylether; ethylene glycol mono-n-butyl ether; ethylenglykolmono-n-butylether; ethylenglykolmonobutylether; Glycol Ether EB; glycol monobutyl ether; glykolmonobutylether; 1-hydroxy-2-n-butoxyethane; monobutyl glycol ether

Ethylene glycol butyl ether acetate (IUPAC Name):
BGA; 2-butoxy-ethylacetaat; 2-butoxyethyl acetate; butoxyethyl acetate; Butylglycol acetate; Butyl Cellosolve® Acetate; butyl ethoxyl acetate; butyl glycol acetate; butylglykolacetat; Butyl Oxitol® Acetate; Eastman® EB Acetate; EGBEA; ethanol, 2-butoxy, acetate; ethyleneglycolbutylether acetate; ethyleenglycolmonobutyletheracetaat; ethylene glycol monobutyl ether acetate; glycol monobutyl ether acetate;

glycolmonobutylether acetate

Ethylene glycol n-hexyl ether (IUPAC Name):
ethanol, 2-(hexyloxy)-; EGHE: ethylene glycol mono hexyl ether; ethylene glycol mono hexyl ether; ethylene glycol monohexyl ether; glycol monohexyl ether; Hexylcellosolve; Hexyl Cellosolve ®; n-Hexyl Cellosolve®; 2-(hexyloxy)ethanol; n-hexylglykol; 3-oxa-1-nonanol

The OECD guidance document on the development and use of chemical categories sets forth a definition of what constitutes a "chemical category, for the purposes of the Challenge Program." Specifically, that definition states that a chemical category under the HPV Challenge Program "is a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity." This category of four mono-substituted ethylene glycol ethers has been selected with this guidance in mind.

Ethylene glycol butyl ether (EGBE) was previously reviewed at SIAM 6, and is included in the category only to fill data gaps and provide supporting data for the other category members. Therefore, a separate dossier on EGBE is not included. Data for EGBE have been added to the dossiers of the other category members only when existing data for those category members are not adequate. The reader should refer to the existing SIDS dossier (at http://cs3-hq.oecd.org/scripts/hpv/) for additional information on EGBE.

1.2 Purity/Impurities/Additives

The purities of commercial monoethylene glycol products are as follows:

Ethylene glycol propyl ether:	> 99.0% w/w (Eastman Chemical Company, 2001a)
Ethylene glycol butyl ether:	≥ 99.4% w/w (Eastman Chemical Company, 2005)
Ethylene glycol butyl ether acetate:	> 99.0% w/w (Eastman Chemical Company, 2001b)
Ethylene glycol n-hexyl ether:	≥ 98-100% w/w (Dow, 2005)

1.3 Physico-Chemical properties

Table 1 Summary of physico-chemical properties

Chemical	Physical State	Melting Point (°C)	Boiling Point[a] (°C)	Relative Density	Vapour Pressure[b] (hPa)	Water Solubility[b] (g/l)	Log Pow	Henry's Law Constant[a,c] (atm-m^3/mole)
EGPE 2807-30-9	liquid	≈-60[d]	150-152[d]	0.913[e]	1.3[d]	Miscible[d]	0.075[c]	7.38 E-8
EGBE 111-76-2	liquid	<-75[f]	170[g]	0.90[g]	0.8[g]	Miscible[h]	0.81[i]	1.6 E-6
EGBEA 112-07-2	liquid	-64[g]	184-195[g]	0.94[g]	0.4[g]	15[g]	1.57[c] 1.51[g]	6.38 E-6
EGHE 112-25-4	liquid	-50.1[g]	208.1[g]	0.89[g]	0.067[g]	9.9[g]	1.55[c] 1.97[j]	1.73 E-7

[a]at 1013 hPa; [b]at 20-25 ° C; [c]Estimated using EPIWIN [The EPI (Estimation Programs Interface) Suite™ developed by the Environmental Protection Agency Office of Pollution Prevention Toxics and Syracuse Research Corporation (SRC)(2000)]; [d]ECETOC 2005; [e]Boatman and Knaak, 2001; [f] Riddick, 1986; [g]Verschueren, 1996; [h] Hoechst AG, 1997; [i]BASF AG, 1987; [j]BASF AG, 1989a.

For the most part, category members have similar properties. All members are liquids at ambient temperatures, with relatively low melting points ranging from –64° C to <–40°C. Boiling points range from 150° to 208°C, with values generally increasing with higher molecular weight. Relative densities are similar (0.89-0.94), and are slightly less than water. Vapour pressures are correspondingly low, ranging from 0.067 to 1.3 hPa at 20-25°C. Water solubility ranges from soluble (9.9 g/l) to miscible. Measured partition coefficients (Log Pows) range from 0.81 to 1.97, and calculated values are somewhat lower (0.076 to 1.57), with values generally increasing with increasing alkyl chain length and decreasing polarity. EGBE (which has a free hydroxyl group) is more hydrophilic (lower Log Pow) than EGBEA (which lacks a free hydroxyl group). The partition coefficients of all category members are all sufficiently low to suggest limited tendency to partition to soil or to concentrate in fat. Estimated Henry's Law Constant values range from 7.37E-8 to 6.38E-6, indicating limited potential for volatilization to air from water.

1.4 Category Justification

Using a category approach for screening level hazard assessment for the glycol ethers described above is appropriate based on the following attributes that these materials have in common:

The Category Members Have Similar Molecular Structure and Functionality

The category members are closely related structurally, and can be represented by the following generic molecular structure:

$HO(CH_2\ CH_2O)R$ or $CH_3C(=O)O(CH_2\ CH_2O)R$

Ethylene glycol ether Ethylene glycol ether acetate

Where R = normally linked alkyl (propyl, butyl, or hexyl)

All monoethylene glycol ethers have an alkyl group attached to an ethylene glycol group via the ether function, with the difference between the glycol ethers being the particular alkyl group. In the case of the glycol ethers, the other end of the molecule possesses a hydroxyl group, but in the case of the glycol ether acetates, the hydroxyl group is esterified with an acetic acid group.

Category Members Exhibit Similar Physical and Environmental Fate Properties

As shown in Sections 1.3 and 2.2, the category members demonstrate similar physical and environmental fate properties except for slow hydrolysis of acetylated glycol ether in the environment (See hydrolysis discussion below.).

Category Members Exhibit Similar Metabolic Fate, Absorption and Mammalian Toxicity

It is appropriate for the glycol ether acetate EGBEA to be included in this category since available evidence demonstrates that glycol ether acetates are rapidly hydrolyzed to their glycol ether counterparts by esterases present in blood and other tissues. Since the acetates are absorbed to a similar extent as the glycol ethers and are rapidly hydrolyzed to their corresponding glycol ethers by esterases *in vivo,* the patterns of metabolic elimination for glycol ethers and their acetates should be nearly identical. Mono-substituted glycol ethers are substrates for alcohol dehydrogenase (ADH), which catalyzes the conversion of their terminal alcohols to aldehydes. Further conversion of the aldehydes by aldehyde dehydrogenase produces alkoxyacetic acids, which are the major urinary metabolites of mono-substituted glycol ethers and their acetates and the predominant metabolites

responsible for the toxicities of the mono-substituted glycol ethers. Additional information supporting these statements is found in Section 3.1.1.

As mentioned above, glycol ether acetates are rapidly hydrolyzed to their corresponding glycol ethers by mammalian carboxylases. However, the EPIWIN/Hydrowin model predicts that these materials do not hydrolyze readily in water at near neutral pH. Therefore, these materials may not hydrolyze rapidly in the environment. For this reason, the glycol ethers and glycol ether acetates should be considered as separate subgroups for aquatic toxicity, and data for the glycol ethers cannot be used to fill aquatic endpoints for the glycol ether acetates (or vice versa). Accordingly, data for ethylene glycol butyl ether acetate will be presented separately for these endpoints.

Conclusion

In conclusion, the four substances that comprise the monoethylene glycol ethers category all have similar molecular structures and functionality. The only differences in the molecules are whether the alkyl function on the glycol ether backbone is propyl, butyl, or hexyl, and whether or not the hydroxyl group is free or acetylated. The acetylated glycol ether EGBEA should be metabolized rapidly to the corresponding glycol ether EGBE *in vivo,* but is not expected to hydrolyze rapidly to EGBE in the environment. The data provided in the robust summaries and SIAR follow a pattern that is consistent with the close molecular and metabolic similarity of the category members, and confirm the validity of the category.

2 GENERAL INFORMATION ON EXPOSURE

Manufacture/Production

Alkyl glycol ethers are manufactured in a closed, continuous process by reacting ethylene oxide with an anhydrous alcohol in the presence of a suitable catalyst. Depending on the molar ratios of the reactants, and other process parameters, the product mixtures obtained contain varying amounts of the monoethylene-, diethylene-, triethylene-, and higher glycol ethers. Typically, the products in these mixtures are separated and purified by fractional distillation (Boatman et al, 2001). The reactor columns, distillation columns and lines between them and to the storage tanks are closed and under pressure. The storage tanks may have pressure relief vents on them.

In the Unites States there are approximately six different manufacturing sites for the ethylene glycol ethers in this category. These are plant sites for Dow Chemical Company, Eastman Chemical Company, Equistar Chemicals LP, and Shell Chemical Company. There is one manufacturing plant or company in Canada, two in Mexico, two in Brazil, four in Western Europe, one or two in Eastern Europe, and four-five in Japan (Chinn et al., 2000).

2.1 Production Volumes and Use Pattern

Production Volume/Manufacturing Capacity

According to Chinn et al., (2000), total manufacturing capacity in Canada is 11,000 metric tons of glycol ethers; in Mexico capacity is 26,000 metric tons; in Brazil, 51,000 metric tons, in Western Europe, 725,000 metric tons, in Eastern Europe, 10-15,000 metric tons, and in Japan, 60-78,000 metric tons. Please note that these figures are in manufacturing capacity the actual manufacturing volume is not given. In addition, these figures are for ethylene based glycol ethers and acetates in general and not specifically for the category members. Therefore the above figures, which are the only figures available, are greater than likely manufacturing volume for the category members themselves.

U.S. Manufacturing volumes for category members are given below, based on the 2002 US EPA TSCA Inventory Update Report:

2807-30-9: Ethylene glycol propyl ether: 4,540 – 22,700 metric tons in the U.S.
111-76-2: Ethylene glycol butyl ether: 45,400 – 227,000 metric tons in the U.S.
112-07-2: Ethylene glycol butyl ether acetate: 4,540 – 22,700 metric tons in the U.S.
112-25-4: Ethylene glycol n-hexyl ether: 454 – 4,540 metric tons in the U.S.

European production volumes (production, not capacity) in 2003 were as follows (BIAC, 2004):

2807-30-9: Ethylene glycol propyl ether: no known production.
111-76-2: Ethylene glycol butyl ether: 160,000 metric tons.
112-07-2: Ethylene glycol butyl ether acetate: 13,000 metric tons.
112-25-4: Ethylene glycol n-hexyl ether: <1000 metric tons.

Uses and Applications for Monoethylene Glycol Ethers

Chemical	CAS No.	Use / Application	Source(s)
EGPE	2807-30-9	Variety of surface coatings, cleaners and intermediates. Coalescing agents in water-based coatings and printing applications.	Chinn et al. (2000); Nordic Council of Ministers (2005)
EGBE	111-76-2	Used as a coupling agent for water-based coatings, in vinyl and acrylic paints and varnishes, and as a solvent for nitrocellulose resins, varnishes, enamels, spray lacquers, dry cleaning compounds, textiles, and cosmetics. Also used as a mutual solvent for "soluble" mineral oils to hold soap in solution and to improve emulsifying properties. Used in printing inks, detergents, metal cleaning, fire foams, oil field chemicals, pharmaceutical manufacture, agricultural chemicals, leather manufacture and finishing, adhesives, chemical intermediates. The cosmetics use is only in hair dyes.	Sax and Lewis (1997); OSPA (2002); Nordic Council of Ministers (2005)
EGBEA	112-07-2	High boiling solvent for nitrocellulose lacquers, epoxy resins, multicolor lacquers; film-coalescing aid for polyvinyl acetate latex. Surface coating solvent and fugitive plasticizer in latex adhesive formulations. Used in screen printing inks, meal cleaning, leather finishing.	Sax and Lewis (1997); Chinn et al. (2000); OSPA (2002)
EGHE	112-25-4	High boiling solvent. Coalescing agent in latex paints and cleaners.	Sax and Lewis (1997); Chinn et al. (2000)

2.2 Environmental Exposure and Fate

Category members are released to the environment in substantial quantities as a result of their use as solvents. The physical chemical properties of category members summarized in Section 1.3 and Table 1 are similar, with one difference being the lower water solubilities and higher partition coefficients of EGHE and the ester EGBEA. Data for Henry's Law Constant, photodegradation rate constants, and environmental transport for all category members were estimated (calculated) using standard methods. As shown in Table 2, environmental fate parameters are similar for category members.

Table 2 Environmental fate parameters for category members

Chemical	Photodeg. OH radical rate constant [a] (cm^3/molecule-sec) $T_{1/2}$	Bioconcentration Factor (log BCF) [a]	Predicted Environmental Distribution (Level III fugacity model)[a]			
			Air (%)	Water (%)	Soil (%)	Sed. (%)
EGPE 2807-30-9	21.6128 E-12 5.9 hours	0.50	4.11	70.8	24.9	0.119
EGBE 111-76-2	23 E-12 5.5 hours	0.50	11.4	84.2	4.19	0.132
EGBEA 112-07-2	21.2328 E-12 6.0 hours	0.463	11.1	87.4	1.37	0.162
EGHE 112-25-4	26.3395 E-12 4.9 hours	0.732	8.83	86.4	4.54	0.195

[a] estimated using EPIWIN. Inputs to the EPIWIN program were CAS Nos., measured melting points, boiling points, vapor pressures and water solubilities (where applicable). Emission rates inputted were 1000 kg/hr to air and 500 kg/hr to water.

2.2.1 Sources of Environmental Exposure

Category members have similar production and use patterns. For these reasons, environmental exposures are similar, with qualitative differences. Category members are manufactured in primarily enclosed, continuous reactors and distillation columns. Environmental releases to the atmosphere and water do occur during manufacture, from process vents and aqueous streams, but aqueous waste streams are subject to in-plant biodegradative wastewater treatment. Environmental releases are expected to occur to a much greater extent during use of these chemicals as solvents and coalescing aids in coatings and printing ink formulations and in cleaners and adhesives. These emissions are primarily to the atmosphere through evaporation, and to a lesser extent to water. Although some category members may be used as industrial intermediates that are converted to other chemicals, all are solvents with wide, dispersive uses.

Category members are formulated into a variety of products such as coatings, varnishes, cleaners, etc. as discussed in Section 2.1. Typically, the formulation is carried out in enclosed equipment vessels, which strictly limits the opportunity for evaporation and release. Since formulation is essentially addition and mixing of chemical components into products for packing and distribution, minimal waste or emissions occur at this stage. The most significant environmental releases of category members are expected to take place during the application or enduse of products containing the members. These applications include applying surface coatings, cleaning and printing operations.

We investigated the U.S. Toxic Release Inventory (TRI) for release information on the specific category members. However, due to the TRI reporting requirement being applicable to the entire class of ethylene glycol ethers, the data cannot be broken out to specifically represent the category members. Therefore, there is limited usefulness in providing this data, as it is not applicable. If releases of the category members were to occur, they would be primarily to the air and water compartments.

2.2.2 Photodegradation

Calculated rate constants of the category members with atmospheric hydroxyl radicals fall within a relatively narrow range of 21.2 E-12 to 26.3 E-12. These values suggest photodegradation would

occur at a moderate rate when the category members enter the atmosphere at appreciable concentrations.

2.2.3 Stability in Water

The EPIWIN/Hydrowin program is not able to estimate stability in water (hydrolysis) for the glycol ethers, because it cannot calculate the hydrolysis rate constant for the ether function (R-O-R, where R=organic alkyl group). Ether groups are generally stable to water under neutral conditions and ambient temperatures. The ether function is hydrolyzed by heating in the presence of halogen acids, particularly hydrogen iodide (Fieser and Fieser, 1960). No measured water stability data have been found for the ether acetate (EGBEA), but it can be expected that the acetate ester group of this category member is subject to hydrolysis, with the rate depending on temperature, pH, and other conditions. EPIWIN/Hydrowin indicates that the ester grouping for acetates is subject to hydrolysis, and this model estimates a rate constant of 2.632E-001 L/mol-sec at 25 degrees C at pH>8, and half lives of 30.478 days at pH 8 and 304.777 days at pH 7.

2.2.4 Transport between Environmental Compartments

Level III fugacity modeling indicates that members of this glycol ether category will tend to partition to water predominately, and to a lesser extent to air and soil. Minor differences between category members result from differing Henry's Law Constants and water solubilities, which are affected by the length of the alkyl group, or for EGBEA, which is a less water-soluble ester compared with the ether EGBE. Level I fugacity modeling has been conducted for EGBE and EGBEA. This modeling predicts that 2-5% of the ethers will partition to soil and most will be found in water (Staples *et al.,* 1998; Mackay and Patterson, 1981).

2.2.5 Biodegradation

Table 3 Biodegradation rates for category members and surrogates

Category Member	Biodegradation Rate
EGPE 2807-30-9	100% after 20 days (APHA)[a]
EGBE 111-76-2	88% after 20 days (APHA)[a, *] 100% after 5 days (OECD 302B: Modified Zahn-Wellens)[b] 95% after 28 day (OECD 301E: Modified Screening Test)[b]
EGBEA 112-07-2	72% after 20 days (APHA)[a] > 90% after 6.5 days (OECD 302B: Modified Zahn-Wellens)[c] 96% after 14 days (ISO 7827) [d]
EGHE 112-25-4	100% after 20 days (APHA)[a]

[a] Waggy, 1987; [b] Huels AG; [c] Zahn and Wellens, 1980; [d]BASF AG, 1989b.
* Data are not listed in the dossier presented at SIAM 6.

Guideline biodegradation studies have been conducted for all category members (Table 3). The results indicate that the category members biodegrade readily.

2.2.6 Bioaccumulation

No data were located. EPIWIN-generated log BCF values for EGPE, EGBEA and EGHE are 0.50, 0.463 and 0.732, respectively, indicating little potential for these chemicals to bioaccumulate.

2.3 Human Exposure

Human exposures to category members occur primarily via inhalation and dermal contact. Exposures occur to some extent during manufacture, but to a greater extent during multiple uses as solvents and coalescing aids in surface coatings, printing inks, adhesives and cleaners.

2.3.1 Occupational Exposure

Worker exposures are limited during manufacture by the enclosed, continuous nature of the manufacturing process, and may occur primarily with process control sampling or possible process upsets or spills. Worker exposures are also limited during the formulation step, since formulation takes place in mostly enclosed mixers, where the chemical components are added through pipes or small openings, with local exhaust and engineering controls. These operations are now typically automated. Automation carries through to dispensing the formulation into containers for distribution. Occupational exposures are much more likely to take place during the application or use of surface coatings, printing inks, adhesives and cleaners that contain category members as components in formulations. In most cases, industrial applications of these products are subject to engineering controls, such as exhaust systems on equipment to minimize workplace concentrations, and positive workplace ventilation and work practices. Data on number of workers potentially exposed at all the global manufacturing sites are not available. EGBEA in a printing scenario showed a TLV of 12.7 mg/m^3 (ECETOC, 2005). Please refer to Appendix I in the back of the SIAR for more detailed, tabulated worker exposure information on EGBEA.

2.3.2 Consumer Exposure

Although most uses of the category members are industrial and workplace, some consumer exposure may occur through the use of these chemicals in consumer products.

According to the US National Institutes of Health Household Products Database (2005)*, EGPE is found in the following products:

- Liquid adhesives at 1-3% concentration
- Varnish at 4-6% concentration
- Liquid sander at 5-10% concentration
- Stone sealer (concentration not given)
- Liquid window cleaner at 0.1-1% concentration.
- Carpet spot and stain remover at 1-5% concentration

*It should be noted that the US National Institutes of Health Household Products Database has been found to not always be current or correct.

Consumer and general population exposure to environmental concentrations of category members may also occur. Since category members do not persist in the environment, environmental concentrations are expected to be very low to negligible, except possibly near industrial operations using products containing category members.

3 HUMAN HEALTH HAZARDS

3.1 Effects on Human Health

3.1.1 Toxicokinetics, Metabolism and Distribution

Absorption

Results of in vitro studies with human and rat skin indicate that EGPE is rapidly absorbed through the skin (Barber and Kohlberg, 1989). The in vitro dermal absorption rates for EGPE in human stratum corneum (from abdominal skin) and full-thickness rat skin are 0.58 +/- 0.39 and 2.30 +/- 0.79 milligrams/cm2/hr, respectively. However, results of a study in which rats were administered approximately 450 mg/kg by the dermal route indicated absorption of less than 27% of the material during a 6-hr exposure period (Boatman et al., 1998). The majority (74%) of the radioactivity was recovered either as unabsorbed liquid or in washings of application sites.

Metabolism

Glycol ether acetates are rapidly hydrolyzed to their glycol ether counterparts by esterases present in blood and other tissues. Results of an in vitro study performed by BASF indicate that the half-lives of methoxy- (EGMEA), ethoxy (EGEEA), and butoxyethylacetate (EGBEA) in rat plasma are 11.75, 9.92 and 0.96 minutes, respectively (BASF, 1985). In this study, the appearance of the corresponding glycol ethers was noted, but not quantified. EGMEA and EGEEA are good substrates for mouse nasal carboxylase under enzyme saturating and subsaturating conditions (Stott and McKenna, 1985). EGEEA is rapidly converted to ethylene glycol ethyl ether (EGEE) following inhalation exposure in humans with a half-life for the appearance of EGEE in expired air of 3 to 11 minutes (Groeseneken et al., 1987a,b). EGMEA and EGEEA are also rapidly metabolized to ethylene glycol monomethyl ether (EGME) and EGEE in rats following inhalation exposure (Römer et al., 1985; Gargas et al., 2000). Since EGBEA is structurally related to EGMEA and EGEEA, it is likely that EGBEA is rapidly converted to EGBE in vivo.

Mono-substituted glycol ethers (i.e. EGPE, EGBE and EGHE) are substrates for alcohol dehydrogenase (ADH), which catalyzes the conversion of their terminal alcohols to aldehydes (Asamoe et al, 1998, Ghanayem et al., 1987a). Using liver homogenate from Wistar rats, Aasmoe and coworkers (1998) demonstrated that a single isozyme of alcohol dehydrogenase (ADH-3) was responsible for oxidizing EGPE, EGBE and EGHE. The respective V_{max} (3.04, 5.78 and 1.66 nmol NADH/min/mg protein) and K_m (0.23, 0.27 and 0.15 mM) values for EGPE, EGBE and EGHE varied as follows: EGBE > EGPE > EGHE. These data suggest that at equivalent concentrations, metabolism of EGPE is less rapid than EGBE and more rapid than EGHE.

Further conversion of the aldehydes by aldehyde dehydrogenase produces alkoxyacetic acids, which are the predominant urinary metabolites of mono substituted glycol ethers (Boatman et al., 1998; Ghanayem et al., 1987b). The conversion of the terminal alcohols to the alkoxyacetic acids occurs rapidly. Alkoxyacetic acids formed from EGPE and EGBE are responsible for red blood cell hemolysis in rodents (see Section 3.1.2) but do not produce reproductive or frank teratogenic effects as noted for the alkoxyacetic acids formed from EGME and EGEE (see Section 3.1.8). Ethylene glycol is a minor metabolite of EGPE (and other glycol ethers and glycol ether acetates in experimental animals) (Boatman et al., 1998; Boatman and Knaak, 2001) Sulfate and glucuronide conjugation of the parent glycol ethers may occur and glycine (rodents) and glutamine (humans) conjugates of the alkoxyacetic acid metabolites may also be produced (Boatman et al., 1998; Ghanayem et al., 1987b; Rettenmeier et al., 1993), and their formation contributes to detoxification (Ghanayem et al., 1987a).

Elimination

Regardless of whether EGPE is administered i.v., dermally, orally, or by inhalation, elimination of EGPE in rats is rapid, with approximately 80% being eliminated in the urine within 12 hours as 2-propoxyacetic acid (PAA) and its glycine conjugate (Boatman et al., 1998). At an oral dose of 150 mg/kg, EGPE had an elimination half-life of 0.20 hr (versus 0.13 hr at 50 mg/kg), suggesting saturation of metabolism or excretion. Elimination of PAA also appeared to be saturated at this dose. Following oral administration of either 15 or 150 mg/kg radiolabelled EGPE, 97% and 96%, of the administered doses were recovered by 72 hours, respectively.

The time course of ethyoxyacetic acid excretion during and after inhalation exposure to EGEEA in man is similar to that of EGEE. For both materials, the maximal excretion rate is reached 3-4 hours after exposure is terminated, and the half-life of elimination for both materials is 21-24 hours (Groseneken et al., 1986, 1987b). Since EGBEA is structurally related to EGEEA, and EGBEA is rapidly converted to EGBE by rat plasma, it is likely that the elimination of EGBEA follows the same time course as that of EGBE. In male and female F344 rats and B6C3F1 mice exposed by inhalation to 31.2, 62.5, or 125 ppm (rats) or 62.5, 125 or 250 ppm (mice) EGBE for 1 day, 2 weeks and 3, 6, 12, and 18 months, elimination of EGBE was more rapid in mice than rats (Dill et al., 1998). Half-lives of elimination from blood in mice and rats following 1 day of exposure to 62.5 ppm were 3 min (mice) and 9 min (rats) for EGBE. After prolonged exposure, elimination rates of EGBE decreased in both species, resulting in longer blood residence times. Unlike EGBE, BAA was not rapidly cleared from the blood. In rats, females excreted significantly less BAA in urine than males, regardless of exposure concentration. As shown in Section 3.1.5, the repeat-dose toxicity of EGBE is consistent with more rapid elimination of EGBE in mice than rats, and more rapid excretion of BAA in male rats than females.

Conclusion

Glycol ether acetates are rapidly hydrolyzed to their glycol ether counterparts by esterases present in blood and other tissues. Mono-substituted glycol ethers such as EGBE are substrates for alcohol dehydrogenase (ADH), which catalyzes the conversion of their terminal alcohols to aldehydes. Further conversion of the aldehydes by aldehyde dehydrogenase produces alkoxyacetic acids, which are the predominant metabolites responsible for mammalian toxicity of the glycol ethers. Regardless of route of administration, EGPE and EGBE are rapidly excreted from experimental animals. The Km and Vmax for metabolism of EGHE by alcohol dehydrogenase are higher than values for EGPE and EGBE, suggesting that elimination of EGHE is somewhat slower than that of EGPE and EGBE.

3.1.2 Acute Toxicity

The acute toxicity of the category members is summarized in Table 4.

Table 4 Acute mammalian toxicity for category members

Category member	Acute Oral LD_{50} (mg/kg bw)	Acute Rat Inhalation LC_{50} (ppm)	Acute Rabbit Dermal LD_{50} (mg/kg bw)
EGPE 2807-30-9	3089[a] (rat) 1774[a] (mouse)	> 2132[b] (6 hr)	1337[c]
EGBE 111-76-2	1746[a] (rat) 1519[a] (mouse)	450[d] (4 hr)	435[c]
EGBEA 112-07-2	2400[e] (rat)	> 400[e] (4 hr)	1500[e]
EGHE 112-25-4	739[f] (rat)	> 85[g] (4 hr LCLo)	721[f]

LD_{50} = lethal dose in 50% of animals; LC_{50} = lethal conc. in 50% of animals; LCLo = lowest lethal conc.
[a] Krasavage and Terhaar, 1981a; [b]Katz, 1978; [c] Krasavage and Terhaar, 1981b; [d] Bushy Run, 1980; [e] Truhaut et al. 1979; [f] Ballantyne and Myers, 1989; [g] Klonne *et al*. 1987.

Studies in Animals

Inhalation

Acute inhalation data are available for all category members. Available data in rats indicate that the 4 hour LC50 values are > 85 ppm (508 mg/m^3), and increase with molecular weight. Signs of toxicity in rats administered toxic concentrations of EGBE by inhalation included rapid, shallow breathing, loss of coordination and red staining around the urogenital area. Autopsy of animals that died revealed enlarged, discoloured kidneys and red fluid in the bladder.

Dermal

All category members have been tested for acute dermal toxicity in rabbits. The LD_{50} values range from 435 to 1500 mg/kg bw. Animals dermally exposed to toxic concentrations of EGPE, EGBE and EGBEA exhibited prostration, hypothermia and hemoglobinuria and gross changes in the kidney, spleen, intestines and/or liver. Signs of toxicity in animals administered EGHE included salivation, sluggishness, unsteady gait, skin irritation and ulceration, and comatose appearance.

Oral

Adequate acute oral toxicity studies have been performed for all category members. Oral LD_{50} values in rats range from 739 (EGHE) to 3089 mg/kg bw (EGPE), with values increasing with decreasing molecular weight. Oral LD_{50} values for EGPE and EGBE in mice are slightly lower than those of rats.

Clinical signs of toxicity in rats and mice given toxic concentrations of EGPE, EGBEA and EGBE were inactivity, labored breathing, rapid respiration, anorexia, slight to moderate weakness, tremors, hemoglobinuria and/or hematuria, prostration, and gross changes in the kidneys. Signs of toxicity observed in rats administered EGHE by the oral route included sluggishness, unsteady gait, and prostrated appearance.

Studies in Humans

As reported in the dossier presented at SIAM 6, humans that have ingested cleaning fluids containing 9-13% EGBE (approximately 30-60 ml EGBE ingested) exhibited one or more of the following symptoms during hospitalization: coma, breathing difficulties, metabolic acidosis, dilated pupils, decreased hemoglobin, and hematuria (Rambourg-Schepens, 1988; Gijsenbergh, 1989;

Bauer et al., 1992). Recovery from these symptoms was complete after administration of fluids, dialysis and/or mechanical ventilation for 8 -15 days. Since blood morphology, reticulocyte counts and mean cellular volumes were not measured in these studies, it is not clear if decreased hemoglobin and/or hematuria were due to hemolysis or hemodilution as a result of administration of large volumes of fluid. Humans exposed for 4-8 hours to EGBE at 0.55 and 0.94 mg/l experienced nasal and ocular irritation, metallic taste, increased nasal mucous discharge, headache and vomiting, but did not have increased erythrocyte fragility (Carpenter et al., 1956).

In a well-monitored case study that was published after SIAM 6 (and therefore not included in the previous dossier for EGBE), an 18-year old male deliberately consumed between 360-480 ml of a glass cleaner containing 22% EGBE on two separate occasions (Gualtieri et al., 2003). The patient went to the hospital 3 and 6 hours after the first and second episodes (respectively). At the times of admission, initial laboratory values, including CBC, electrolytes and hepatic function tests were normal. Approximately 10 hours after the first ingestion, the patient developed severe CNS depression, metabolic acidosis, hematuria and mild elevation of hepatic enzymes. Administration of i.v. fluids and sodium bicarbonate did not seem to help his condition. Dialysis, oral administration of ethanol and i.v. treatment with thiamine, folic acid and pyridoxine initiated approximately 24 and 8 hours after the first and second episodes (respectively) were effective therapies on both occasions. Despite having a BAA concentration of 4.86 mM 16 hours after his first ingestion and 2.07 mM after his second ingestion, there was no evidence of hemolysis.

Studies in Vitro

As mentioned above, alkoxyacetic acids formed from EGPE and EGBE (PAA and BAA, respectively) are responsible for red blood cell hemolysis in rodents. The acute toxicity of alkoxyacetic acids to red blood cells ranks in the following order: butoxyacetic acid > propoxyacetic acid ≈ pentoxyacetic acid > ethoxyacetic acid > methoxyacetic acid (Ghanayem *et al*., 1989). Results of in vitro studies indicate that human red blood cells are more resistant to the hemolytic effects of PAA and BAA than blood cells from rats (Bartnik et al, 1987; Ghanayem and Sullivan, 1993; Udden, 1994; Udden and Patton, 1994). PAA caused nearly complete hemolysis of red blood cells from rats at 5 mM, but had no effect on human red blood cells (Boatman *et al*., 1993). Concentrations of BAA required to produce hemolysis human red blood cells are at least 10 times higher than those required for rat red blood cells.

Results of studies by Ghanayem and Sullivan (1993) show that the effect of BAA on red blood cells is species-dependent. Whereas red blood cells of the rat, mouse, hamster, rabbit and baboon were susceptible to in vitro hemolysis by BAA at 1 and 2 mM, blood from pigs, dogs, cats, guinea pigs and humans was resistant. Udden (1994) showed that red blood cells from older humans or people with diseases such as hereditary spherocytosis or sickle cell disease were not susceptible to BAA-induced hemolysis under conditions that caused extensive hemolysis of rat red blood cells. An accepted PBPK model demonstrates that even at saturated vapor concentrations of EGBE, it is not possible for hemolytic blood concentrations of BAA to be reached in humans by the inhalation route of exposure (Corley et al., 1994).

Conclusion

Oral LD_{50} values in rats for all category members range from 739 (EGHE) to 3089 mg/kg bw (EGPE), with values increasing with molecular weight. Four to six hour LC_{50} values in rats range from > 85 ppm (508 mg/m^3, EGHE) to > 2132 ppm (9061 mg/m^3, EGPE). Dermal LD_{50} values in rabbits range from 435 mg/kg bw (EGBE) to 1500 mg/kg bw (EGBEA). Signs of acute toxicity in rats and rabbits are consistent with hemolysis (with the exception of EGHE) and non-specific CNS depression typical of organic solvents in general. Alkoxyacetic acid metabolites, PAA and BAA, are responsible for the red blood cell hemolysis. Signs of toxicity in humans deliberately ingesting

cleaning fluids containing 9-22% EGBE are similar to those of rats, with the exception of hemolysis. Although decreased blood hemoglobin and/or hemoglobinuria were observed in some of the human cases, it is not clear if this was due to hemolysis or hemodilution as a result of administration of large volumes of fluid. Red blood cells of humans are many-fold more resistant to toxicity from EGPE and EGBE *in vitro* than those of rats.

3.1.3 Irritation

Skin Irritation

Studies in Animals

Skin irritation data are available for all members of the category. The bulk of the evidence suggests that most of these chemicals cause slight to moderate, but reversible irritation to the skin (Katz *et al*., 1984; Katz 1978; Krasavage and Terhaar, 1981b; Ballantyne and Myers, 1987; Truhaut *et al*. 1979; Boatman and Knaak, 2001). EGBEA appears to be less irritating to skin and EGHE more irritating to the skin than EGPE or EGBE.

Eye Irritation

Studies in Animals

Eye irritation data are available for all members of the category. The category members cause moderate to severe, but reversible irritation to rabbit eyes (Ballantyne and Myers, 1987; Katz *et al*., 1984; Jacobs and Martens, 1989; Katz, 1978; Krasavage and Terhaar, 1981b). EGHE appears to be more irritating to the eyes than the other category members, and EGBEA does not appear to be as irritating to eyes as EGBE (Truhaut *et al*. 1979; Jacobs and Martens, 1989; Boatman and Knaak, 2001).

3.1.4 Sensitisation

Results of adequate studies indicate that EGPE and EGBE are not sensitizers in experimental animals or humans (Katz et al., 1984; Greenspan et al., 1985; Shepard 1988a,b; Unilever, 1989).

3.1.5 Repeated Dose Toxicity

Repeated dose inhalation or oral toxicity studies have been performed on all category members (Table 5). Effects noted in rats, mice or rabbits treated with moderate doses of EGPE, EGBE and EGBEA by either route of administration are consistent with hemolytic toxicity. Since the studies performed with EGBEA are not up to current standards, and EGBEA is rapidly hydroyzed to EGBE in blood and other tissues, results of the NTP study with EGBE are expected to be indicative of the toxicity of EGBEA. Although tested in a non-guideline study, EGBEA was found to produce a hemolytic response in rats and rabbits similar to that seen in the NTP study with EGBE.

Studies in Animals

Inhalation

Results of two 14-week inhalation studies conducted in Sprague-Dawley rats at exposure levels of 100, 200, or 400 ppm (425, 850, or 1700 mg/m^3, 6h/day, 5d/wk) EGPE, indicate that the repeated exposure, NOAEL in this species is 100 ppm (Katz, 1987; Bernard, 1989). Effects noted in rats repeatedly exposed to concentrations of EGPE $\geq$ 200 ppm (850 mg/m^3) by inhalation are indicative of toxicity to red blood cells and resulting sequelae. Hemolysis results in a decrease in the number

of circulating red blood cells, increased plasma hemoglobin, hemoglobinuria, focal necrosis of the liver, splenic congestion, and deposition of hemoglobin in the kidneys (Boatman and Knaak, 2001).

In F344 rats and B6C3F1 mice, the repeated exposures to 31, 62.5, 125, 250, or 500 ppm (150, 302, 603, 1207, or 2415 mg/m^3) EGBE (6h/day, 5d/wk for 14 weeks) resulted in NOAELs of < 31 ppm (150 mg/m^3) and 62.5 ppm (302 mg/m^3), respectively (NTP, 2000). Effects noted at the LOAELs and higher concentrations were similar to those of rats exposed to EGPE (i.e. hemolytic anemia and histological lesions consistent with hemolytic anemia in liver, kidney, bone marrow, and/or spleen). For EGBE, notable inflammation and hyperplasia were present in the forestomachs of treated animals.

In a repeated exposure (6h/day, 5d/wk for 13 weeks) inhalation study performed at exposure levels of 20, 41, or 71 ppm (120, 245, or 425 mg/m^3) EGHE in F344 rats, the reported NOAEL by the investigators was 41 ppm (245 mg/m^3). Decreases in body weight and increases in male kidney and female liver weights occurring at this concentration were considered to be adaptive (and not adverse) since there were no correlative changes in histopathology or serum chemistry (Klonne et al., 1987). The changes in liver enzymes in animals exposed to 71 ppm (425 mg/m^3) are difficult to interpret since levels of 3 out of 4 enzymes were decreased and only 1 out of 4 was increased. Whereas the effects on the kidney were not dose-dependent, liver weights increased in a dose-dependent manner and were not reversed after 4 weeks of recovery in animals exposed to 71 ppm. No effects on red blood cells or histologic changes in the liver or kidney were noted at concentrations up to and including the highest concentration tested (71 ppm or 425 mg/m^3).

As shown in Section 3.1.2, the toxicity of alkoxyacetic acids to red blood cells ranks in the following order: butoxyacetic acid > propoxyacetic acid ≈ pentoxyacetic acid > ethoxyacetic acid > methoxyacetic acid (Ghanayem *et al*., 1989). The fact that the repeated dose NOAEL for red blood cell toxicity in the rat was lower for EGBE (< 31 ppm) than EGPE (100 ppm) is consistent with this scheme.

Oral

By gavage administration, the repeated dose (5d/wk for 6 week) NOAEL for EGPE in the Sprague-Dawley rat is < 195 mg/kg bw/day, the lowest dose tested (Katz *et al*., 1984, Krasavage and Vlaovic, 1982). Effects noted in rats repeatedly administered concentrations of EGPE ≥ 195 mg/kg bw by gavage are similar to those observed in rats exposed to 200 ppm EGPE by inhalation for 14 weeks.

Conclusion

Red blood cell toxicity and its associated effects in the liver, spleen and kidney of rodents and rabbits are reported following repeated exposures for 14 weeks to moderate doses of EGPE and EGBE by inhalation or gavage. The fact that the NOAEL for repeated dose inhalation toxicity of EGBE (150 mg/m^3) in rats is less than that of EGPE (425 mg/m^3) is consistent with red blood cells being more sensitive to EGBE than EGPE. Red blood cell toxicity and histopathological changes in the liver and kidney were not seen in rats exposed for 14 weeks with up to 71 ppm (425 mg/m^3) EGHE by inhalation, suggesting that this material is not as potent a hemolytic agent as EGBE. Significant reproductive organ toxicity was not noted in any of the repeated dose studies.

Table 5 Repeated dose toxicity for category members

Category Member	Species/ Exposure	Dose in ppm (mg/m^3)	Gross Changes	Histopathological Changes	Clin. Chem/Hemat. Changes
EGPE 2807-30-9 (Katz, 1987)	SD rat, 6 hr/d, 5 d/wk, 14 wk (inhalation)	100[a] (425) 200 (850) 400 (1700)	red facial hair ↑ kidney, spleen wt, red urine ↓ bw, ↑ kidney, heart spleen wt, red urine No neurotoxicity	none pigment dep in spleen, renal tubules pigment dep in spleen, renal tubules	none ↓ rbc, hb, hct, ↑ plt, polychrom ↓ rbc, hb, hct, ↑ MCV, MCH, ↑ plt, retic, polychrom, HJ bodies
(Bernard, 1989)	SD rat, 6 hr/d, 5 d/wk, 14 wk (inhalation)	100[a] (425) 200 (850) 400 (1700)	red facial hair ↑ spleen wt, red urine, nasal discharge, sialorrhea same as 200 ppm	none pigment in spleen, kidney and liver same as 200 ppm	not measured
(Katz *et al*., 1984, Krasavage and Vlaovic, 1982)	SD rat, 5 d/wk, 6 wk (gavage)	195[b] 390 780 1560	red urine, ↑ heart wt ↑ heart, liver, brain spleen wt, red urine ↑ heart, liver, spleen, kidney wt, red urine, weakness same as 780 mg/kg plus ↓ bw, feed consump	kidney hemosiderin kidney hemosiderin, splenic congestion same as 390 mg/kg plus hyperker of stomach same as 780 mg/kg plus protein casts and hyaline droplets in kidney	↓ rbc, hb ↓ rbc, hb ↓ rbc, hb, ↑ MCV, MCH ↓ rbc, hb, ↑ MCV, MCH
EGBE 111-76-2 (NTP, 2000)*	F344 rat, 6 hr/d, 5 d/wk, 14 wk (inhalation)	31[b] (150) 62.5 (302) 125 (603) 250 (1207) 500 (2415)	None None ↑ kidney, liver wt ↑ kidney, liver wt ↑ kidney, liver wt	lesions consistent with hemolytic anemia in liver, kidney, forestomach, bone marrow, and/or spleen at all doses except lowest	red blood cell toxicity at all doses
(NTP, 2000)*	B6C3F1 mice, 6 hr/d, 5 d/wk, 14 wk (inhalation)	31[b] (150) 62.5 (302) 125 (603) 250 (1207) 500 (2415)	none none none ↑ kidney, liver wt ↑ kidney, liver wt	none none same as rat (above) same as rat (above) same as rat (above)	none none red blood cell tox red blood cell tox red blood cell tox
EGBEA 112-07-2	No reliable data				
EGHE 112-25-4 (Klonne et al., 1987)	F344 rat, 6 hr/d, 5 d/wk, 13 wk (inhalation)	20 (120) 41[a] (245) 71 (425)	urogenital wetness, ↑ kidney wt ↓ bw, ↑ kidney, liver wt, , urogenital wetness ↓ bw, ↑ kidney, liver wt	None None none	None None ↓ AST, ALT, SDH, ↑ ALP

[a] No observable adverse effect level (systemic effects). Dose is in mg/kg bw/day (for oral experiments) and ppm (for inhalation experiments) unless listed otherwise. The number of deaths is listed (if significant); [b] No observable effect level (NOAEL) less than lowest dose; [c] Difficult to determine whether listed dose was considered to be NOAEL; [d] Study was given a reliability rating of 4 (not assignable). * Study was performed after SIAM 6 and therefore is not described in previous dossier

NZW = New Zealand White, dep = deposition, hb = hemoglobin, hc = hematocrit, plt = platelets, retic = reticulocytes, polychrom = polychromasia, HJ = Howell-Jolly, MCV = mean corpuscular volume, MCH = mean corpuscular hemoglobin, AST = aspartate aminotransferase, ALT = alanine aminotransferase, SDH = sorbitol dehydrogenase, ALP = alkaline phosphatase.

3.1.6 Mutagenicity

Genetic toxicity tests that have been performed on the category members are shown in Table 6.

Table 6 Genotoxicity of category members

Category Member	Ames Test (w/wout activation	Mammalian Cell Mutagenesis[a]	Cytogenicity[a]	SCE assay[a]	Mouse Micronucleus (in vivo)
EGPE 2807-30-9	No data	No data	No data	No data	No data
EGBE 111-76-2	Negative (1,2*) Positive, 97a (3) Negative, 97a (4)	Negative (5[b]; 6) Positive[b,c] (7)	Negative (1,2*, 7[c], 8)	Negative (1,2*,8) Positive[c] (7)	Negative (2*,7)
EGBEA 112-07-2	No data	No data	No data	No data	No data
EGHE 112-25-4	Negative (9)	Negative (10)	Negative (8)	Negative (5)	No data

[a] Chinese Hamster Ovary Cell unless listed otherwise; [b]HGPRT assay; [c]V79 cells
* Study was performed after SIAM 6 and therefore is not described in previous dossier
(1) NTP, 1993; (2) NTP, 2000; (3) Hoflack et al., 1995. Given a reliability rating of 4 because the primary reference was not available for review; (4) Gollapudi et al., 1996. Given a reliability rating of 4 because the primary reference was not available for review; (5) Slesinski and Weil, 1980. Given a reliability rating of 4 because the primary reference was not available for review (6) Chiewchunwit and Au, 1995. Given a reliability rating of 4 because the primary reference was not available for review; (7) Elias et al,. 1996. Given a reliability rating of 4 because the primary reference was not available for review; (8) Guzzie, 1985; (9) Marples, 1985; (10) Slesinski et al., 1988. Given a reliability rating of 4 because the primary reference was not available for review

Studies in Animals

In vitro Studies

Ames tests (in the absence and presence of metabolic activation) have been performed with up to 10,000 micrograms/plate EGBE and 15,000 micrograms/plate EGHE, in S. typhimurium strains TA97, TA98, TA100, TA1535 and TA1537 (EGBE) and TA98, TA100, TA1535, TA1537 and TA1538 (EGHE). Results of each of these studies were negative.At high concentrations (≥ 2.2 mg/plate), Hoflack et al. (1995) reported a positive result in strain 97a. This work was repeated by a different investigator at concentrations up to 10 mg/plate, and the result was negative (Gollapudi et al. 1996). EGBE and EGHE also tested negative in mammalian cell mutagenesis tests in Chinese Hamster Ovary (CHO) cells that were not available for review. At very high concentrations (20-75 mM), EGBE was positive for mutagenicity to the HGPRT locus in V79 cells (Elias et al., 1996). However, the absence of reported data and exceedingly high concentrations employed make this latter study of limited relevance for predicting the genotoxic potential of EGBE (Elliot and Ashby, 1997).

In vitro cytogenicity and sister chromatid exchange assays (SCE) with EGBE (up to 5000 micrograms/ml, 42.1 mM) and EGHE (up to 400 micrograms/ml) in CHO cells with and without metabolic activation were negative. In contrast, a SCE assay performed with V79 cells was weakly positive at 15 – 25 mM (Elias et al., 1996). The reason for positive and negative results at similar concentrations is unclear.

Studies in Animals

In vivo Studies

Micronucleus studies in F344/N rats and B6C3F1 mice given up to 450 mg/kg bw (rats) and 1,100 mg/kg bw (mice) EGBE in 3 separate i.p. doses, and CD-1 mice given up to 800 mg/kg bw EGBE in a single i.p. dose were negative, indicating that EGBE is not toxic to chromosomes. A review by Elliott and Ashby (1997) reports that all in vivo genetic tests that have been performed with EGBE were negative.

Conclusion

The majority of genetic toxicity studies that have been performed with EGBE and all studies performed with EGHE are negative. The positive Ames test in Salmonella strain TA 97a is likely to be anomalous, since it was not repeatable. The additional positive results that have been reported occurred in unconventional tests (V79 HGPRT and SCE) at high concentrations (15-75 mM). Results of both in vivo genetic studies with EGBE were negative. Based on the results of the studies with EGHE and the core studies with EGBE, EGPE and EGBEA are not likely to cause genetic toxicity.

3.1.7 Carcinogenicity

In a 2-year inhalation study conducted by the NTP after SIAM 6 (NTP, 2000), the incidences of combined benign plus malignant pheochromocytomas of the adrenal medulla in female rats exposed to 0, 31.2, 62.5 or 125 ppm EGBE were 3/50 (6%), 4/50 (8%), 1/49 (2%) and 8/49 (16%), respectively. The incidence of this lesion in female rats exposed to the high concentration (16%) was not significantly different from control (6%), but exceeded the historical control range (2-13%). The incidences of forestomach squamous cell papilloma and squamous cell papilloma or carcinoma (combined) occurred with a positive trend in female mice, and the incidences in females exposed to 250 ppm (10 and 12%) were increased relative to study (0%) and historical controls (0-2% and 0-3%, respectively). The incidences of forestomach squamous cell papilloma in male mice exposed to 125 or 250 ppm (2 at each dose) also were greater than historical controls. A positive trend toward and increase in hemangiosarcoma was observed in male mice. The incidence of this lesion was increased in males exposed to 250 ppm with regard to chamber and historical controls. The incidence of hepatocellular carcinoma in male mice increased in a dose-dependent manner and was significantly higher in those exposed to 250 ppm relative to the study control, but did not exceed historical control values. There was no difference in the combined incidence of hepatocellular adenoma and carcinoma between treated and control male mice, and there was a decrease in the incidence of hepatocellular adenoma in female mice exposed to 125 ppm. Subsequent tests revealed that the liver neoplasms were not due to the presence of H. hepaticus infection.

Reviews and ongoing studies suggest that the tumors observed with EGBE in two-year rodent studies are not relevant to human carcinogenic risk (CIR, 2002; Cunningham, 2002; Boatman *et al*., 2004). Reasons for these conclusions are as follows. First, EGBE is not genotoxic. This was the conclusion of the NTP and is supported by other work including a review by Elliot and Ashby (1997). Second, liver neoplasms (in particular hemangiosarcomas) found in male mice (but not female mice or rats) were likely produced as a consequence of oxidative stress subsequent to red blood cell hemolysis and hemosiderin (iron) deposition in the liver (Xue *et al.* 1999). Humans, who are insensitive to the hemolytic effects of EGBE, and have higher levels of hepatic antioxidant capacity compared to rodents, will show no similar hematotoxic response, increased oxidative stress, or liver tumor development. Third, forestomach tumors in mice are not likely to be relevant to human risk assessment because they were caused by irritation in an organ for which man has no structurally and functionally similar counterpart. Lastly, pheochromocytomas in the rat are induced

by a number of unrelated substances but there are no known chemical inducers of human adrenal medullary tumors (Lynch *et al*., 1996). The significance of the effects can also be questioned bearing in mind the lack of a clear dose response relationship and the lack of significant difference from the concurrent control. The U.S. EPA in its 1999 IRIS review of EGBE found the tumors in the NTP study "of uncertain relevance" to any human cancer risk (www.epa.gov/iris/subst/0500.htm). The data were evaluated by IARC in June 2004 and EGBE was classified as IARC Group 3 (inadequate evidence of carcinogenicity in humans and limited evidence of carcinogenicity in animals). In 2000, the EU classification of EGBE was reviewed under the European Commission process for the classification and labeling of dangerous substances. It was decided that based on the data available there was no significant hazard for human carcinogenicity and there was no support for a category 3 (carcinogen) classification (www.esig.org). This decision was reconfirmed in 2004.

3.1.8 Toxicity for Reproduction

A reproductive toxicity test has been performed on EGBE, reproductive organ toxicity has been examined in animals given EGPE, EGBEA and EGHE repeatedly for 6 to 40 weeks (Table 7), and developmental toxicity tests have been performed on EGPE, EGBE and EGHE (Table 8). Results of the repeated dose toxicity studies indicate that there was no significant effect of treatment with any of the category members on any reproductive organ examined (Table 7).

Studies in Animals

Effects on Fertility

Results of a 2-generation, continuous breeding study in CD1-mice exposed by drinking water to 720, 1,340, or 2,050 mg/kg bw/day EGBE (Heindel *et al.,* 1990) indicate parental and offspring NOAELs of < 720 and 720 mg/l, respectively. Parental animals exposed to 720 mg/l exhibited increased relative kidney (females only) and liver (males and females) weights. Although live pup weights from animals exposed to 720 mg/kg bw/day were significantly reduced, this is not considered to be biologically significant since the magnitude of the decrease compared to controls was small (3%). Parental animals treated with 1,340 and 2,050 mg/kg bw/day exhibited significantly decreased body weight, water consumption and increased kidney weight. Both mid and high dose animals produced significantly fewer litters/pair and fewer pups/litter and had pups with lower weight than controls.

In a study designed to assess the effects of EGME, EGEE, EGPE and EGBE on the testes, mixed cultures of Sertoli and germ cells were incubated with 5-20 mM of their alkoxy acetic acid metabolites (methoxy-, ethoxy-, propoxy- and butoxyacetic acids, respectively), and testes from male rats receiving oral doses of the glycol ethers for four days were examined (Gray et al., 1985). Propoxyacetic acid (PAA) was toxic to pachytene spermatocytes at a concentration of 20 mM and was slightly toxic at 10 mM. There was no effect of PAA on testicular weights or morphology in rats treated with 776 mg/kg bw/day by gavage for 4 days. Butoxyacetic acid had no effect on cultured cells at 20 mM and did not produce toxicity in vivo at 868 mg/kg bw/day. In contrast, 5 mM methoxyacetic acid (MAA) produced toxicity to pachytene spermatocytes, and treatment with 592 mg/kg bw/day MAA by gavage for 4 days produced testicular toxicity in rats. Similar toxicity (although less severe) was noted in cells treated with 5 mM ethoxyacetic acid (EAA) and rats treated with 684 mg/kg bw/day EAA be gavage for 4 days. These results suggest that alkoxyacetic acid metabolites are responsible for testicular toxicity of the ethylene glycol ethers and that the ability of the glycol ethers to cause testicular toxicity decreases with increasing chain length, with at least a four-fold lower concentration of MAA required to produce toxicity than PAA.

Developmental Toxicity

Results of the developmental toxicity studies conducted on category members EGPE, EGBE, and EGHE (Table 8) indicate that the members of the category are not teratogens. The NOAELs for developmental toxicity are greater than 500 ppm or 2125 mg/m^3 (rabbit-EGPE), 100 ppm or 425 mg/m^3 (rat-EGPE), 50 ppm or 241 mg/m^3 (rat EGBE) and 100 ppm or 483 mg/m^3 (rabbit EGBE) and greater than 79.2 ppm or 474 mg/m^3 (rat and rabbit-EGHE). Inhalation of a maternally toxic concentration of EGBE (100 ppm or 483 mg/m^3 in the rat and 200 ppm or 966 mg/m^3 in the rabbit) throughout gestation was associated with embryotoxicity, as evidenced by an increased number of resorptions, and a decreased number of implantations. An increase in the number of fetuses with skeletal variations was noted in offspring of rats exposed to maternally toxic concentrations of EGPE by inhalation (≥ 200 ppm or 966 mg/m^3). In rats exposed to EGHE and rabbits exposed to EGHE or EGPE by inhalation, no effects on the fetus were noted (even at concentrations that produced maternal toxicity).

Conclusion

Altogether, results of these studies indicate that the glycol ethers in this category are not selectively toxic to the reproductive system, embryo or developing fetus. Fertility is only affected at a high concentration of EGBE (≥ 1,300 mg/kg bw/day) that also is associated with parental toxicity. In the repeated dose toxicity studies, there was no significant effect of treatment on male or female sex organs. The NOAELs for developmental toxicity of the category members are greater than 241 and 474 mg/m^3 in the rat and rabbit, respectively. Repeated inhalation of maternally toxic doses of EGPE and EGBE that cause hemolysis is associated with developmental toxicity in the rat and rabbit. In rats exposed to EGHE and rabbits exposed to EGHE or EGPE by inhalation, no developmental effects were noted (even at concentrations that produced maternal toxicity). Based on the structural similarities between the members, developmental toxicity data for the tested glycol ethers is expected to be predictive of data for EGBEA.

Table 7: Reproductive toxicity of category members

Category Member	Animal	Treatment	Effects
EGPE 2807-30-9 (Katz, 1987; Bernard 1989)	SD rat, Exam of reproductive organs	Inhalation, 100 (425) 200 (850), 400 (1700) ppm (mg/m^3) 6 hr/d, 5 d/wk for 14 weeks	No significant effect of treatment on weights or histology of reproductive organs.
(Katz *et al*., 1984, Krasavage and Vlaovic, 1982)	SD male rat, exam of reproductive organs	Gavage, 195 to 1560 mg/kg bw/d, 5 d/wk for 6 weeks	No significant effect of treatment on weights or histology of reproductive organs.
	JCL-ICR mouse, weight of reproductive organs[a]	Gavage, 500 to 2000 mg/kg bw/d, 5 d/wk for 5 weeks	No significant effect of treatment on weights of reproductive organs. Morphological results were not presented.
EGBE 111-76-2 (Heindel *et al.,* 1990)	CD-1 mouse, 2-generation continuous breeding	Drinking water 720, 1340, 2050 mg/kg bw/d for 98 days	NOAEL (parental) < 720* NOAEL (offspring) = 720 720 (parental) -↑ liver, kidney wt 720 (offspring) – ↓ bw (3%), not biologically significant > = 1340 (parental) – death ,↓ bw, fertility (due to effects on female). No effect on sperm or testes. > = 1340 (offspring) - ↓ live pups/litter, pup weight
(NTP, 2000)**	F344 rat, B6C3F1 (mouse), exam of reproductive organs	Inhalation, 31-500 ppm (150-- 2415 mg/m^3), 6 hr/d, 5 d/wk for 14 wk	No significant effect of treatment on weights or histology of reproductive organs.
(NTP, 2000)**	F344 rat, B6C3F1 (mouse), exam of reproductive organs	Inhalation, 31-125 ppm (150 –603 mg/m^3) (rat), 62.5-250 ppm (302--1207 mg/m^3) (mouse), 6 hr/d, 5 d/wk for 104 wk	No significant effect of treatment on weights or histology of reproductive organs.
EGBEA 112-07-2	No reliable data		
EGHE 112-25-4 (Klonne *et al*., 1987)	F344 rat, exam of reproductive organs	Inhalation, 20, 41, 71 ppm, (120, 245, 425 mg/m^3) 6 hr/d, 5 d/wk for 13 wk	There was no effect of treatment on weight of testes or histology of reproductive organs (types not stated).

NOAEL = No observable adverse effect level; SD = Sprague Dawley; F344 = Fischer 344

[a] Given a reliability rating of 4

* NOAEL for parental toxicity reported in dossier at SIAM 6 was 720 mg/l. Further examination of data suggest parental toxicity occurred at this dose (refer to dossier for EGBEA for explanation).

** Study was performed after SIAM 6

Table 8 Developmental Toxicity of category members

Category Member	Animal	Treatment ppm (mg/m^3)	Effects
EGPE 2807-30-9 (Krasavage and Hosenfeld 1989, Krasavage et al 1990)	NZ White Rabbit	Inhalation, 125, 250, 500 ppm (531, 1062, 2125 mg/m^3), 6 hr/d, day 6-18 of gestation	NOAEL (maternal) = 250 ppm. NOAEL (fetal) >= 500 ppm. 500 ppm (maternal) - ↓ bw gain
(Krasavage and Katz, 1984, 1985)	SD rat	Inhalation, 100, 200, 300, 400 ppm, (425, 850, 1275, 1700 mg/m^3) 6 hr/d, day 6-15 of gestation	NOAEL (maternal) < 100 ppm NOAEL (fetal) = 100 ppm 100 ppm (maternal) - red urine (N=1), polychromasia, reticulocytes 200 ppm (maternal) - red urine, ↓ feed, rbc, ↑ spleen wt, MCV, MCH, plus same changes as at 100 ppm 300 ppm (maternal) - same as at 200 ppm plus hemosiderin in spleen, thymic and liver changes > = 200 ppm (fetal) - increased incidence of skeletal variants
EGBE* 111-76-2 (Tyl et al., 1984)	F344 rat	Inhalation, 25, 50, 100, 200 ppm (121, 241, 483, 966 mg/m^3) 6 hr/d, day 6-15 of gestation	NOAEL (maternal) = 50 ppm NOAEL (developmental) = 50 ppm** NOAEL (teratogenicity) = 200 ppm 100 ppm (maternal) – anemia, ↓ feed consumption, bw 200 ppm (maternal)- same as 100 ppm plus reproductive toxicity > = 100 ppm (developmental) – ↑ skeletal variants
(Tyl et al., 1984)	NZ White rabbit	Inhalation, 25, 50, 100, 200 ppm (121, 241, 483, 966 mg/m^3) 6 hr/d, day 6-18 of gestation	NOAEL (maternal) = 100 ppm*** NOAEL (developmental) = 100 ppm NOAEL (embryotoxicity) = 100 ppm NOAEL (teratogenicity) = 200 ppm 200 ppm (maternal) - ↑ lethality, ↓ bw 200 ppm (embryo) – ↓ implantations
EGBEA 112-07-2	No data		
EGHE 112-25-4 (Tyl et al. 1989)	F344 rat	Inhalation, 20.8, 41.4, 79.2 ppm (124, 248, 474 mg/m^3) 6 hr/d, day 6-15 of gestation	NOAEL (maternal) = 20.8 ppm. NOAEL (fetal) >= 79.2 ppm. 41.4 ppm (maternal) - ↓ bw gain 79.2 ppm (maternal) - ↓ bw, bw gain, food consumption, ↑ water consumption, lacrimation
(Tyl et al., 1989)	NZ White Rabbit	Inhalation, 20.8, 41.1, 79.2 ppm, (124, 248, 474 mg/m^3) 6 hr/day, day 6-18 of gestation	NOAEL (maternal) = 41.1 ppm NOAEL (fetal) >= 79.2 ppm 79.2 ppm (maternal) - ↓ bw gain

NOAEL = No observable adverse effect level; SD = Sprague Dawley; F344 = Fischer 344; NZ = New Zealand
*All data for EGBE shown in this table were drawn from the SIDS dossier agreed at SIAM 6.
** Further examination of data suggests the NOAEL for developmental effects in the rat is 100 ppm (refer to dossier for EGBEA for explanation).
*** Further examination of data suggests the NOAEL for maternal effects in the rabbit is 50 ppm (refer to dossier for EGBEA for explanation).

3.2 Initial Assessment for Human Health

Results of pharmacokinetic studies indicate that EGPE and EGBE are rapidly metabolized and eliminated after acute administration, and that glycol ether acetates are rapidly converted to their corresponding glycol ethers *in vivo*. The category members are of low-moderate acute toxicity. Signs of acute toxicity in rats, rabbits and mice are consistent with hemolysis (with the exception of EGHE) and non-specific CNS depression (which is typical of many solvents). Alkoxyacetic acids are responsible for hemolysis. In vitro, red blood cells of humans are at least 10-fold more resistant to hemolysis from EGPE and EGBE than those of rats. EGBE-induced hemolysis is not unequivocally demonstrated in humans deliberately ingesting products containing 9-22% EGBE. All category members are irritating to skin and eyes, with EGBEA less irritating and EGHE more irritating than the other category members. EGPE and EGBE are not sensitizers in experimental animals or humans. The results of repeated dose toxicity tests indicate that the members of this category act similarly in rats, rabbits and mice, with EGBE having greater potency than EGPE or EGHE with regard to red blood cell toxicity. EGBE and EGHE are not mutagenic or clastogenic. The tumors observed with EGBE in two-year rodent studies (forestomach tumors in mice and liver tumors secondary to hemosiderin (iron) deposition in the liver of male mice) are not relevant to human carcinogenic risk. The results of reproductive and developmental toxicity studies indicate that the glycol ethers in this category are not selectively toxic to the reproductive system or developing fetus.

4 HAZARDS TO THE ENVIRONMENT

4.1 Aquatic Effects

As mentioned above, glycol ether acetates are rapidly hydrolyzed to their corresponding glycol ethers by mammalian carboxylases. However, the EPIWIN/Hydrowin model predicts that these materials do not hydrolyze readily in water. Therefore, these materials may not hydrolyze rapidly in the environment. For this reason, the glycol ethers (EGPE, EGBE and EGHE) and EGBEA should be considered separately for aquatic toxicity, and data for the glycol ethers cannot be used to fill aquatic endpoints for EGBEA (or vice versa). As shown in Tables 9 and 10, adequate aquatic toxicity data exist for most of the category members. Data for EGBE are included for comparative purposes and are not used to fill any endpoints.

Table 9 Aquatic toxicity of glycol ethers

Chemical	Fish Acute Toxicity 96-h LC_{50} (mg/l)[a]	Invertebrate Acute Toxicity 48-h EC_{50} (mg/l)[b]	Algae Acute Toxicity 72-h EC_{50} (mg/l)[a]
EGPE 2807-30-9	4926[a] >5000[b] (1)	> 5000 (1)[c] 4622[a]	2587[a]
EGBE 111-76-2	2137 (2) 1700 (3)*	> 1000 (1)[c*] 835 (2)	> 1000 (4)
EGHE 112-25-4	> 94 and <215 (5) 140[b] (1)	145 (6) 305 (1)[c]	98[d] (7) 198[e] (7)

[a] estimated using EPIWIN; [b] Given a reliability score of 4; [c] Data listed in reference as LC_{50};
[d] biomass; [e] growth rate, * Data are not present in SIDS dossier agreed at SIAM 6
(1) Waggy, 1987; (2) Bartlett, 1979; (3) Waggy and Payne, 1974; (4) Dill and Milazzo, 1988;
(5) BASF AG, 1994; (6) BASF AG, 1990; (7) BASF AG, 1989c

Toxicity to Fish, Invertebrates and Algae

The LC_{50} values for the glycol ethers in fish range from 94 to > 5000 mg/l, with the glycol ether with the longest chain length and highest log Pow value (EGHE) having a lower LC_{50} value than the category members with shorter chain lengths and lower log Pow values (EGPE and EGBE). The lowest LC_{50} or EC_{50} values for glycol ethers are from EGHE. For EGHE, the 96-hour LC_{50} for *Brachydanio rerio* (zebra fish) was 94-215 mg/l the 48-hour EC_{50} for *Daphnia magna* was 145 mg/l and the 72-hour EC_{50} values for biomass and growth rate of algae (*Scenedesmus subspicatus*) were 98 and 198 mg/l, respectively. The ECOSAR-estimated LC_{50} value for EGPE in fish is 4926 mg/l. This is similar to an experimental value of > 5000 mg/l, which was reported in a Union Carbide summary document that did not contain any experimental details.

The EC/LC_{50} values for the category members in Daphnia magna range from 145 to > 5000 mg/l. The ECOSAR-estimated EC_{50} value in Daphnia (4622 mg/l) is similar to the experimental value of > 5000 mg/l. The EC_{50} values for the glycol ethers in invertebrates follow a similar pattern as fish (i.e. the EC_{50} values decrease with increasing chain length and log Pow), and are of a similar magnitude as those in fish.

Acute toxicity data for algae are available for the glycol ethers EGBE and EGHE (Table 9). Available data indicate that EGHE ($EC_{50\ (biomass)}$ = 198 mg/l) is more toxic than EGBE ($EC_{50\ (growth\ rate)} \geq 1000$ mg/l). This pattern of increased toxicity of EGHE compared to the other glycol ethers is similar to that observed in fish and Daphnia, and is consistent with longer chain length and decreased polarity. Therefore, for EGPE, the EC_{50} value is predicted to be ≥1000 mg/l. The value estimated by EPIWIN/ECOSAR (2,587 mg/l) is in agreement with this prediction. This value is likely to be valid, since EPIWIN-generated LC/EC_{50} values for EGPE in fish and Daphnia are similar to experimental values.

Table 10 Aquatic toxicity of EGBEA

Chemical	Fish Acute Toxicity 96-h LC_{50} (mg/l)[a]	Invertebrate Acute Toxicity 48-h EC_{50} (mg/l)[b]	Algae Acute Toxicity 72-h EC_{50} (mg/l)[c]
EGBEA 112-07-2	28.3 (1) 31 (2)	37[a] -143 (1)(3)(4)	> 500 (5) 520[B] (1) 1570[C] (1)

[a]data listed in reference as LC50; [b]biomass; [c]growth
(1) Devillers et al., 2002; (2) Waggy and Payne 1974; (3) Waggy, 1987;; 4) BASF AG, 1989b; (5) BASF AG, 1989d

Aquatic toxicity data are available for EGBEA. The 96-hour LC_{50} values in rainbow trout and fathead minnow were 28.3 and 31 mg/l, the 48-hour LC_{50} for *Daphnia magna* was 143 mg/l and the 72-hour EC_{50} value for biomass of algae (*Scenedesmus subspicatus*) was >500 mg/l. The effect of EGBEA on the reproduction of *Ceriodaphnia dubia* also has been tested (INERIS, 2001; Devillers *et al.,* 2003). The 7 day NOEC and EC_{10} value (with confidence interval) for this material are 16.4 and 30.40 (9.89-37.73) mg/l, respectively.

The fact that the 48-96 hour EC/LC_{50} values for EGBEA are lower than its corresponding glycol ether (EGBE) suggests that the acetate moiety may drive the aquatic toxicity by lowering hydrophilicity and water solubility and increasing the log ~~P~~Kow. This supports the separation of the glycol ethers and acetate into two separate groups for aquatic toxicity endpoints.

Toxicity to Microorganisms

Toxicity data for bacteria are available for all category members. The results indicate that the toxicity of the category members to bacteria follows a similar pattern as toxicity to fish or Daphnia,

with the category members with the highest log Pow values (EGHE and EGBEA) having the lower IC_{50} values (770 and 96 mg/l, respectively) than EGPE and EGBE (>1000 and >5000 mg/l respectively) (BASF AG, 1989; Waggy, 1987).

4.2 Terrestrial Effects

No data were located on terrestrial effects.

4.3 Other Environmental Effects

No other data were located.

4.4 Initial Assessment for the Environment

In conclusion, aquatic toxicity tests in combination with ECOSAR modeling indicate that the category members with log Pow values < 1 (EGPE and EGBE) are of low toxicity to fish and aquatic invertebrates (LC/EC_{50} values are 835 mg/l or greater) and the category members with log Pow values > 1 (EGHE and EGBEA) are moderately toxic to these organisms (LC/EC_{50} values are approximately 20-300 mg/l). EGBE and EGBEA are of low toxicity and EGHE is of moderate toxicity to algae. Results of ECOSAR modeling for EGPE toxicity to algae are consistent with the high experimental LC_{50} value for EGBE and the low log Pow of EGPE. Based on physical and chemical properties, if released into the aquatic environment, these materials would tend to remain in the water column. Releases to land would tend to move to surface water or groundwater and not accumulate in soil, and releases into the air would be photoxidized or washed out via rainfall. Based on low log Pow and estimated bioconcentration factor values, the category members do not have a significant potential to bioconcentrate within aquatic organisms or be adsorbed onto sediments. Although the category members are not expected to undergo appreciable hydrolysis, they are readily biodegraded in the aqueous environment. Therefore, they are not expected to be a significant hazard to aquatic species. Based on the tendency of these materials to move to water, they are not expected to be a hazard to terrestrial species.

5 RECOMMENDATIONS

Human health: The substances in the category possess properties indicating a hazard for human health (reversible eye and skin irritation, reversible CNS depression). These hazards do not warrant further work. However, they should nevertheless be noted by chemical safety professionals and users. Hemolysis and associated organ toxicity are noted in rats, mice and rabbits exposed to EGPE and EGBE. Humans are many-fold less sensitive to these effects and associated organ toxicity. Countries may desire to investigate any exposure scenarios that were not presented by the Sponsor country.

Environment: EGPE, EGBE, EGHE are of low priority for further work because of their low hazard profile. EGBEA possesses properties indicating a hazard for the environment. These hazards do not warrant further work as they are related to acute toxicity which may become evident only at very high exposure levels **and the substance is readily biodegradable**. However, they should be noted by chemical safety professionals and users.

6 REFERENCES

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APPENDIX I – EXPOSURE DATA FOR EGBEA

Coatings industry

Activity	Number of measurements	Mean (mg/m^3)	Range [or 95th percentile]	Reference
Paint manufacture		4.5 mg/m^3		Vincent 1999
Paint – spraying	4	1.2	0.1-3.1	Vincent 1999
Paint – curtain coating	5	0.5	0.5-0.5	Vincent 1999
Printing	4	12.7	4.6-26.5	Veulemans 1987
Unspecified use	3	10.6	8.9-11.7	Veulemans 1987
Screen printing		4.9 mg/m3 (max)		Clapp et al. 1984
Screen printing	19	2.9mg/m3	0.1-10 mg/m3	Johanson et al. 1989
Silk screening	61	3.6	0.5-35 [11]	Johanson et al. 1989
Screen washing	3	0.7	0.5-1	Johanson et al. 1989
Offset printing	8	1.1	0.5-2.7	Johanson et al. 1989
Flexography	2	<0.1	<0.1	Johanson et al. 1989
Printshop	41	2.2 (max 14.3)	[0.2-6.3]	OSPA, 2002
Printshop Solvent Reclaim	6	0.8 (max 2.3)	[0.3-1.9]	OSPA, 2002
Printing Other	2	19.6 (max 22.2)		OSPA, 2002
Printing industry	41	5.7	0.5-35 [30]	Vincent 1999
Chemical industry	4		<0.1	Vincent 1999
Rubber and plastics	28	2.3	0.1-7 [6.9]	Vincent 1999
Metal finishing	19	1.4	0.5-6 [6]	Vincent 1999
Electrical engineering	2		<0.1	Vincent 1999
Communication equipment	8	1.7		Vincent 1999

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SIDS Dossier

and

Robust Study Summaries

for CAS No. 2807-30-9

Existing Chemical	:	ID: 2807-30-9
CAS No.	:	2807-30-9
EINECS Name	:	2-(propyloxy)ethanol
EINECS No.	:	220-548-6
TSCA Name	:	Ethanol, 2-propoxy-
Molecular Formula	:	C5H12O2
Structural Formula	:	O(CCO)CCC

Producer Related Part

Company	:	PCA Services, Inc.
Creation date	:	08.02.2002

Substance Related Part

Company	:	PCA Services, Inc.
Creation date	:	08.02.2002
Memo	:	
Printing date	:	11.05.2004
Revision date	:	07.06.2005
Date of last Update	:	07.06.2005
Number of Pages	:	62
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD AND COMPANY INFORMATION

Type	:	Sponsor Country
Name	:	United States U.S. Environmental Protection Agency Mr. Oscar Hernandez, Director Risk Assessment Division (7403M)
Partner	:	No Partner
Date	:	08.02.2002
Street	:	1200 Pennsylvania Ave., NW
Town	:	Washington, DC 20460
Country	:	USA
Phone	:	202-564-7641
Telefax	:	
Telex	:	
Cedex	:	

1.0.2 LOCATION OF PRODUCTION SITE

Company	:	Eastman Chemical Company
Town	:	Kingsport, Tennessee
Company	:	The Dow Chemical Company
Town	:	Midland, Michigan (Corporate Headquarters)

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

Substance type	:	organic
Physical status	:	liquid
Purity	:	> 99 % w/w
Source	:	Eastman Chemical Company
Reliability	:	(1) valid without restriction

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

2-propoxyethanol

Eastman EP ®solvent

EGPE

EP

ethylene glycol monopropyl ether

ethylene glycol propyl ether

n-Propyl Oxitol® Glycol

Propyl CELLOSOLVE®

propyl glycol

1.3 IMPURITIES

CAS-No : 107-21-1
EINECS-Name : Ethylene glycol
Molecular formula : C2H6O2
Value : 0.1 % w/w maximum
Source : Eastman Chemical Company

CAS-No : 71-23-8
EINECS-Name : n-Propanol
Molecular formula : C3H8O
Value : 0.05 % w/w maximum
Source : Eastman Chemical Company

CAS-No : 6881-94-3
EINECS-Name : Diethyleneglycol monopropyl ether
Molecular formula : C7H16O3
Value : 0.05 % w/w maximum
Source : Eastman Chemical Company

CAS-No :
EINECS-Name : Water
Value : 0.05% maximum
Source : Eastman Chemical Company

1.4 ADDITIVES

Remark : No additives typically

1.5 QUANTITY

Quantity : U.S. Production: 4.54-22.73 thousand metric tons
Source : 2002 TSCA Inventory Update Report
Reliability : (1) valid without restriction. Up to date reference.

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

Type	:	Type
Category	:	Wide Dispersive Use
Source	:	Chinn H, Anderson E and Yoneyama M, Glycol Ethers, CEH Marketing Research Report, SRI International. 2000.
Reliability	:	(1) valid without restriction. Up to date reference.
Type	:	Use
Category	:	Solvent in surface coatings, coalescing aid in water surface coatings and printing applications.
Source	:	Chinn H, Anderson E and Yoneyama M, Glycol Ethers, CEH Marketing Research Report, SRI International. 2000.
Reliability	:	(1) valid without restriction. Up to date reference.

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

1.9 SOURCE OF EXPOSURE

	:	
Source of exposure	:	Human exposure during manufacture
Remark	:	Manufactured in closed systems. Some inhalation or dermal exposure may occur during sampling. Exposure potential during manufacture is less than during intended use.
Source of exposure	:	Human exposure during intended use.
Remark	:	Occupational exposure can occur via inhalation and dermal contact during applications of surface coatings and printing inks containing ethylene glycol propyl ether (EGPE) as a solvent or coalescing aid. Exposure is typically minimized by the use of engineering controls and appropriate workplace practices.
Source of exposure	:	Environmental exposure
Remark	:	EGPE may be released to the environment into air or water during manufacture. Such releases are minimized through the use of closed systems, engineering controls and biodegradative treatment of aqueous waste streams. EGPE is also released to the environment during use as a coatings and printing inks solvent through evaporation. Some of these applications may use open processing, but often with engineering controls.

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

1.14.2 MAJOR ACCIDENT HAZARDS

1.14.3 AIR POLLUTION

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value : = -60 ° C
Decomposition :
Sublimation :
Method : other: unknown
Year :
GLP : no data
Test substance : as prescribed by 1.1-1.4
Reliability : (2) valid with restrictions. Published value
Flag : Critical study for SIDS endpoint
(10)

Value : = -90 ° C
Decomposition : no at ° C
Sublimation : no
Method : other
Year :
GLP : no
Test substance : as prescribed by 1.1-1.4
Source : Eastman Chemical Company unpublished data
Reliability : (2) valid with restrictions. Test conditions are unknown.

2.2 BOILING POINT

Value : = 150-152 ° C
Decomposition :
Method : other: unknown
Year :
GLP : no data
Test substance : as prescribed by 1.1-1.4
Reliability : (2) valid with restrictions. Published value.
Flag : Critical study for SIDS endpoint
28.04.2004 (10)

Value : = 149 ° C at 1013 hPa
Decomposition : no
Method : other
Year :
GLP : no
Test substance : as prescribed by 1.1-1.4
Reliability : (2) valid with restrictions. Published value.
28.04.2004 (5)

2.3 DENSITY

Type : density
Value : = .913 at 25 degrees C
Method : other
Year :
GLP : no data
Test substance : as prescribed by 1.1 -1.4
Reliability : (2) valid with restrictions. Published value.
04.28.2004 (5)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : = 1.3 hPa at 25° C
Decomposition :
Method : other: unknown
Year :
GLP : no data
Test substance : as prescribed by 1.1-1.4
Decomposition :
Reliability : (2) valid with restrictions. Published value.
Flag : Critical study for SIDS endpoint
04.28.2004 (10)

Value : = 3.87 hPa at 25° C
Decomposition : no
Method : other: unknown
Year :
GLP : no data
Test substance : as prescribed by 1.1-1.4
Decomposition : no
Reliability : (2) valid with restrictions. Published value.
04.28.2004 (5)

2.5 PARTITION COEFFICIENT

Log pow : = .075 at ° C
Method : other: calculated using the EPIWIN KOWWIN (v1.66) program
Year : 2001
GLP : no
Test substance : as prescribed by 1.1-1.4
Remark : The CAS No. 2807-30-9 was inputted into the model.
Reliability : (2) valid with restrictions. Data were obtained by modeling.
Flag : Critical study for SIDS endpoint

2.6.1 WATER SOLUBILITY

Value :
Qualitative : completely soluble
Pka :
PH :
Method : other: unknown
Year :
GLP : no data
Test substance : as prescribed by 1.1-1.4
Reliability : (2) valid with restrictions. Published reference.
Flag : Critical study for SIDS endpoint
(10)

Value : = 1000 g/l at 20 ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C

Method	:	other
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1-1.4
Remark	:	Substance is miscible with water.
Source	:	Eastman Chemical Company unpublished data
Reliability	:	(2) valid with restrictions. Test conditions are unknown.

2.6.2 SURFACE TENSION

2.7 FLASH POINT

2.8 AUTO FLAMMABILITY

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	other
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Direct photolysis		
Halflife t1/2	:	= 5.9 hour(s) (12-hour day)
Degradation	:	% after
Indirect photolysis	:	
Sensitizer	:	OH
Conc. of sens.	:	1.5E6 OH/cm3
Rate constant	:	21.6128E-12 cm3/molecule-sec.
Degradation	:	50 % after 5.939 hours
Quantum yield	:	
Deg. Product	:	
Method	:	other: calculated using the EPIWIN AOP (v1.90) program
Year	:	2003
GLP	:	no
Test substance	:	as prescribed by 1.1-1.4
Remark	:	The input to the EPIWIN Aop program was the SMILES code for CAS No. 2807-30-9. No other variables influence this calculation.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint

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
Deg. Product	:	
Method	:	other: calculated using EPIWIN Hydrowin (v1.67) program with CAS No. 2807-30-9 as the input. No other variables influence this calculation.
Year	:	2001
GLP	:	no
Test substance	:	as prescribed by 1.1-1.4
Remark	:	The EPIWIN HYDROWIN (v1.67) program was used to estimate the abiotic rate of hydrolysis in water under neutral conditions. This program cannot estimate the rate of hydrolysis under these conditions for ethers. In general, ether linkages are highly resistant to abiotic hydrolysis in a neutral aqueous environment.
Reliability	:	(4) not assignable

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	volatility
Media	:	water - air

Air (level III)	:	4.11 %
Water (level III)	:	70.8 %
Soil (level III)	:	24.9 %
Biota (level II / III)	:	0.119 %
Method	:	other: EPIWIN Fugacity Level III
Year	:	2004
Test substance	:	as prescribed by 1.1-1.4
Remark	:	Measured inputs to the EPIWIN program are melting point (-60 degrees C), boiling point (151 degrees C), vapor pressure (1 mm Hg), and water solubility (1000 g/l). Emission rates inputted were air (1000 kg/hr), water (500 kg/hr) and soil and sediment (0 kg/hr). The EPIWIN Henry (v3.10) model estimates a Henry's Law Constant of 7.38E-008 atm-m3/mole at 25 degrees C (Bond Estimate). The EPIWIN PCKOC (v1.66) model estimates a Koc=1 (soil-sediment partition constant). The EPIWIN BCF (v2.14) program estimates a BCF (Bioconcentration Factor) of 3.162 and a Log BCF of 0.500. The Level III Fugacity model estimates half-lives of 12 hours in air, 360 hours in water, 360 hours in soil and 1440 hours in sediment.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	other:non-acclimated sewage microorganisms
Contact time	:	
Degradation	:	= 100 % after 20 day
Result	:	readily biodegradable
Kinetic of test substance	:	5 day = 13 **%** 10 day = 66 **%** 20 day = 100 **%** **%** **%**
Deg. Product	:	not measured
Method	:	other: as described in "Standard Methods for the Examination of Water and Wastewater", 16th ed.", USPHA, Washington, D.C., 1985.
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The measured and calculated theoretical oxygen demands were 1.94 and 2.15 mg/mg. After 5, 10 and 20 days of incubation, the percent biooxidation was 13, 66 and 100% (respectively).
Test condition	:	A modified version of the biochemical oxygen demand (BOD) method published in "Standard Methods for the Examination of Water and Wastewater", 16th edition, Am. Public Health Association, 1985 was used. A discussion of these modifications appears in Price et al., "Brine shrimp bioassay and seawater BOD of petrochemicals", J. Water Poll. Control Fed., Jan. 1974. Nonacclimated domestic sewage organisms were used as seed in the test. Domestic wastewater was filtered through glass wool and added (3

ml/bottle) as seed material to clean BOD bottles. A buffered, aerated solution containing minerals was then added. Small amounts of test material were added from a 0.1 % stock solution to yield concentrations of 3, 7 and 10 mg/l. A control with no test material also was run. At least two of the concentrations were tested in duplicate. Dissolved oxygen (DO) was monitored five times during the course of the 20-day test. The solution was reaerated when the DO dropped below 4.0 mg/l. Reaeration (if needed) was accomplished by dividing the BOD bottle contents between 2 BOD bottles, sealing, shaking them twenty times, returning contents to the original BOD bottle, recording the oxygen level, resealing, and returning the BOD bottle to the incubator. Samples were analyzed routinely for nitrites and nitrates. Results of the tests were expressed in terms of % biooxidation calculated as the cumulative oxygen uptake for the test material minus a control x 100 / initial concentration of test material x theoretical oxygen demand.

Test substance : Test material was propyl CELLOSOLVE®.
Reliability : (2) valid with restrictions. Comparable to guideline study with acceptable restrictions. Purity was not stated.
Flag : Critical study for SIDS endpoint
15.02.2002 (33)

3.6 BOD5, COD OR BOD5/COD RATIO

3.7 BIOACCUMULATION

BCF : 3.162
Elimination :
Method : BCFwin v2.15
Year : 2004
GLP :
Test substance : as prescribed by 1.1 - 1.4
Remark : The estimated Log BCF = 0.500. Measured inputs to the EPIWIN program are melting point (-60 degrees C), boiling point (151 degrees C), vapor pressure (1 mm Hg), and water solubility (1000 g/l).
Reliability : (2) valid with restrictions. Data were obtained by modeling.

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	m > 5000
Method	:	other: EPA/ASTM
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Test condition	:	Ten fish were tested per concentration (not listed). Additional details were not listed.
Test substance	:	Test material was propyl CELLOSOLVE®. Purity was not listed.
Reliability	:	(4) not assignable. There are not enough details to assign a reliability rating.
Flag	:	Supporting study for SIDS endpoint

15.02.2002 (33)

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	
Analytical monitoring	:	no
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	A no effect level of > 100 microliters/l was reported.
Reliability	:	(4) not assignable. No experimental details were given.
Flag	:	Supporting study for SIDS endpoint.

11.02.2002 (16)

Species	:	other: fish
Endpoint	:	LC50
Exposure period	:	96 hours
Unit	:	mg/l
Analytical monitoring	:	N/A
NOEC	:	
EC50	:	4925.616
Method	:	EPIWIN ECOSAR (v0.99)
Year	:	2004
GLP	:	N/A
Test substance	:	as prescribed by 1.1 – 1.4
Remark	:	Measured inputs to the EPIWIN program are melting point (-60 degrees C), boiling point (151 degrees C), vapor pressure (1 mm Hg), and water solubility (1000 g/l).
Reliability	:	(2) valid with restrictions. Data were obtained by an approved model.

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	c = 2137

Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	other TS: ethylene glycol butyl ether (CAS No. 111-76-2)
Result	:	Exposure to 2800 mg/l test material caused 100% lethality by 24 hours. Exposure to 2100 mg/l caused 30% lethality by 24 hours and 40% mortality by 96 hours. None of the fish exposed to 1550 mg/l died by 96 hours. The 24, 48, 72 and 96-hour LC50 values (and 95% confidence interval) were 2185 (2069-2318), 2185(2069-2318), 2185(2069-2318) and 2137 (2022-2263) mg/l.
Test condition	:	Raw Lake Huron water dechlorinated with activated carbon was used in the test. The dissolved oxygen, total alkalinity, hardness, and specific conductivity, pH, turbidity (as ppm SiO2) and color (APHA) were 9.6 mg/l, 89 mg/l as CaCO3, 101 mg/l was CaCO3, 192 micromhos/cm, 7.8, 1 ppm, and < 5, respectively. The water also contained the following minerals and chemicals: alkyl benzene sulfonate (< 0.1 ppm), arsenic < 0.005 ppm, chlorine (6.2 ppm), fluoride (<0.07 ppm), iron (< 0.1 ppm), magnesium (6 ppm), nitrate (1.2 ppm), sulfate (15 ppm), and total dissolved solids (100 ppm). Barium, cadmium, chromium, copper, cyanide, lead, manganese, phenols, selenium, silver, zinc, PCB and mercury concentrations were less than the limits of detection. Test fish were acclimated in the water at 12 degrees C for at least 10 days prior to testing. The test followed guidelines in the EPA publication "Methods for acute toxicity tests with fish, macroinvertebrates and amphibians, Ecological Research Series EPA-660/3-75-009", 1975. Fish (0.3 g, 21.9 mm) were fed until 24 hours prior to the test and were placed in bioassay vessels (a 22 x 24.5 cm round aquarium containing 8 liters of test water) 24 hours before adding the test material. Ten fish were added separately to each aquarium. The aquaria were aerated. Fish were exposed to 1550, 2100 and 2800 mg/ml test material. If no deaths occurred in 24 hours, aeration was stopped and the test material was added with 2 liters of water. Any vessel containing dead fish was not used. Temperature was maintained at 12 +/- 1 degrees C. The average loading was 0.3 g/l. Fish were observed daily for 96 hours. Death was defined as no gill movement and no response to prodding. Dead fish were removed from tanks. The LC50 value and its 95 % confidence interval were calculated using Thompson's moving average.
Test substance	:	Test material was DOWANOL EB (typical production grade). Purity was not specified, but is likely to be high.
Reliability	:	(2) valid with restrictions. Comparable to guideline study with acceptable restrictions. Dissolved oxygen, conductance and pH were not measured at study termination.

(3)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	static
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	m > 5000
Method	:	other:EPA/ASTM
Year	:	1987
GLP	:	no data

Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Lighting conditions, method of calculating the LC50 value, numbers of deaths at each concentration, condition of controls and purity and solubility/insolubility of the test material were not listed. Data were listed as LC50 values, rather than EC50 values.
Result	:	Total hardness, alkalinity, pH and conductivity of the test and holding water were 55 mg/l as CaCO3, 36 mg/l as CaCO3, 6.7, and 250 micromhos/cm. The LC50 value was greater than the highest concentration tested (5000 mg/l).
Test condition	:	Daphnia magna stocks were originally obtained from the EPA laboratory at Duluth, MN. They were maintained at 20-22 degrees C in a series of 600 ml beakers filled with Kanawha River water obtained from the South Side Boat Ramp (Charleston, SC). Daphnia were fed three times a week with a laboratory-prepared food consisting of trout food, yeast and alfalfa powder. Daphnia used in the test were offspring of 20-50 gravid females isolated for 24 hours. A series of from 5-10 equidistant concentrations based on results of fish toxicity studies (plus control) were tested. Tests were conducted in 250 ml beakers containing 100 ml of test solution (in Kanawha River water) and 5 Daphnia (less than 24 hours old). Tests were run in duplicate. Dissolved oxygen and pH were determined initially and at 48 hours for all test solutions (dissolved oxygen values were not listed). Total hardness, alkalinity, pH and conductivity of the test and holding water were 55 mg/l as CaCO3, 36 mg/l as CaCO3, 6.7, and 250 micromhos/cm. Mortalities were recorded at 24 and 48 hours.
Test substance	:	Test material was propyl CELLOSOLVE®.
Reliability	:	(2) valid with restrictions. Basic data given.
Flag	:	Critical study for SIDS endpoint

15.02.2002 (33)

Type	:	static
Species	:	Daphnia sp. (Crustacea)
Exposure period	:	96 hour(s)
Unit	:	
Analytical monitoring	:	no data
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	A no effect level of > 100 microliters/l is reported. No other details are given.
Reliability	:	(4) not assignable

11.02.2002 (15)

Species	:	Daphnia magna (Crustacea)
Endpoint	:	
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	N/A
NOEC	:	
EC50	:	4622.326
Method	:	EPIWIN ECOSAR (v0.99)
Year	:	2004
GLP	:	N/A
Test substance	:	as prescribed by 1.1 – 1.4

Remark	:	Measured inputs to the EPIWIN program are melting point (-60 degrees C), boiling point (151 degrees C), vapor pressure (1 mm Hg), and water solubility (1000 g/l).
Reliability	:	(2) valid with restrictions. Data were obtained by an approved model.

Type	:	static
Species	:	other:flatworm
Exposure period	:	96 hour(s)
Unit	:	
Analytical monitoring	:	no data
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	A no effect level of > 100 microliters/l is reported. No other details are given.
Reliability	:	(4) not assignable

15.02.2002 (16)

Type	:	static
Species	:	other:snail
Exposure period	:	96 hour(s)
Unit	:	
Analytical monitoring	:	no data
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	A no effect level of > 100 microliters/l is reported. No other details are given.
Reliability	:	(4) not assignable

15.02.2002 (16)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Green algae
Endpoint	:	EC50
Exposure period	:	96 hours
Unit	:	mg/l
Analytical monitoring	:	no
NOEC	:	
EC50	:	2587.382 mg/L
Method	:	EPIWIN ECOSAR (v0.99)
Year	:	2003
GLP	:	N/A
Test substance	:	as prescribed by 1.1 – 1.4
Remark	:	Measured inputs to the program were melting point (-60 degrees C), boiling point (151 degrees C), vapor pressure (1 mm Hg), and water solubility (1000 g/l).
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint

Species	:	Selenastrum capricornutum (Algae)
Endpoint	:	growth rate
Exposure period	:	7 day
Unit	:	mg/l
Analytical monitoring	:	no

NOEC	:	m = 125
EC50	:	c > 1000
Method	:	other:Printz algal assay:Bottle test
Year	:	1988
GLP	:	yes
Test substance	:	other TS: ethylene glycol monobutyl ether, (CAS No. 111-76-2)
Remark	:	The percent inhibition at Days 2 and Day 3 were not calculated. However, raw data were provided for these time points. The average cell counts on Day 3 (or 72 hours) for cells treated with 0, 63, 125, 250, 500 and 1000 mg/l were 989792, 917371, 1054417, 1062728, 886310 and 615797, respectively. Therefore, the percent inhibition for the highest concentration (10000 mg/l) was 989792 (control value) – 615797/989792 x 100 = 37.8 %. Therefore, the 72 hour EC50 value also was > 1000 mg/l.
Result	:	The initial and final pH values ranged from 7.4-7.6 and 7.7-7.8, respectively. On day 4, concentrations up to 500 mg/l produced a 3.5-14.7 % increase in the number of cells/ml and a 2-13.3 % increase in total cell volume (TCV). A concentration of 1000 mg/l induced a 24.3 and 19.9 % inhibition in cell number and TCV at 4 days (respectively). At 7 days, 63 and 125 mg/l had no effect on the number or TCV of cells. A concentration of 250 mg/l produced 4.2 and 4.3% decreases in cell number and TCV, respectively (only significant for TCV). A concentration of 500 mg/l produced 12.2 and 7.1 % decreases in cell number and TCV, respectively. At 1000 mg/l, the percent decreases in cell number and TCV were 30.4 and 20.6, respectively. The 4 and 7-day EC50 values for inhibition of growth were greater than the highest concentration used (1000 mg/l).
Test condition	:	A stock solution of 6.67 ml test material in sterile-filtered algal assay medium was prepared by weighing 0.6674 g of the test material and diluting it to 100 ml. The algal inoculum was prepared from a 7-day old stock culture. The stock was diluted with algal assay medium to contain approximately 500,000 cells/ml. A range finding test indicated that the EC50 was between 100 and 1000 mg/l. The definitive test consisted of a series of 5 test concentrations (63, 125, 250, 500 and 1000 mg/l) at volumes of 50 ml, with 3 replicates each and six replicate controls. Tests were performed in 125 ml erlenmeyer flasks. One ml of the algal inoculum was added to each flask (giving a nominal concentration of approximately 10,000 cells/ml). A counting blank for each test and control concentration did not contain algae. Flasks were incubated at 24 +/- 2 degrees C, and were continuously shaken (100 oscillations/ min), and illuminated (4304 +/- 430 lux). The pH of each vessel was recorded at the start and end of the test. Cell growth was assessed by measuring both the number (cells/ml) and size (total cell volume/ml) of the algal population on Days 2, 3, 4, and 7 of exposure with a Coulter Counter. Cells were counted in duplicate. All counts were corrected for background count and dilution factor. All particles having volumes of 10 to 320 cubic microns were counted. The percent inhibition of growth was calculated compared to control. Data for the number of cells/ml and total cell volume/ml were compared to the control using Dunnett's t test.
Test substance	:	Test material was Dowanol EB glycol ether with a purity of 99.7%.
Reliability	:	(1) valid without restriction. The study is comparable to a guideline study.
Flag	:	Supporting study for SIDS endpoint

(8)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type	:	aquatic
Species	:	other bacteria: sewer microorganisms
Exposure period	:	16 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
IC50	:	m > 1000
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The IC50 value was greater than the highest concentration tested (1000 mg/l).
Test condition	:	Selected concentrations (not listed) were incubated for 16 hours at 23 degrees C on a shaker table in the presence of nutrients, buffer, growth substrate, and sewer microorganisms. Toxicity was indicated when the resulting turbidity was at (or less than) 50% of the control (IC50). Details of the test are published in: Alsop et al., "Bacterial Growth Inhibition Tests", J. Water Pollution Control Federation, Vol 52: No. 10, October, 1980.
Reliability	:	(2) valid with restrictions. Basic data given. Purity of the test material is unknown.

15.02.2002 (33)

Type	:	aquatic
Species	:	other bacteria: Microtox
Exposure period	:	
Unit	:	mg/l
Analytical monitoring	:	no data
EC50	:	= 2000
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Test condition	:	Microtox bacteria and procedures were used. No other details were given.
Reliability	:	(4) not assignable. There is not enough information to assign a reliability rating.

15.02.2002 (33)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

Species	:	other terrestrial plant: ryegrass, lettuce, radish
Endpoint	:	other: germination, hypocotyl growth, root growth
Exposure period	:	
Unit	:	
Remark	:	A no effect level of > 100 microliters/l was reported for germination, hypocotyl growth and root growth of ryegrass, radish and lettuce.

Reliability : (4) not assignable. There are not enough details to assign a reliability rating.

15.02.2002 (16)

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	other: Charles River CD(BR)
Sex	:	male
Number of animals	:	25
Vehicle	:	
Value	:	= 3089 mg/kg bw
Method	:	other
Year	:	1981
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The acute oral toxicity of ethylene glycol monobutyl ether (EGBE, CAS No. 111-76-2) also was tested in this study. The LD50 values in both fasted and rats (and the confidence intervals) were 14.80 (11.2-19.5) mM/kg, or 1746 (1322-2301) mg/kg.
Result	:	The LD50 value in fasted rats (and its confidence interval) was 29.70 (22.5-39.2) mM/kg, or 3089 (2340-4077) mg/kg. The LD50 value in fed rats (and its confidence interval) was 59.40 (45.0-78.4) mM/kg, or 6178 (4680-8154) mg/kg. The majority of deaths occurred within the first 3 days. The number of deaths at each dose was not stated. Clinical signs of toxicity for both fed and fasted animals (numbers of animals affected were not stated) were inactivity, labored breathing, rapid respiration, anorexia, slight to moderate weakness, tremors, prostration and death. Animals that died exhibited bloody urine, and/or blood in the stomach and intestines. These conditions were not noted in survivors autopsied at termination.
Test condition	:	The acute oral LD50 values of test material were determined in separate groups of fasted and fed animals (150-200 g). Groups of 5 animals were given various doses of undiluted test material by gavage. Doses given were calculated on a mM/kg basis, and progressed by a factor of two (individual doses given were not listed). General appearance and activity, pharmacologic and toxicologic signs and mortality were checked twice daily (except on weekends and holidays). The appearance of stools and urine was noted. Individual body weights were recorded prior to testing and at the end of the 2-week observation period. Animals that died and all survivors were necropsied and examined for gross pathology. The LD50 value with its 95% confidence interval was calculated using the method of Thompson and Weil.
Test substance	:	Purity of the test material was > 99.1%.
Reliability	:	(2) valid with restrictions. Basic data given. Females were not tested. Individual doses used and the number of deaths at each dose is not listed.
Flag	:	Critical study for SIDS endpoint

15.02.2002 (21)

Type	:	LD50
Species	:	rat
Strain	:	other:COBS/CD/(SD)/BR
Sex	:	male
Number of animals	:	25
Vehicle	:	
Value	:	= 3089 mg/kg bw
Method	:	other

Year	:	1984
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The LD50 value (and 95% confidence limit) was 3089(2090-4576) mg/kg. Clinical signs of toxicity were abnormal respiratory patterns, weakness, anorexia, hemoglobinuria, tremors, prostration and death. The numbers of individual deaths and numbers of animals exhibiting clinical signs at each concentration were not listed.
Test condition	:	Groups of 5 male rats (150-200 g) were gavaged with 10.5, 21.0, 42.0, 84.0 and 168.0 mmol/kg (approx. 1090, 2180, 4360, 8720 or 17,470 mg/kg). Animals were fasted 16-20 hr prior to treatment. General appearance and activity, toxicologic signs and mortality were checked twice daily for 14 days (except during weekends and holidays). Animals were weighed before and at the end of the study. The appearance of stool and urine were noted. The LD50 value and 95% confidence interval were calculated by the method of Weil.
Test substance	:	The purity of the test material was analyzed as 99.5%. The main impurities were 2-n-butoxyethanol, triethylene glycol n-butyl ether and isopropoxy ethanol (quantities were not listed).
Reliability	:	(2) valid with restrictions. Basic data given. The effect on females was not characterized. The individual numbers of deaths at each dose were not listed.

15.02.2002 (15)

Type	:	LD50
Species	:	mouse
Strain	:	CD-1
Sex	:	male
Number of animals	:	25
Vehicle	:	
Value	:	= 1774 mg/kg bw
Method	:	other
Year	:	1981
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The acute oral toxicity of ethylene glycol monobutyl ether (EGBE, CAS No. 111-76-2) also was tested in this study. The LD50 value in fasted mice (and the confidence interval) was 12.87 (9.7-17.0) mM/kg, or 1519 (1145-2006) mg/kg. The LD50 value in fed mice (and the confidence interval) was 16.99 (10.9-26.4) mM/kg, or 2005 (1286-3115) mg/kg.
Result	:	The LD50 value in fasted mice (and its 95% confidence interval) was 17.06 (12.9-22.5) mM/kg, or 1774 (1342-2340) mg/kg. The LD50 value in fed mice (and its 95% confidence interval) was 29.70 (20.1-44.0) mM/kg, or 3089 (2090-4576) mg/kg. The numbers of deaths at each dose were not given. Clinical signs of toxicity for both fed and fasted animals (numbers of animals affected were not stated) were inactivity, labored breathing, rapid respiration, anorexia, slight to moderate weakness, tremors, prostration and death. Fasted animals that died exhibited bloody urine, and/or blood in the stomach and intestines. These conditions were not noted in survivors autopsied at termination.
Test condition	:	The acute oral LD50 values of test material were determined in fasted and fed animals (15-17 g), with a period of 2 months between experiments. Groups of 5 animals were given various doses of undiluted test material by gavage. Doses given were calculated on a mM/kg basis, and progressed by a factor of two (individual doses given were not listed). General appearance and activity, pharmacologic and toxicologic signs and mortality were checked twice daily (except on weekends and holidays).

The appearance of stools and urine was noted. Individual body weights were recorded prior to testing and at the end of the 2-week observation period. Animals that died and all survivors were necropsied and examined for gross pathology.

The LD50 value with its 95% confidence interval was calculated using the method of Thompson and Weil.

Test substance : Purity of the test material was > 99.1%.
Reliability : (2) valid with restrictions. Basic data given. The effect on females was not characterized. The individual number of deaths at each dose was not listed.

15.02.2002 (21)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC50
Species : rat
Strain : other:COBS CD(SD)BR
Sex : male
Number of animals : 20
Vehicle :
Exposure time : 6 hour(s)
Value : > 2132 ppm
Method : other
Year : 1984
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : Analytical concentrations for 250 or 500 ppm were not listed. It is assumed that 1121 and 2132 ppm were the analytical concentrations for the 1000 and 2000 ppm groups, respectively.
Result : The LC50 value was greater than 2132 ppm (the highest vapor concentration attainable without formation of aerosol). No deaths were observed over the 14 day observation period. Body weight gains were normal. Hemoglobinuria was seen in animals treated with 1121 and 2132 ppm (numbers of animals affected were not listed). No other signs of toxicity were observed.
Test condition : Groups of 4 rats (150-200g) were exposed to nominal concentrations of 0, 250, 500, 1000 or 2000 ppm test material for 6 hours in 20-liter inhalation chambers. The highest vapor concentration attainable was 2000 ppm. Vapors were produced by slight heating of the liquid. The vapors were diluted with oil-free compressed air prior to entering the chambers. Additional information about generation of the gas was not listed. Concentrations were analyzed at least once per hour. The animals were observed for clinical signs and mortality daily for 14 days. Body weights were determined twice weekly.
Test substance : The purity of the test material was 99.5%. The main impurities were 2-n-butoxyethanol, triethylene glycol n-butyl ether and isopropoxy ethanol (quantities were not listed).
Reliability : (2) valid with restrictions. Basic data given. Females were not tested.
15.02.2002 (15)

Type : LC50
Species : rat
Strain :
Sex : male
Number of animals : 20
Vehicle :
Exposure time : 6 hour(s)
Value : > 2132 ppm

Method	:	other
Year	:	1978
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	It is likely that this study is an extension of the first study mentioned in this section (as the LD50 value and author were identical). The LC50 value was estimated to be > 2132 ppm, the highest vapor concentration achievable. A red discolored urine was observed in all animals at concentrations of 1100 ppm and greater. Blood samples were taken from one animal in each group hourly during the 6 hour exposure and at intervals up to 2 weeks following exposure. Hemoglobin concentration and hematocrit were reduced at all levels tested (273-2132 ppm). Gross hemolysis also was observed at concentrations greater than 1100 ppm. The severity of these blood changes increased as a function of concentration and length of exposure. Hemolysis was not detected 24 hours after exposure and hemoglobin and hematocrit returned to control levels within 2 weeks after exposure.
Reliability	:	(2) valid with restrictions. Basic data given. Females were not tested.

15.02.2002 (16)

5.1.3 ACUTE DERMAL TOXICITY

Type	:	LD50
Species	:	rabbit
Strain	:	New Zealand white
Sex	:	male
Number of animals	:	20
Vehicle	:	
Value	:	= 1337 mg/kg bw
Method	:	other
Year	:	1981
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The acute dermal toxicity of ethylene glycol monobutyl ether (EGBE, CAS No. 111-76-2) also was tested in this study. The LD50 value (and the confidence interval) was 435(330-578) mg/kg.
Result	:	The LD50 value (and its confidence interval) was 12.86(9.7-17.0) mmoles/kg, or 1337(1009-1768) mg/kg. The number of individual deaths at each dose was not stated. Anorexia, slight depression, cyanosis, ataxia and soft feces were seen at lower doses and salivation, nasal discharge, iritis, significant depression, labored breathing and prostration were seen at higher doses (doses not stated). Two of the low dose animals exhibited abnormal pathology. One animal in the 541 mg/kg group had red spots on the surface of the thymus and another had poor differentiation of the cortex and medulla of the kidney. All animals in the other groups had abnormal pathology. Animals dosed with 1092 mg/kg had a discolored margin of the liver (N=1), enlarged kidney (N=3), dark red kidney (N=1), poor differentiation of the cortex and medulla of the kidney (N=4), dark red stomach (N=1), and red discoloration of the large and small intestine (N=1). These changes were observed in 4-5 animals treated with 2184 mg/kg. One animal treated with 2184 mg/kg had a pale liver, and another had an enlarged spleen. Red discoloration of the large and small intestines and kidney toxicity also were found in 3 animals treated with 4368 mg/kg. Administration of 2184 mg/kg (the highest dose tested at which enough animals survived to make an evaluation) produced slight skin irritation.
Test condition	:	Rabbits were quarantined and acclimated for at least 3 weeks prior to

treatment and were randomly assigned to groups of 5 animals each. Back skin was closely clipped, but was not abraded. Depending on the volume administered, one or more pads were placed over the site. The pads were held in close contact with the skin by an occlusive wrap of dental dam. Test material was injected into the pad under the wrap using a long stainless steel intubation needle. Doses administered were 5.2, 10.5, 21.0 or 42.0 mmol/kg (541, 1092, 2184 or 4368 mg/kg, respectively). The edges of the dental dam were sealed using adhesive tape. The wrap was removed after 24 hours, and the amount of residual material remaining was estimated and removed.

All animals were observed twice daily for mortality and once a day for abnormal signs. Dermal responses were scored on Days 1, 3, 7, 10 and 14 (using the method of Draize). Individual body weights were recorded prior to dosing, on Day 7, and at death or termination (day 14). Survivors were killed on Day 14. All animals (including those that died) were autopsied. Gross pathology was recorded for all rabbits. The LD50 value and confidence interval were calculated using the method of Thompson and Weil.

Test substance : Purity of test material was > 99.1%.
Reliability : (2) valid with restrictions. Basic data given. Females were not tested. Individual doses used and the number of deaths at each dose is not listed.

15.02.2002 (22)

Type : LD50
Species : guinea pig
Strain :
Sex :
Number of animals : 20
Vehicle :
Method : other
Year : 1984
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : The test is also described in "Katz GV. 1978. Basic toxicity of 2-propoxyethanol. Eastman Kodak Report HS&HFL No. 78-144, dated 11-30-78."
Result : All animals exposed to 5 ml/kg died and all exposed to 1 ml/kg survived. Therefore, the dermal LD50 value was between these two doses (estimated as 1 to 5 g/kg).
Test condition : Test material was applied to the depilated abdomen of 5 guinea pigs/dose at 1, 5, 10, or 20 ml/kg under an occlusive wrap for 24 hours. Test material was placed on a Webril pad which was glued to a strip of rubber dental dam. The dental dam was wrapped around the entire trunk of the guinea pig and was removed after 24 hours. Observations were made 24 hours, and 1 and 2 weeks after dosing. Body weights were determined before and 2 weeks after dosing. The LD50 value was estimated as greater than the largest dose causing no mortality or between two doses (as appropriate).
Test substance : The purity of the test material was 99.5%. The main impurities were 2-n-butoxyethanol, triethylene glycol n-butyl ether and isopropoxy ethanol (quantities were not listed).
Reliability : (2) valid with restrictions. Basic data given. An exact LD50 value was not determined.

15.02.2002 (15)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

5.2.1 SKIN IRRITATION

Species	:	guinea pig
Concentration	:	
Exposure	:	occlusive
Exposure time	:	24 hour(s)
Number of animals	:	20
PDII	:	
Result	:	slightly irritating
EC classification	:	
Method	:	other
Year	:	1984
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Results are also described in "Krasavage WJ, Terhaar CJ. 1981. Comparative toxicity of nine glycol ethers: II. Acute dermal LD50." HS&HFL Report TX-81-38, Eastman Kodak Co., July 1981 and "Katz GV. 1978. Basic toxicity of 2-propoxyethanol. Eastman Kodak Report HS&HFL No. 78-144, dated 11-30-78." In this test, the concentration of test material that produced slight irritation was 0.9 g/kg, which was the highest dose at which enough animals survived to make a determination.
Result	:	Test material produced slight irritation (doses were not stated). Erythema and edema resolved within 1 week. Desquamation was observed 1 and 2 weeks after removal of the wrap.
Test condition	:	Test material was applied to a Webril pad which was glued to a strip of rubber dental dam. This was placed on the depilated abdomen of 5 guinea pigs/dose such that animals would be treated with 1, 5, 10, or 20 ml/kg. The dental dam was wrapped around the entire trunk of the guinea pig and was removed after 24 hours. Observations were made 24 hours, and 1 and 2 weeks after dosing.
Test substance	:	The purity of the test material was 99.5%. The main impurities were 2-n-butoxyethanol, triethylene glycol n-butyl ether and isopropoxy ethanol (quantities were not listed).
Reliability	:	(2) valid with restrictions. Basic data given. The number of animals affected was not stated.

15.02.2002 (15)

Species	:	guinea pig
Concentration	:	undiluted
Exposure	:	open
Exposure time	:	
Number of animals	:	5
PDII	:	
Result	:	slightly irritating
EC classification	:	
Method	:	other
Year	:	1984
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The test is also described in "Katz GV. 1978. Basic toxicity of 2-propoxyethanol. Eastman Kodak Report HS&HFL No. 78-144, dated 11-30-78."
Result	:	None of the animals died. The effect on body weight was not listed. A slight exacerbation of the effects seen at 24 hours was seen after treatment with 10 doses.
Test condition	:	A group of 5 guinea pigs received 0.5 ml test material on close-clipped back skin. The treated area of skin was depilated and observed 24 hours

after application. Test material was reapplied to the area for a total of 10 daily doses over 11 days (treatment on Sunday was omitted). The skin was clipped on day 7 and depilated 24 hours after the 10th dose. Observations were compared to those made 24 hr after dosing. An increase in severity in any one sign (types not stated but assumed to be erythema, edema and desquamation) was indicative of exacerbation. Animals were weighed prior to the first dose and after the last dose.

Test substance : The purity of the test material was analyzed as 99.5%. The main impurities were 2-n-butoxyethanol, triethylene glycol n-butyl ether and isopropoxy ethanol (quantities were not listed).

Reliability : (2) valid with restrictions. Basic data given. The number of animals affected was not listed.

15.02.2002 (15)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.1 ml
Exposure Time	:	
Comment	:	
Number of animals	:	3
Result	:	irritating
EC classification	:	
Method	:	Draize Test
Year	:	1984
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The test is also described in "Katz GV. 1978. Basic toxicity of 2-propoxyethanol. Eastman Kodak Report HS&HFL No. 78-144, dated 11-30-78."
Result	:	Test material produced moderate to strong irritation. It caused severe erythema and moderate edema of the conjunctiva. Iritis and staining of the adnexa and cornea were also present. Some degree of corneal opacity was seen in all eyes tested. All responses resolved within 14 days. Prompt irrigation had a palliative effect.
Test condition	:	One eye each of six rabbits was treated by dropping 0.1 ml of test material into the conjunctival sac formed by pulling the lower eyelid away from the eye. The lids were then held together for approximately 1 second and released. The conjunctival sac and the surface of the treated eye in three rabbits were immediately washed with distilled water. The untreated eye of each animal served as a control. The eyes were evaluated within 1 min and 1, 24, 48 hr and 14 days after treatment. Ocular lesions were graded according to guidelines outlined by Draize. Floresce® in sodium ophthalmic solution was dropped on the cornea of each eye 24 hr after treatment. The eye and conjunctival sac were flushed with distilled water and the presence or absence of staining was noted.
Test substance	:	The purity of the test material was 99.5%. The main impurities were 2-n-butoxyethanol, triethylene glycol n-butyl ether and isopropoxy ethanol (quantities were not listed).
Reliability	:	(2) valid with restrictions. Basic data given. The number of animals affected was not listed.

15.02.2002 (15)

5.3 SENSITIZATION

Type : other:footpad injection

Species	:	guinea pig
Concentration	:	Induction 1 % Challenge 10 %
Number of animals	:	25
Vehicle	:	other: Freund's complete adjuvant
Result	:	not sensitizing
Classification	:	
Method	:	OECD Guide-line 406 "Skin Sensitization"
Year	:	1988
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The test material did not cause irritation or sensitization. Scores of all animals were 0. All animals gained weight normally.
Test condition	:	A total of 25 male CRL:(HA)BR Hartley guinea pigs (347-556 g, 6-9 weeks old) were used in the studies. They had free access to food and water. Five animals were used in a primary irritation study. Hair was clipped from their backs and 0.3 ml of a 1% solution of test material in a mixture of acetone, dioxane and guinea pig fat (7:2:1) was applied to the clipped area. The animals were depilated and scored for edema and erythema 24 and 48 hours later. The highest average score for either day dictated the concentration to be used in the challenge dose of the sensitization study. The average was 0; therefore a 10% solution was used. For the sensitization study, 10 animals were injected in the footpad with 0.05 ml Freund's complete adjuvant and an additional 10 were injected with the adjuvant containing 1% test material. The hair was clipped from the backs of the animals 7 days later. A 10% solution of test material in acetone, dioxane and guinea pig fat (7:2:1) was applied to the clipped area. The animals were depilated and scored for edema and erythema 24 and 48 hours later. In both studies, the reactions were scored as follows for erythema: 0 = none, 1= just discernable or slight, 2 = easily determined or moderate and 3 = dark red or strong. The edema scores were 0 = none, 1 = just discernable to touch or slight, 2 = easily determined or moderate, and 3 = difficult to pick up a fold of skin or strong.
Test substance	:	The purity of the test material was not listed.
Reliability	:	(2) valid with restrictions. Guideline study; however, the purity of the test material was not listed.

15.02.2002 (31)

Type	:	other: foot pad injection
Species	:	guinea pig
Concentration	:	Induction 1 % Challenge 1 %
Number of animals	:	10
Vehicle	:	
Result	:	
Classification	:	
Method	:	other
Year	:	1984
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The test is also described in "Katz GV. 1978. Basic toxicity of 2-propoxyethanol. Eastman Kodak Report HS&HFL No. 78-144, dated 11-30-78."
Result	:	A weak positive response was noted in 1/5 animals treated with test material.

Test condition	:	A group of 5 guinea pigs received a footpad injection (0.05 ml) of Freund's complete adjuvant. After 1 week, 0.3 ml of a 1% solution (acetone-base solvent) of the test material was applied (drop on) to the depilated back of the guinea pigs to assess irritation potential. Subsequently, 2 groups of 5 animals received a footpad injection (0.05 ml) of Freund's complete adjuvant with and without 1% of the test material. A challenge dose of 0.3 ml of test material was dropped on depilated back skin 1 week later. Observations were made 24 and 48 hr later.
Test substance	:	The purity of the test material was analyzed as 99.5%. The main impurities were 2-n-butoxyethanol, triethylene glycol n-butyl ether and isopropoxy ethanol (quantities were not listed).
Reliability	:	(1) valid without restriction. The study was comparable to a guideline study.

15.02.2002 (15)

Type	:	Buehler Test
Species	:	guinea pig
Number of animals	:	20
Vehicle	:	water
Result	:	not sensitizing
Classification	:	
Method	:	OECD Guide-line 406 "Skin Sensitization"
Year	:	1988
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	No signs of irritation were seen in the irritation or challenge tests. No serious lesions were noted. Animals gained weight normally.
Test condition	:	Groups of 3 (HA)BR Hartley guinea pigs (sex and weight not stated) were treated with 2 ml of 12.5, 25.0, 50.0 or 100% test material applied to a fiber pad (4 x 10 mm). Test material was diluted in distilled water (where appropriate). Backs of the animals were clipped before pads were applied. Pads were held in place by wrapping surgical dental dam around the torso and securing it in place. Patches were removed and skin was wiped off 6 hours later. Skin was scored 24 and 48 hours after application. There was no irritation noted at 100%; therefore this dose was used in the challenge test. Male and female guinea pigs approximately 4-6 weeks old (391-512 g) were used in the sensitization studies. They had free access to food and water. Test material (100%) was applied to the backs of 10 guinea pigs (5/sex) on fiber pads as described above. Patches were removed and skin was wiped off 6 hours later. This procedure was repeated weekly for 3 weeks. Another group of 5 animals/sex was not treated (it is not stated whether they were sham controls). Two weeks later, the material (100%) was applied to the backs of all animals (including controls) on the opposite side of the midline from where test material was previously given. Animals were evaluated for skin reactions 24 and 48 hours later. Animals were weighed on the day of first induction and again when challenged.
Reliability	:	(2) valid with restrictions. OECD Guideline study; however, the purity of the test material was not listed.

15.02.2002 (30)

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male/female
Strain	:	other:CRL:CD(SD)BR
Route of admin.	:	inhalation
Exposure period	:	14 weeks

Frequency of treatment	:	6 hr/day, 5 days/week
Post obs. period	:	
Doses	:	100, 200, 400 ppm
Control group	:	yes
NOAEL	:	= 100 ppm
LOAEL	:	= 200 ppm
Method	:	other
Year	:	1987
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The mean (+/ SD) analytical exposure concentrations were 101 +/- 5, 199 +/- 14, and 407 +/- 18 ppm. They were very close to target concentrations (100, 200 and 400 ppm) and will be referred to as 100, 200 and 400 ppm. Nominal concentrations were 122 +/- 3, 233 +/- 11 and 491 +/- 14 ppm. Aerosolization did not occur. Overall mean temperature and relative humidity varied from 21-22 degrees C and 46-57%, respectively. There were no deaths or clinical signs observed during exposure. Following exposure, animals exhibited lacrimation (one control male, 2 males exposed to 100 ppm, 2 females exposed to 200 ppm and one animal per sex exposed to 400 ppm), red or brown discoloration of facial hair (one control male and 9 control females, 5 males per treatment group, 13 females in the 100 ppm group, all females in the 200 ppm group, and 8 females in the 400 ppm group) , and a nasal discharge (one control male, 3 males and 5 females exposed to 100 ppm, 3 males and 6 females exposed to 200 ppm, and 7 males and four females exposed to 400 ppm) . Both treated (N = 3 in 100 ppm group and N=5 in each of the other groups) and control females (N=8) exhibited rales. Red urine was observed in 1-6 males (at various times) and all females exposed to 400 ppm and in one male and 8 females (1-2/day) exposed to 200 ppm. The majority of the observations of red urine were made on the morning following the first exposure after an exposure-free weekend. Urine from 12/12 high dose (400 ppm) females and 6/12 females exposed to 200 ppm was hemolyzed (trace to highly positive). Males and females exposed to 200 or 400 ppm exhibited a decrease in red blood cell count and hemoglobin concentration. Hematocrit also was decreased in high dose males and mid and high dose females. Mean corpuscular volume (MCV) and hemoglobin (MCH) were increased in high dose males and females. Platelet counts were also increased in mid and high dose females. Reticulocyte counts in high dose males and females were 2 and 5 times those of controls, respectively. There was an increase in polychromasia in blood of high dose males and mid and high dose females, and an increased incidence of Howell-Jolly bodies in high dose females. None of the clinical chemistry changes observed was of significant magnitude to reflect organ-specific toxicity. There was a significant decrease in body weight gain in high dose males on Day 7. All eyes were normal. There was a significant increase in kidney weights in males at all concentrations. This was not concentration-dependent and was greatest in the 100 ppm group. Relative kidney weights were increased in males exposed to 200 or 400 ppm, or females exposed to 400 ppm. Absolute and relative spleen weights were increased in males exposed to 400 ppm and females exposed to 200 or 400 ppm. The relative heart weights of males exposed to 400 ppm was increased. All other organ weights were similar to controls. No gross lesions were observed in treated animals. Pigment deposition (morphologically similar to hemosiderin) was found in the spleen of all high

dose males and Kupffer cells of the liver and renal tubules of most high dose male and females. Pigment deposition also was observed in the renal tubules of mid dose males and females, spleen (mid dose males) and liver (mid dose females). Pigment deposition also was seen in livers of control rats.

There were no compound-related changes observed in rats exposed to 100 ppm. There was no statistically significant effect of treatment on histology of reproductive organs.

Test condition : A pretest screen performed on 6 males and 6 females showed that they were virus-free and did not have any abnormalities in hematologies, clinical chemistries and internal organs. An initial opthalmoscopy examination was performed on 63 male and 60 female rats. Three males were excluded from the study following the initial examination. Water was available ad libitum, and food was available during nonexposure periods only.

Exposures were conducted in 4.2 m3 stainless steel and glass inhalation chambers. Chambers were maintained under negative pressure and at 13 air changes per hour. Groups of fifteen male (208 +/- 8.8 g) and fifteen female (186 +/- 9.4 g) weanling rats (approximately 8 weeks old) were exposed to 0 (control), 100, 200 or 400 ppm vapor for 6 hours per day, 5 days per week (including holidays) for a total of 67-69 exposures spanning 14 weeks. Vapor was generated by metering the test material dropwise into a heated glass bead-packed column supplied with metered, dried, oil-free compressed air. Controls received filtered air only. Chamber vapor concentrations, temperature and humidity were measured at least once per hour. Nominal vapor concentrations (volume of test material used/total airflow) were calculated daily. The concentration of background nongaseous material was measured in the high concentration chamber twice daily to insure that aerosolization was not occurring. Animal cage assignments were rotated daily to minimize positional effects.

Each rat was examined before and after each exposure. Rats visible through the chamber windows were observed for toxicity during exposure. Twelve females were randomly chosen from each group on Day 70 (immediately after exposure) and housed overnight in metabolism cages with 30 ml collection bottles. Feed and water were available ad libitum. The presence of blood or hemoglobin in the collected urine was determined. Females were chosen because they appeared more sensitive to test material than males. All animals continued to be exposed for the remainder of the test period. A final ophthalmological examination was performed on 60 male and 60 female rats.

Body weights were determined on Day 0, weekly, and on day of termination. Animals were fasted the night before necropsy. Blood from all rats was collected at the time of necropsy from the posterior vena cava. Clinical chemistries included aspartate aminotransferase (AST), alanine aminotransferase (ALT), sorbitol dehydrogenase (SDH), alkaline phosphatase (AP), urea nitrogen (BUN), glucose, creatinine, gamma glutamyl transpeptidase, triglycerides, cholesterol, total protein, albumin, albumin/globulin (AG) ratio, total bilirubin, calcium, phosphorus, potassium, sodium, and chloride. Hematological tests included hemoglobin, hematocrit, red blood, white blood cell (total and differential) and platelet counts, red blood cell indices, and cellular morphology.

The following organs were weighed at necropsy: liver, spleen, heart, testes, kidneys, thymus, brain, ovaries and adrenal gland. Paired organs were weighed together. These tissues plus nasal passages, trachea, lungs, aorta, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon,

rectum, pancreas, salivary glands, urinary bladder, pituitary, thyroid, parathyroid, mesenteric lymph nodes, bone marrow (femoral), sciatic nerve, epididymes, male accessory sex glands, ovaries, vagina, uterus, fallopian tubes, rib and gross lesions were fixed in 10% buffered formalin. All tissues from control and high dose groups were examined microscopically. Target organs and gross lesions from other dose groups also were examined.

All numerical data were evaluated with a one-way analysis of variance, Bartlett's test, and Duncan's multiple range test (if parametric). If Bartlett's test indicated non-homogeneity of variance, a two-tailed Student's t-test was used to analyze data. A p value of < 0.05 was the critical value for significance.

Test substance : Purity of the test material was > 99%.
Reliability : (1) valid without restriction. The study was comparable to a guideline study.
Flag : Critical study for SIDS endpoint
15.02.2002 (17)

Species : rat
Sex : male/female
Strain : other:CD(SD)BR
Route of admin. : inhalation
Exposure period : 14 weeks
Frequency of treatment : 6 hr/day, 5 days/week
Post obs. period :
Doses : 100, 200, 400 ppm
Control group : yes
NOAEL : = 100 ppm
LOAEL : = 200 ppm
Method : other
Year : 1989
GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Remark : The no observable adverse effect level listed is for systemic toxicity.
Result : The analytical concentrations of test material were 100 +/-7, 203 +/- 7 and 402 +/- 7 ppm for males and 100 +/- 5, 202 +/- 7 and 402 +/- 6 ppm for females, which were very close to the targeted concentrations of 100, 200 and 400 ppm (and therefore will be referred to as such). The nominal concentrations were 111 +/- 4, 195 +/- 10, and 392 +/- 9 ppm for males and 111 +/- 3, 197 +/- 11 and 391 +/- 9 ppm for females. An aerosol was not present in the high concentration chamber.

Clinical signs consisted of red discoloration of facial hair, nasal discharges and tears, and sialorrhea in rats exposed to 200 or 400 ppm and red, discolored facial hair in females exposed to 100 ppm.

As seen in the previous study, males and females treated with 200 or 400 ppm exhibited signs of red blood cell damage including red, discolored urine, pigment deposition in kidney cells and Kupffer cells of the liver and increased amounts of pigment in the spleen. Spleen weights in the high dose groups were greater than control.

No neurologic deficits in motor or sensory function were detected in treated rats. Rats exposed to 400 ppm also did not have any lesions in the peripheral or central nervous systems.

Test condition : Groups of 10 male (236 +/-6 g) and 10 female (177 +/- 8 g) rats were exposed to 0 (control), 100, 200 and 400 ppm test material 6 hours/day, 5 days/week for 14 weeks. Exposure conditions were similar to those described in the previous summary. Parameters measured during the study

included clinical signs and body weight gain. A functional observational battery (FOB) was used to detect functional impairment of the nervous system 4 days prior to exposure and 4, 10, 32, 60 and 95 days after the initial exposure. The FOB was designed to comply with EPA guidelines (40 CFR Part 798.6050, as published on Sept 217, 1985 and amended on May 20, 1987). It consisted of an observational procedure to detect unusual responses in activity, coordination, behavior and changes in sensory function. Forelimb and hindlimb grip strength were also quantitatively evaluated. Historical positive control data were used to demonstrate the sensitivity of the FOB.

At the end of the exposure period, 5 male and 5 female rats from each group were fixed by intravascular perfusion and central nervous system (CNS) and peripheral nervous system (PNS) tissues were examined after staining. The PNS also was examined following plastic embedment and staining of the sciatic and tibial nerves. All animals were necropsied and abdominal and thoracic organs were examined for macroscopic lesions and brain, liver, kidney and spleen weights were measured.

Data for the number of defecations, urinations, and vocalizations were transformed by the addition of 0.5 to each count, and then the square root (to make the variances independent of the means). Where appropriate, data were analyzed with Bartlett's test, one way analysis of variance, and Duncan's multiple range test. The evaluation of the FOB included the relationship between test material concentration and the incidence and severity of any neurotoxic effect. Any sign that appeared to be different from control was statistically analyzed using contingency table methods and Dunnett's test (modified for proportions). Loglinear models were fit to three-way contingency tables and both goodness of fit and level of statistical significance were determined. If significant dose-behavior interactions were detected (or were close to being significant), Dunnett's test (one-tail) was used to compare values from treated animals to controls.

Test substance : Purity of the test material was 99.9 and 99.8% at the beginning and end of the study, respectively.

Conclusion : The no adverse effect level (NOAEL) for neurotoxic effects was greater than 400 ppm (the highest concentration tested). The NOAEL for systemic effects was 100 ppm. Higher concentrations caused red blood cell toxicity.

Reliability : (2) valid with restrictions. Acceptable, well-documented study report which meets basic scientific principles.

15.02.2002 (4)

Species	:	rat
Sex	:	male
Strain	:	other: CR(COBS)CD:BR
Route of admin.	:	gavage
Exposure period	:	6 weeks
Frequency of treatment	:	5 days/week (29-33 doses over 44 days)
Post obs. period	:	
Doses	:	195, 390, 780, 1560 mg/kg
Control group	:	yes
NOAEL	:	< 195
Method	:	other
Year	:	1982
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Hyaline droplet degeneration was observed in the proximal convoluted tubules of all 10 control rats. Therefore, this finding in the high dose animals does not appear to be related to test material administration.
Result	:	All doses: Two high dose animals (1560 mg/kg) and one animal given 780

mg/kg died spontaneously, and two animals in the 780 mg/kg group and 1 in the 390 mg/kg died of intubation error. All others survived to term. The hemoglobin concentration and red cell count were lower than control in all groups of treated animals. There was no effect of treatment on clinical chemistries. There was no effect of treatment on the testes.

1560 mg/kg: There was a reduction in body weight gain at Day 3 and terminal body weight. Feed consumption at Days 3, 6, and 13 was reduced. Mean corpuscular volume (MCV) and hemoglobin (MCH) were increased, and hematocrit was decreased. Absolute and relative spleen weights and relative liver, kidney and heart weights were increased. All animals had bloody urine after the first dose and until termination. Other clinical signs included weakness, labored breathing, prostration and rales in some rats. Enlarged, dark spleens and splenic congestion were evident in 4/10 and 6/10 animals that were necropsied, respectively. Other pathological changes observed included hyperkeratosis of the stomach (9/10), focal hemosiderin in the liver (3/10), and proteinaceous casts (8/10) and hemosiderin (8/10) in the kidney and hyaline droplet degeneration of the proximal convoluted tubules (6/10).

780 mg/kg: MCV and MCH were increased, and mean corpuscular hemoglobin concentration (MCHC) was decreased. Absolute and relative spleen weights and relative liver, heart and kidney weights were increased. All animals had bloody urine after the first dose and until termination. Other clinical signs included weakness, labored breathing, prostration and rales in some rats. Enlarged, dark spleens, and splenic congestion were evident in 5/8 and 5/10 animals that were necropsied, respectively. Other pathological changes observed included hyperkeratosis and acanthosis of the stomach (9/10), extramedullary hematopoesis in the spleen (4/10), and hemosiderin (8/10) in the kidney.

390 mg/kg: Relative spleen, heart, brain and liver weights were increased. All animals had bloody urine after the first dose and until termination. Other clinical signs included weakness, labored breathing, prostration and rales in some rats. An enlarged dark spleen was evident in 1/9 animals that were necropsied. Other pathological changes observed included splenic congestion (10/10), extramedullary hematopoesis in the spleen (3/10), and hemosiderin (2/10) in the kidney.

195 mg/kg: Bloody urine was observed after the first dose and at Days 21 or 28 (2 rats). Relative heart weight was increased. Hemosiderin was evident in the kidneys of 2/10 animals.

Test condition **:** Two hundred and eighty rats (avg. weight 235.7 +/- 15.1 g) were randomly assigned to nine treatment groups of 30 rats each and one control group of 30 rats. Nine different test compounds (including ethylene glycol monopropyl ether) were randomly assigned to the treatment groups. The treatment group for ethylene glycol monopropyl ether (EP) was divided into 3 groups of 10 rats each. Each of these groups received one of 3 doses of EP. Doses equivalent to 1/8, ¼ or 1/2 the acute oral (fasted) LD50 value (3.75, 7.5 and 15 mmoles/kg bw) were administered to each group by gavage (undiluted), 5 days/week for 6 weeks. After one dose, it was noted that EP produced severe hematuria at all doses. Therefore, an additional group of 10 rats was treated with material at 1/16 of the LD50 value (1.88 mmol/kg). The doses given on a mg/kg basis were 195, 390, 780 and 1560 mg/kg, respectively. Control animals received a volume of distilled water equal to the largest volume of test material given. All doses were recalculated weekly to adjust for changes in body weight.

Animals were supplied water and feed ad libitum. Individual body weights and food consumption were recorded on days 0, 3, 6, 13, 20, 27, 34 and 41

of the study. Animals were observed daily (except for weekends) for mortality and clinical signs of toxicity. The appearance of urine and feces on dropping trays also was noted.

Blood was drawn from the inferior vena cava just prior to autopsy for hematologic and serum hematology and clinical chemistry determinations (hemoglobin, hematocrit, red blood cell count, red cell indices (mean corpuscular volume, hemoglobin and hemoglobin concentration), total and relative white cell counts, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase, lactic dehydrogenase, urea nitrogen, creatinine and glucose.

Animals that died spontaneously were autopsied and moribund animals and those that survived to term were euthanized and autopsied. The following tissues were collected, fixed and examined microscopically: lung, heart, thymus, kidneys, liver, spleen, brain, salivary glands, stomach cecum, colon, duodenum, jejunum, ileum, pancreas, esophagus, adrenal glands, pituitary, thyroid, parathyroid, trachea, mesenteric lymph nodes, testes, epididymis, prostate, seminal vesicles, coagulating gland, bone marrow, tongue, eyes and nasal cavities. The liver, kidneys, heart, testes, brain and spleen were trimmed and weighed before fixation.

Reliability : (1) valid without restriction. The study was comparable to a guideline study.
Flag : Critical study for SIDS endpoint
15.02.2002 (15) (24)

Species : rat
Sex : male
Strain : other:CRL:COBS CD(SD)BR
Route of admin. : inhalation
Exposure period : 10 consecutive days
Frequency of treatment : 6 hr/day
Post obs. period :
Doses : 784 ppm
Control group : yes
Method : other
Year : 1983
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : Groups of ten male rats were exposed to 0 or 784 +/- 92 ppm test material, 6 hrs/day for 10 consecutive days. Exposures took place in 4200 liter chambers maintained at 21-23 degrees C and approximately 50% relative humidity. Details describing gas generation were not listed. A battery of pulmonary function tests was performed on all animals after exposures were completed.

No differences in spontaneous mechanics, flow characteristics or nitrogen washout were seen. The only changes in lung volume divisions were a slight decreased in functional residual capacity and marginally lower values for residual volume and total lung capacity. These changes were not significant; however, together they may have indicated the presence of a slight degree of pulmonary edema. There were no changes in compliance although there were slight variations in certain pressure volume relationships. These changes were discounted as not biologically significant since there were no accompanying changes in flow-volume characteristics. In conclusion, there were no significant alterations in pulmonary function of treated animals.

The dose administered caused systemic toxicity, as evidenced by increased weight of and histological alterations in the spleen (congestion in

9/10 animals, extramedullary hematopoiesis in 5/10, and hemosiderosis in the red pulp in 9/10 animals) and spleen. The no observable adverse effect levels for effects on
pulmonary function and systemic toxicity are therefore > 784 and < 784 ppm, respectively.

The study was designed to assess pulmonary function at a systemically toxic dose. It is considered to be of long enough duration to adequately address this endpoint.

Reliability : (2) valid with restrictions. Basic data given. The study was designed to assess pulmonary function at a systemically toxic dose.

15.02.2002 (32)

Species	:	rat
Sex	:	male/female
Strain	:	other:COBS CD(SD)BR
Route of admin.	:	inhalation
Exposure period	:	2 weeks
Frequency of treatment	:	6 hr/day, 5 days/week for 11 exposures
Post obs. period	:	
Doses	:	100, 200, 400, 800 ppm
Control group	:	yes
NOAEL	:	= 200 ppm
LOAEL	:	= 400 ppm
Method	:	other
Year	:	1984
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Duration of test was shorter than 28 days.
Test substance	:	The purity of the test material was analyzed as 99.5%. The main impurities were 2-n-butoxyethanol, triethylene glycol n-butyl ether and isopropoxy ethanol (quantities were not listed).
Reliability	:	(4) not assignable. Not enough details are present to assign a reliability rating.

15.02.2002 (9) (15)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	S. typhimurium strains TA100, TA1535, TA1537, TA97, TA98.
Concentration	:	0, 100, 333, 1000, 3333 or 10000 micrograms/plate
Cytotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 471 "Genetic Toxicology: Salmonella typhimurium Reverse Mutation Assay"
Year	:	1993
GLP	:	yes
Test substance	:	other TS: ethylene glycol monobutyl ether (CAS No. 111-76-2), purity > 99%
Result	:	The number of mutant colonies in controls in the absence of S-9 were 164 +/- 5.5 for TA 100, 30 +/- 4.9 for TA1535, 11 +/- 3.2 for 1537, 180 +/- 15.1 for TA97 and 25 +/- 2.3 for TA98. Addition of S-9 had no significant effect on control mutation indices (with the exception of a decrease from 30 +/- 4.9 to 12-14 in TA1535 with 10-30% rat or hamster S-9 and an increase from 25 +/- 2.3 to 40 +/- 0.6 in TA98 with 30% rat S-9). Treatment with test material had no effect on the number of mutant

colonies in the presence or absence of S-9. The number of mutant colonies ranged from 112-169 for TA 100 with or without S-9, from 22-39 for TA1535 without S-9 and from 7-14 for TA1535 with S-9, from 9-14 for 1537 with or without S-9, from 130-215 for TA97 with or without S-9, and from 11-33 for TA98 with or without hamster S-9 or 10% rat S-9 and from 34-42 for TA98 with 30% rat S-9.

Positive controls induced at least a 2-fold increase in the number of mutant colonies.

Test condition : Test material was incubated with S. typhimurium strains TA97, TA98, TA100, TA1535 and TA1537 either in buffer or S9 mix from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver for 20 minutes at 37 degrees C. Top agar supplemented with L-histidine and d-biotin was added, and the contents were mixed and poured onto the surfaces of minimal glucose agar plated. Histidine-independent mutant colonies were counted following incubation for 2 days at 37 degrees C. Each trial consisted of triplicate plates of concurrent positive and negative (solvent) controls and 5 concentrations (100, 333, 1000, 3333, 10000 micrograms/plate) of test material. The positive controls were sodium azide (for TA100 and TA1535), 9-aminoacridine (for TA97 and TA1537), and 4-nitro-o-phenylenediamine (TA98) in the absence of S9 and 2-aminoanthracene for all strains in the presence of S9. Concentrations of positive controls were not listed.

A positive response was defined as a reproducible, dose-dependent increase in colonies in any one strain. An equivocal response was an increase that was not dose-related, reproducible or was not of sufficient magnitude to support a determination of mutagenicity. There was no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.

Reliability : (2) valid with restrictions. Guideline study with acceptable restrictions.

Flag : Supporting study for mutagenicity endpoint

(28) (29) (34)

Type : Ames test
System of testing : S. typhimurium strains TA98, TA100, TA1535, TA1537, TA1538
Concentration : 0.3 to 15 micrograms/plate
Cytotoxic conc. : 10 mg/plate
Metabolic activation : with and without
Result : negative
Method : other
Year : 1985
GLP : yes
Test substance : other TS: ethylene glycol monohexyl ether (CAS No. 112-25-4)
Result : Test concentrations did not deviate more than 2.5% from stated concentrations. In the tests without metabolic activation, toxicity was observed at 15 and 10 mg/plate in all strains. In the tests without metabolic activation, toxicity was found at 15 mg/plate with all strains, and at 10 mg/plate in strains TA98, TA1537 and TA1538.

The number of mutant colonies in negative controls ranged from an average of 6 (TA1537 without activation) to 140 (TA100 without activation). Tests were valid, as positive controls induced anywhere from 83 (TA1535 with activation) to 1847 colonies (TA1535 without activation). The number of colonies observed in cultures treated with nontoxic concentrations of test material ranged from 4 (in TA1537 without metabolic activation) to 139 (TA100 with activation). No concentration of test material induced a 2-fold increase in the number of mutant colonies (with respect to control) in any system.

Test condition	:	The test substance was dissolved in ethanol to a concentration of 300 mg/ml. All subsequent dilutions were made in ethanol on each day of testing. Dilutions were made so that 50 microliters would deliver the required dose. All dilutions were gravimetrically analyzed. A preliminary toxicity test was performed with strain TA100 to determine concentrations to use in the test. Test chemical was added at five doses chosen to span a range that included nontoxic to moderately toxic concentrations (0.3, 1, 3, 10 and 15 mg/plate). All concentrations were tested in triplicate. Since this test showed that 100 microliters of ethanol vehicle was toxic, test material (and vehicle) was added in 50 microliter aliquots. The following positive controls (0.01 mg) were tested: 4-nitro-o-phenylenediamine (TA98 and TA 1538 without activation), sodium azide (TA100 and TA1535 without activation), 9-aminoacridine (TA1537 without activation), and 2-aminoanthracene (all strains with activation). Sterility checks were run concurrently. S-9 liver homogenate was prepared from Aroclor 1254-induced Sprague-Dawley male rats. For tests with metabolic activation, 0.5 ml of S-9 mix containing 50 microliters of S9 was added per plate. For tests without metabolic activation, 50 microliters of phosphate buffered saline were added. Treated cultures were incubated for 48-72 hours (temperature not stated). Colonies were counted using standard methods. The criterion for a positive result was at least a 2-fold, dose-dependent increase in the number of mutant colonies compared to the control.
Test substance	:	Purity of test substance was 98.4% (by weight).
Reliability	:	(1) valid without restriction. The study is comparable to a guideline study.
Flag	:	Supporting study for mutagenicity endpoint

(26)

Type	:	Cytogenetic assay
System of testing	:	Chinese hamster ovary (CHO) cells
Concentration	:	2513, 3750 and 5000 micrograms/ml
Cytotoxicity conc.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	Other: Galloway, S.M. et al. (1987). Environ. Mol. Mutagen. 10(Suppl10), 1-175
Year	:	1987
GLP	:	yes
Test substance	:	other TS: ethylene glycol monobutyl ether (CAS No. 111-76-2)
Remark	:	Butoxyethanol induced cell cycle delay but not chromosomal aberration.
Result	:	The results of the first experiment (with a 10.5 hour harvest time) were negative. However, since test material caused a significant cell cycle delay, there was not a sufficient number of first-division metaphase cells at harvest. Therefore, the experiment was repeated with an increased incubation time prior to the addition of colcemid. The results of this experiment (20.5 hour harvest time) were positive at 5000 micrograms/ml (7 % of cells with aberrations vs. 0 % in controls) but did not show a dose response relationship. An additional test with a similar harvest time (20.7) as the second test was negative. Mitomycin C caused a dose-dependent increase in the percentage of cells with aberrations all tests without S-9 (with the exception of test 2, which showed an inverse relationship of aberrations with dose). It was thought that the doses of mitomycin C were mislabeled in this experiment. Cyclophosphamide induced a dose-dependent increase cells with

aberrations in the experiment with S-9. Therefore, the test was valid.

The types of aberrations observed were not listed.

Test condition : Testing was performed as reported by Galloway et al. Environ Mol Mutagen 10(Suppl 10):1-175, 1987. Test material was tested in cultured Chinese hamster ovary cells for induction of chromosomal aberrations in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Each test consisted of concurrent solvent and positive controls [mitomycin C without S-9 (0.25 and 0.75 micrograms/ml in trial 1 and 0.05 and 0.08 micrograms/ml in trials 2 and 3) and cyclophosphamide with S-9 (7.5 and 37.5 micrograms/ml)] and three concentrations of test material (2513, 3750 and 5000 micrograms/ml). The highest dose used was one that produced some cytotoxicity (% lethality was not listed). One test per dose was conducted, and tests yielding equivocal or positive results were repeated.

In the tests without S-9, cells were incubated with test material for 8.5 hours. Colcemid was then added and the incubation was continued for 2 hours. For the test with S-9, cells were treated with test material and S9 for 2 hours, after which the medium was removed. Cells were then incubated for 8.5 hours in fresh medium, with colcemid present for the last 2 hours. All cells were harvested by mitotic shake-off, fixed and stained with Giemsa. The incubation period was extended if cell cycle delay was anticipated.

Cells were selected for scoring based on good morphology and completeness of karyotype (21 +/- 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. One or two hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the dose response curve and individual dose points. A linear regression trend test vs. the log of the dose was used. For a single trial, a significant difference for one dose point ($p < 0.05$) and a significant trend ($p < 0.015$) were considered weak evidence for a positive response. Significant differences for 2 or more doses indicated a positive response. A positive trend test in the absence of a significant increase at any one dose was considered equivocal.

Reliability : (2) valid with restrictions. Comparable to guideline study with acceptable restrictions. Purity of the test material was not given.

Flag : Supporting study for chromosomal aberration endpoint

19.02.2002 (28) (29)

Type : Cytogenetic assay
System of testing : Chinese Hamster Ovary Cell
Concentration : 0.1 to 0.4 mg/ml (without activation); 0.08 to 0.4 mg/ml (with activation)
Cytotoxic conc. : 0.8 mg/ml
Metabolic activation : with and without
Result : negative
Method : other
Year : 1985
GLP : yes
Test substance : other TS: ethylene glycol monohexyl ether (CAS No. 112-25-4)
Result : The percentage of aberrant cells in cultures treated with vehicle, 0.1, 0.2 or 0.4 mg/ml test material for 6 hours in the absence of activation was 4 +/- 0, 2 +/- 0, 4 +/- 2.83, and 5 +/- 1.41, respectively (no significant difference). The values obtained after 10 hours of incubation were 1+/- 1.41, 2 +/- 2.83,

4 +/- 0 , and 4 +/- 2.83, respectively (no significant difference). The positive control (TEM) induced 26% of cells to be aberrant after a 6-hour incubation period (tests at 10 hours were not performed).

The percentage of aberrant cells in cultures treated with vehicle, 0.08, 0.1 or 0.2 mg/ml test material for 6 hours in the presence of activation was 5 +/- 1.41, 2 +/- 2.83, 4 +/- 2.83, and 3 +/- 4.24 respectively (no significant difference). The values obtained after 10 hours of incubation with vehicle, S-9 homogenate and 0.2, 0.3 or 0.4 mg/ml test material were 4 +/- 0, 2 +/- 2.83, 3 +/- 4.24, and 3 +/- 1.41, respectively (no significant difference). The positive control (cyclophosphamide) induced 26% of cells to be aberrant after a 6 -hour incubation period (tests at 10 hours were not performed).

There also was no significant difference in the types of aberrations found between treated and negative control cells. Most aberrations were chromatid breaks or gaps.

Test material did not induce an increase in aberrations. The test was valid, as control incidences were within historical limits, and the positive controls induced a significantly greater percentage of aberrants than controls.

Test condition : S-9 liver homogenate was prepared from Aroclor 1254-induced, male Sprague-Dawley rats and was screened for metabolic activity by the supplier. Typically, 1.0 of a complete metabolic activation system (including S-9 and cofactors) was added to each 4.0 ml of culture medium.

CHO-K1-BH4 (subclone D1) cells were passed once after receipt and were frozen in liquid nitrogen. Stock cultures were prepared from cells thawed at approximately 1- to 2-month intervals. Cells used in tests without S-9 were from passage 7 after thawing, and cells used with S-9 were from passage 3.

Dilutions of test chemical were made in ethanol immediately prior to testing and were verified by gravimetric analyses. Cells (5 x 10E5) were exposed to the highest 3 concentrations of test material that were shown in a preliminary experiment not to produce excessive mitotic inhibition (0.1, 0.2 or 0.4 mg/ml without S-9 or 0.08, 0.1 or 0.2 mg/ml with S-9 in 6 hr experiment or 0.2, 0.3, and 0.4 mg/ml with S-9 in 10-hour experiment) or appropriate positive (15 micrograms/ml cyclophosphamide and triethylenemelamine) and negative (0.5% ethanol) controls for 6 or 10 hours, and harvested. For experiments with metabolic activation, cells were preexposed to test chemical and S-9 for two hours, rinsed, and incubated for an additional 4 or 8 hours. Colchicine was added during the last two hours. Tests were duplicated. The incubation temperature was not listed.

Chromosomes were prepared using standard procedures. A total of 50 cells/culture/harvest interval was examined for chromosome damage. The incidence of chromosome damage was determined for the highest 3 doses that did not produce excessive inhibition of cell division. The number of chromatid and chromosome aberrations, and the total number of aberrations per 50 cells examined (with and without including gaps in the total) were determined.

The Fisher's Exact Test (one-tailed) was used to analyze data. A test was considered positive if a value for at least one test concentration was different from control at the $p < 0.05$ level, and there was evidence of a concentration-dependent effect or reproducibility between duplicate cultures.

A positive effect of treatment was one that caused a statistically significant, dose-related increase in the frequency of structural chromosomal aberrations. A statistically significant effect for at least one dose level that is reproduced in both cultures was considered to be equivocal. A single positive effect in 1 of 2 cultures per dose level was evaluated with respect to the historical control data to help determine possible biological significance.

Test substance : Test sample was 98.4% pure (by weight). Impurities were 0.045% water, 0.62% N-hexanol and 0.68% N-octanol.

Reliability : (1) valid without restriction. The study is comparable to a guideline study.

Flag : Supporting study for chromosomal aberration endpoint

(13)

5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay

Species : other: mouse and rat

Sex : male

Strain : other: F344/N (rat) and B6C3F1 (mouse)

Route of admin. : i.p.

Exposure period : 72 hours

Doses : Three doses of 7.03, 14.06, 28.12, 56.25, 112.5, 225, 450 mg/kg (rats) and 17.19, 34.38, 68.78, 137.5, 275, 550 and 1100 mg/kg (mice), separated by 24 hours

Result : negative

Method : other:Shelby et al. 1993. Environ Mol Mutagen 21:160-179.

Year : 2000

GLP : no data

Test substance : other TS: ethylene glycol monobutyl ether (CAS No. 111-76-2)

Result : Two of five rats given 450 mg/kg and all mice given 1,100 mg/kg died. There were no other deaths. No other information about toxicity was given. There was no effect of treatment on the number of micronucleated cells in either rats or mice. The number of micronucleated polychromatic erythrocytes (PCEs)/1000 polychromatic erythrocytes ranged from 1.2-2.2 +/- 0.8 in treated rats (compared to 1.9 +/- 0.2 in controls) and from 2.3-3.8 +/- 0.8 in treated mice (compared to 2.5 +/- 0.2 in controls).

The positive control induced 21.0 +/- 0.4 and 12.9 +/- 1.3 micronucleated PCEs/1000 PCEs in rats and mice, respectively.

Test condition : Published toxicity data were used to select doses. Factors affecting dose selection included solubility, toxicity and the extent of cell cycle delay caused by the material. Male rats and mice (5 animals/group) were injected i.p. 3 times at 24 hours with test material dissolved in phosphate-buffered saline (PBS). Rats were given 7.03, 14.06, 28.12, 56.25, 112.5, 225 or 450 mg/kg and mice were given 17.19, 34.38, 68.78, 137.5, 275, 550 or 1100 mg/kg at each injection). The total dosing volume was 0.4 ml. Negative and positive control animals were injected with the same volume of PBS or cyclophosphamide (7.50 and 10 mg/kg in rats and mice, respectively). The animals were killed 24 hours after the final injection, and blood smears were prepared from bone marrow cells obtained from femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells.

The results were tabulated as the mean of the pooled results from all animals. The frequency of micronucleated cells among PCEs was analyzed by a program that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the solvent control group. In the presence of excess binomial variation (as detected by a binomial

dispersion test), the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation.

An individual trial was considered positive if the trend test P value was less than or equal to 0.025 or if the P value for any single dose group was less than or equal to 0.025 divided by the number of dose groups. The magnitude and reproducibility of the effects was taken into consideration when making conclusions about the results.

Reliability : (2) valid with restrictions. Comparable to guideline study with acceptable restrictions. Purity of the test material was not listed.

Flag : Supporting study for chromosomal aberration endpoint

19.02.2002 (29)

5.7 CARCINOGENICITY

5.8 TOXICITY TO REPRODUCTION

Species	:	rat
Sex	:	male/female
Strain	:	other:CRL:CD(SD)BR
Route of admin.	:	inhalation
Exposure period	:	14 weeks
Frequency of treatment	:	6 hr/day, 5 days/week
Post obs. period	:	
Doses	:	100, 200, 400 ppm
Control group	:	yes
NOAEL	:	= 100 ppm
LOAEL	:	= 200 ppm
Method	:	other
Year	:	1987
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The results of this study are described in detail in Section 5.4. It was given a reliability rating of 1 for the repeated dose toxicity endpoint. The NOAELs and LOAELs listed above are for systemic toxicity. The NOAEL for toxicity to reproductive organs was 400 ppm.
Result	:	The mean (+/ SD) analytical exposure concentrations were 101 +/- 5, 199 +/- 14, and 407 +/- 18 ppm. They were very close to target concentrations (100, 200 and 400 ppm) and will be referred to as 100, 200 and 400 ppm. Nominal concentrations were 122 +/- 3, 233 +/- 11 and 491 +/- 14 ppm. Aerosolization did not occur. Overall mean temperature and relative humidity varied from 21-22 degrees C and 46-57%, respectively. There were no deaths or clinical signs observed during exposure. No lesions were observed in any of the sex organs.
Test condition	:	A pretest screen performed on 6 males and 6 females showed that they were virus-free and did not have any abnormalities in hematologies, clinical chemistries and internal organs. An initial opthalmoscopy examination was performed on 63 male and 60 female rats. Three males were excluded from the study following the initial examination. Water was available ad libitum, and food was available during nonexposure periods only. Exposures were conducted in 4.2 m3 stainless steel and glass inhalation chambers. Chambers were maintained under negative pressure and at 13 air changes per hour. Fifteen male (208 +/- 8.8 g) and fifteen female (186 +/- 9.4 g) weanling rats (approximately 8 weeks old) were randomized into

4 treatment groups and exposed to 0 (control), 100, 200 or 400 ppm vapor for 6 hours per day, 5 days per week (including holidays) for a total of 67-69 exposures spanning 14 weeks. Vapor was generated by metering the test material dropwise into a heated glass bead-packed column supplied with metered, dried, oil-free compressed air. Controls received filtered air only. Chamber vapor concentrations, temperature and humidity were measured at least once per hour. Nominal vapor concentrations (volume of test material used/total airflow) were calculated daily. The concentration of background nongaseous material was measured in the high concentration chamber twice daily to insure that aerosolization was not occurring. Animal cage assignments were rotated daily to minimize positional effects.

Each rat was examined before and after each exposure. Rats visible through the chamber windows were observed for toxicity during exposure. Twelve females were randomly chosen from each group on Day 70 (immediately after exposure) and housed overnight in metabolism cages with 30 ml collection bottles. Feed and water were available ad libitum. The presence of blood or hemoglobin in the collected urine was determined. Females were chosen because they appeared more sensitive to test material than males. All animals continued to be exposed for the remainder of the test period. A final ophthalmological examination was performed on 60 male and 60 female rats.

Body weights were determined on Day 0, weekly, and on day of termination. Animals were fasted the night before necropsy. Blood from all rats was collected at the time of necropsy from the posterior vena cava. Clinical chemistries included aspartate aminotransferase (AST), alanine aminotransferase (ALT), sorbitol dehydrogenase (SDH), alkaline phosphatase (AP), urea nitrogen (BUN), glucose, creatinine, gamma glutamyl transpeptidase, triglycerides, cholesterol, total protein, albumin, albumin/globulin (AG) ratio, total bilirubin, calcium, phosphorus, potassium, sodium, and chloride. Hematological tests included hemoglobin, hematocrit, red blood, white blood cell (total and differential) and platelet counts, red blood cell indices, and cellular morphology.

The following organs were weighed at necropsy: liver, spleen, heart, testes, kidneys, thymus, brain, ovaries and adrenal gland. Paired organs were weighed together. These tissues plus nasal passages, trachea, lungs, aorta, esophagus, stomach, duodenum, jejunum, ileum, cecum, colon, rectum, pancreas, salivary glands, urinary bladder, pituitary, thyroid, parathyroid, mesenteric lymph nodes, bone marrow (femoral), sciatic nerve, epididymis, male accessory sex glands, ovaries, vagina, uterus, fallopian tubes, rib and gross lesions were fixed in 10% buffered formalin. All tissues from control and high dose groups were examined microscopically. Target organs and gross lesions from other dose groups also were examined.

All numerical data were evaluated with a one-way analysis of variance, Bartlett's test, and Duncan's multiple range test (if parametric). If Bartlett's test indicated non-homogeneity of variance, a two-tailed Student's t-test was used to analyze data. A p value of < 0.05 was the critical value for significance.

Test substance : Purity of the test material was > 99%.

Reliability : (1) valid without restriction. The study was comparable to a guideline study.

Flag : Critical study for SIDS endpoint

15.02.2002 (17)

Species	:	rat
Sex	:	male
Strain	:	other: CR(COBS)CD:BR
Route of admin.	:	gavage
Exposure period	:	6 weeks
Frequency of treatment	:	5 days/week (29-33 doses over 44 days)
Post obs. period	:	
Doses	:	195, 390, 780, 1560 mg/kg
Control group	:	yes
NOAEL	:	< 195
Method	:	other
Year	:	1982
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The NOAEL listed above is the NOAEL for systemic toxicity. The NOAEL for toxicity to male reproductive organs was 1560 mg/kg.
Result	:	Red blood cell hemolysis was noted at all doses. Other systemic effects are described in detail in section 5.4. There was no effect of treatment on weights or histology of reproductive organs.
Test condition	:	Two hundred and eighty rats (avg. weight 235.7 +/- 15.1 g) were randomly assigned to nine treatment groups of 30 rats each and one control group of 30 rats. Nine different test compounds (including ethylene glycol monopropyl ether) were randomly assigned to the treatment groups. The treatment group for ethylene glycol monopropyl ether (EP) was divided into 3 groups of 10 rats each. Each of these groups received one of 3 doses of EP. Doses equivalent to 1/8, ¼ or 1/2 the acute oral (fasted) LD50 value (3.75, 7.5 and 15 mmoles/kg bw) were administered to each group by gavage (undiluted), 5 days/week for 6 weeks. After one dose, it was noted that EP produced severe hematuria at all doses. Therefore, an additional group of 10 rats was treated with material at 1/16 of the LD50 value (1.88 mmol/kg). The doses given on a mg/kg basis were 195, 390, 780 and 1560 mg/kg, respectively. Control animals received a volume of distilled water equal to the largest volume of test material given. All doses were recalculated weekly to adjust for changes in body weight. Animals were supplied water and feed ad libitum. Individual body weights and food consumption were recorded on days 0, 3, 6, 13, 20, 27, 34 and 41 of the study. Animals were observed daily (except for weekends) for mortality and clinical signs of toxicity. The appearance of urine and feces on dropping trays also was noted. Blood was drawn from the inferior vena cava just prior to autopsy for hematologic and serum hematology and clinical chemistry determinations (hemoglobin, hematocrit, red blood cell count, red cell indices (mean corpuscular volume, hemoglobin and hemoglobin concentration), total and relative white cell counts, glutamic oxaloacetic transaminase, glutamic pyruvic transaminase, alkaline phosphatase, lactic dehydrogenase, urea nitrogen, creatinine and glucose. Animals that died spontaneously were autopsied and moribund animals and those that survived to term were euthanized and autopsied. The following tissues were collected, fixed and examined microscopically: lung, heart, thymus, kidneys, liver, spleen, brain, salivary glands, stomach cecum, colon, duodenum, jejunum, ileum, pancreas, esophagus, adrenal glands, pituitary, thyroid, parathyroid, trachea, mesenteric lymph nodes, testes, epididymis, prostate, seminal vesicles, coagulating gland, bone marrow, tongue, eyes and nasal cavities. The liver, kidneys, heart, testes, brain and spleen were trimmed and weighed before fixation.

Reliability	:	(1) valid without restriction. The study was comparable to a guideline study.
Flag	:	Critical study for SIDS endpoint

15.02.2002 (15) (24)

Type	:	other: examination of testes
Species	:	mouse
Sex	:	male
Strain	:	other: JCL-ICR
Route of admin.	:	gavage
Exposure period	:	5 weeks
Frequency of treatment	:	5 days per week
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	
Doses	:	500, 1000, 2000 mg/kg/day
Control group	:	yes
Method	:	other
Year	:	1984
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Ethylene glycol monomethyl and ethyl ethers and acetates and ethylene glycol dimethyl ether were tested in this study and were found to produce decreased testicular weights and leukocyte counts and dose-related atrophy of the seminiferous tubule epithelium.
Result	:	There was no effect of treatment on weights of testes or combined weights of the seminal vesicles and coagulating gland. Whether the test material had any effects on the morphology of blood or the testes was not stated.
Test condition	:	Groups of male mice (6 weeks old) were treated with 500, 1000, or 2000 mg/kg test material by gavage, 5 days/week for 5 weeks. Samples were diluted with water or olive oil. A group of 5 control mice was given water. Animals were euthanized and necropsied a day after the last dose was given. The testes, seminal vesicles and coagulating gland were weighed. Tissues were fixed, stained and examined microscopically. Blood was taken from the posterior vena cava for hematological examination
Test substance	:	Purity of the test material was not listed.
Reliability	:	(4) not assignable. There are not enough details to assign a reliability rating.

17.02.2002 (27)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rabbit
Sex	:	female
Strain	:	New Zealand white
Route of admin.	:	inhalation
Exposure period	:	Days 6-18 of gestation
Frequency of treatment	:	6 hr/day
Duration of test	:	to Day 29 of gestation
Doses	:	125, 250, 500 ppm
Control group	:	yes
NOAEL Maternalt.	:	= 250 ppm
NOAEL Teratogen	:	> 500 ppm
Method	:	other
Year	:	1989

GLP : yes
Test substance : as prescribed by 1.1 - 1.4
Remark : The no observable effect level for the fetus was reported as > 500 ppm since 1) the incidences of some skeletal variants at 250 and 500 ppm groups were less than control and 2) increases in the incidences of specific skeletal variants at 250 and 500 ppm were not observed with the litter as the unit of comparison.

Exposure concentrations were selected based on the results of a probe study in which 800 or 1000 ppm produced a high degree of maternal toxicity (and lethality) and 400 ppm produced slight maternal toxicity (Krasavage WJ. 1989. A developmental toxicity probe study of ethylene glycol monopropyl ether in the rabbit. Eastman Kodak Co. HAEL Report No. 88-0017, dated June 22, 1989.) In this study, none of the doses had a significant effect on the embryo or fetus.

Result : Analytical chamber concentrations were 126 +/- 8, 248 +/- 24 and 511 +/- 16 ppm. Mean nominal concentrations were 183 +/- 20, 379 +/- 29 and 503 +/- 25 ppm, respectively. Chamber humidity and temperature were within acceptable limits and an aerosol was not present.

None of the does died or aborted and only one (from the 125 ppm group) delivered early. One doe in the 500 ppm group had dark red colored urine which was noted on gestation days 7 and 8 only. Does exposed to 500 ppm lost an average of 188 g during the exposure period. These does lost an average of 26 g throughout the study (compared to a gain of 79 g in controls). The body weight gain of does in the other treatment groups was similar to or greater than that of controls. Does exposed to 250 or 500 ppm consumed slightly less food than control during the first week of exposure (not stated if statistically significant).

Mean hematologic parameters, organ weights and pathology of does were not affected by treatment (with the exception of increased absolute and relative spleen weights in the 125 ppm group). The test material had no effect on the pregnancy rate, number of corpora lutea, implantation sites, viable fetuses, or early and late resorptions, pre- and post-implantation losses, mean gravid uterine or fetal weights, or the sex ratio.

Two malformations were observed in offspring from 2 different does treated with 500 ppm. One fetus had a small eye and another had abnormal flexure of one wrist. Neither of these malformations were considered to be related to test material as they were unilateral and occurred spontaneously in rabbits. The total number of external anomalies noted was comparable between controls and those treated with 125, 250 or 500 ppm (N = 2(2 litters), 1 (1 litter), 3 (2 litters) and 3 (2 litters), respectively.

There was no significant difference in the incidence or types of internal soft tissue malformations/variations between groups (N = 80 (15 litters), 61 (13 litters), 60 (12 litters) and 70 (14 litters) in the control and 135, 250 and 500 ppm groups, respectively. The total incidence of fetuses and litters with skeletal anomalies also was similar between groups. Decreased incidences of reduced ossification of cervical centra (No 1.) and Sternebra 6 were seen in most groups of treated animals (compared to controls). There was an increased number of fetuses (but not litters) with an extra (13th) rib in high dose animals. Although the incidence of fetuses with a nonossified 6th sternebra was greater than control in the 250 and 500 ppm groups, the number of litters with an affected fetus was comparable between groups and the incidence of fetuses and litters with a nonossified 5th sternebra was significantly less for the high dose group than the control group. There was a significant increase in reduced ossification of metacarpal 1 in forepaws of animals in the 250 and 500 ppm

groups.

Test condition : Nulliparous female rabbits (5-6 months old) were acclimated for 5 weeks before the start of the study. Body weights were recorded at least once weekly and animals were observed for clinical signs at least once daily during the acclimation period. Six to seven month old male rabbits from the same supplier were used as breeders. The day of successful mating was designated Day 0 of gestation. Ten females per day were mated on each of 6 days to obtain the required number of females. Mated females were randomly assigned to 4 groups of 15 animals according to body weight.

Food and water were available ad libitum (except during exposures).

Groups were exposed to vapor concentrations of 0, 125, 250, 500 ppm test material in stainless steel and glass inhalation chambers (4.2 m3) for 6 hours/day on Days 6-18 of gestation. The control group was exposed to filtered air. Vapor was generated by passing metered air into a glass bead packed column and into inhalation chambers. Chamber concentrations were monitored at least 6 times during exposure. Temperature, relative humidity and airflow rate were monitored every half hour. Nominal concentrations were calculated daily based on the ratio of test material used to the total volume of air. The concentration of background nongaseous material in the chamber with the highest concentration was measured daily to confirm that the material did not aerosolize. The airflow rate was calibrated weekly.

Maternal body weights were recorded on Days 0, 6, 9, 12, 15, 19, 22, 28 and 29 of gestation. Food consumption was recorded on the same days (with the exception of Days 0 and 29). All dams were observed for mortality and signs of toxicity prior to and after each exposure. Animals visible through the chamber windows were observed during exposure for signs of toxicity. All animals were observed twice daily on nonexposure days (except weekends). A detailed examination including examination of the hair, skin, eyes, general activity, feces and urine was conducted on the days body weights were recorded.

Rabbits were killed on Day 29 of gestation. Blood was collected from the inferior vena cava for analysis of total red blood cell counts, hematocrit, and hemoglobin concentration. The thoracic and abdominal viscera of the dams were examined in situ for gross abnormalities. The liver, kidneys, spleen and thymus were weighed and samples were preserved. Gravid uteri (with ovaries attached) were removed and weighed. The ovaries were dissected free and trimmed, and corpora lutea were counted. The uteri of apparently nonpregnant animals were stained and examined for microimplantation sites. Implantation sites in the uteri were counted and categorized as viable or dead fetuses, or early (no placenta or conceptus) or late resorptions. Late resorptions with abnormalities were preserved. Fetuses were removed and examined for external abnormalities. Viable fetuses were weighed, anesthetized and examined for internal soft tissue and skeletal abnormalities. Development of the brain also was evaluated. Prematurely delivered pups and fetuses were examined externally, euthanized (if alive) and preserved if abnormal.

Continuous data were analyzed using a one-way analysis of variance and a Duncan's Multiple Range test (where appropriate). Homogeneity of variances was tested by Bartlett's test. Freeman-Tukey transformations were performed to normalize the distribution (if necessary).
Incidence data were compared using chi-square contingency tables. When the chi-square was significant, each test group was compared to the control group using Fisher's exact test. All analyses were two-tailed. The

criterion for significance was p < 0.05.

Test substance : The purity of the test material was 99.9 and 99.8% before and after test exposures, respectively.

Reliability : (1) valid without restriction. Comparable to guideline study.

Flag : Critical study for SIDS endpoint

15.02.2002 (18) (23)

Species	:	rat
Sex	:	female
Strain	:	other:COBS CD(SD)BR
Route of admin.	:	inhalation
Exposure period	:	days 6-15 of gestation
Frequency of treatment	:	6 hrs/day
Duration of test	:	to Day 20 of gestation
Doses	:	100, 200, 300, 400 ppm
Control group	:	yes
NOAEL Maternalt.	:	< 100 ppm
NOAEL Teratogen	:	= 100 ppm
Method	:	other
Year	:	1984
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4

Remark : The authors stated that the no observable effect for teratogenicity and significant embryo/fetal toxicity was 400 ppm. However, since the incidence of skeletal variants was increased at 200 ppm, the no observable effect level for fetal toxicity (of any kind) is 100 ppm

The skeletal variations observed at 200, 300 and 400 ppm test material are commonly seen in control animals that have been subjected to a mild stress.

The study was audited for quality assurance. The exposure concentrations were selected based on data generated in a probe study (Krasavage WJ and Katz GV. 1983. Inhalation teratology probe in rats. Eastman Kodak Company, Health and Environmental Laboratories Report 152987R).

Result : The overall mean (+/- SD) analytical concentrations of test material were 101 +/- 3, 203 +/- 5, 305 +/- 7 and 405 +/- 12 ppm. Mean nominal concentrations were slightly higher (8-16%), indicating possible loss of some material in the generating system. The mean temperature and humidity were 22-23 degrees C and 47-62%, respectively. Particle count data indicated that an aerosol was not present.

Maternal: One dam exposed to 100 ppm died during the seventh exposure. Clinical signs up to this time were normal. An autopsy revealed that the spleen, liver and renal lymph nodes of this animal were enlarged and petechial hemorrhage was seen in the lungs. Histological examination revealed that the animal died form malignant lymphoma, which was not considered to be related to test material administration. The uterus of the dam contained 11 implantations, and 10 normal and 1 dead embryo. A dam in the 300 ppm group was moribund after the 9th exposure. The animal had an unkempt hair coat, was lethargic and had red urine. The dam was euthanized and autopsied. The adrenals were enlarged, the kidneys were congested and the urinary bladder was inflamed and dilated. Histologic examination revealed acute supprative nephritis, cystitis and tracheitis accompanied by adrenal cortical hemorrhage. These lesions were not considered to be related to treatment. The uterus contained 14 implantations (12 normal, live embryos and 2 resorbed). Data from both of these animals were not included in the results.

Test material exposure had no effect on body weight. Feed consumption in all treated groups (except 100 ppm) was reduced during the first 3 days of exposure. Red urine was found on the dropping trays of 16/30, 30/30 and 28/30 animals after the first exposure to 200, 300 or 400 ppm, respectively. Red urine also was seen in 2 females (1 each from the 300 and 400 ppm groups) after the second exposure.

After the second exposure, red urine was not observed in any of the animals exposed to 200, 300 or 400 ppm. One female exposed to 100 ppm had red urine after the 6th and 7th exposures only. Dams exposed to 200, 300 or 400 ppm had a significant reduction in red blood cell counts and increased mean corpuscular volume (MCV) and hemoglobin (MCH). Reticulocytes and minimal polychromasia of red blood cells were increased at all exposure levels. Ansiosytosis was increased at 300 and 400 ppm, and macrocytosis was increased at 200, 300 and 400 ppm. White blood cell counts were normal (with the exception of increased lymphocytes and decreased polymorphonuclear leukocytes at 300 ppm). Absolute and relative spleen weights were increased in the 200, 300 and 400 ppm groups. Splenic congestion and deposition of hemosiderin and extramedullary hematopoeisis were increased in animals treated with 300 or 400 ppm. Necrosis in the medulla of the thymus and eosinophilic cytoplasmic changes in the liver were also increased in these groups.

Reproductive/fetal data: Pregnancy rate, and the number of corpora lutea, implantation sites, viable fetuses per dam, and resorptions per litter, fetal body weight and fetal sex ratio were not affected by treatment. The total number of external defects in the control, 100, 200, 300 and 400 ppm groups was 1, 3 (3 litters), 1, 5 (five litters) and 2 (2 litters, respectively (no significant difference). Major external effects were observed in two fetuses from treated dams. One fetus from the 300 ppm group had a hypoplastic tail and one from the 400 ppm group had thoracogastroschisis. These were considered to be spontaneous. The incidences of internal soft tissues defects and major skeletal malformations were not altered by treatment. The total number of skeletal variations was significantly greater than control in fetuses from rats treated with 200, 300 or 400 ppm. Increases in the total number of vertebral alterations, and incidences of partial ossification of sternebrae and rudimentary 14th thoracolumbar ribs (1/2 the length of the 13th rib) were observed in these groups.

Test condition : Sexually mature male and female rats were acclimated to the laboratory 3 weeks prior to mating. Males and females were housed 1:2 over a 4-day period to obtain 150 inseminated females. Insemination was verified by daily vaginal smears. The day sperm was found in the vagina was designated Day 0 of gestation. Inseminated females were randomly assigned to 5 groups of 30 animals according to body weight. Food and water were available ad libitum (except during exposures).

Groups were exposed to vapor concentrations of 0, 100, 200, 300 or 400 ppm test material in stainless steel and glass inhalation chambers for 6 hours/day on Days 6-15 of gestation. The control group was exposed to filtered air. Vapor was generated by passing metered air over the surface of the liquid in a three-neck round-bottom flask (36 degrees C). Chamber atmospheres were sampled at least once per hour for concentration, temperature and relative humidity. Nominal concentrations were calculated daily based on the ratio of test material used to the total volume of air. Airborne particle counts were measured twice daily. The animals were rotated daily within the chambers to minimize potential positional effects.

Maternal body weights were recorded on Days 0, 6, 9, 12, 16, 19 and 20 of gestation. Food consumption was recorded on the same days (with the exception of Days 0 and 20). All dams were observed for mortality and

signs of toxicity prior to and after each exposure. Animals visible through the chamber windows were observed during exposure for signs of toxicity. All animals were observed twice daily on nonexposure days.

Rats were killed on Day 20 of gestation. Blood was collected from the inferior vena cava for analysis of total red blood cell, total and differential white blood cell, reticulocyte, nucleated red cell, platelet and Heinz body counts, hemoglobin, hematocrit, and red blood cell indices and morphology. All animals were fasted 10-12 hours before bleeding. Implantation sites in the uteri were counted and categorized as viable or dead fetuses, or early (no placenta or conceptus) or late resorptions. Viable fetuses were removed, sexed, weighed and examined for gross external abnormalities. The ovaries were removed, identified as left or right, and the number of corpora lutea were counted. Approximately one-half of the fetuses from each litter were fixed in Bouin's solution and examined for internal soft tissue abnormalities. The other half were fixed in 95% ethanol, macerated, stained and examined for skeletal defects. The thoracic and abdominal viscera of the dams were examined in situ for gross abnormalities. The liver, kidneys, spleen and thymus were weighed. Portions of these organs plus femur and mesenteric lymph nodes were examined histologically.

Continuous data were analyzed using a one-way analysis of variance and a Duncan's Multiple Range test (where appropriate). Homogeneity of variances was tested by Bartlett's test. Incidence data were compared using chi-square contingency tables (2 x 5). When the chi-square was significant, each test group was compared to the control group using Fisher's exact test (two-tailed). Both the proportion of fetuses affected and the number of litters involved were analyzed. The criterion for significance was $p < 0.05$.

Test substance : Purity of the test material was 99.5%. Impurities were ethylene glycol monobutyl ether (0.13%), triethylene glycol monobutyl ether (0.04%) and ethylene glycol isopropyl ether (0.02%).

Reliability : (1) valid without restriction. The study was comparable to a guideline study.

Flag : Critical study for SIDS endpoint

15.02.2002 (19) (20)

Species : mouse
Sex : female
Strain : CD-1
Route of admin. :
Exposure period : days 6-13 of gestation
Frequency of treatment : daily
Duration of test : to gestation day 22
Doses : 2000 mg/kg/day
Control group : yes
NOAEL Maternalt. : > 2000 mg/kg bw
NOAEL Teratogen : > 2000 mg/kg bw
Method : other
Year : 1987
GLP : no data
Test substance : as prescribed by 1.1 – 1.4
Result : The mortality rate in treated dams was 1/49, versus 0/50 controls. There was a slight decrease in body weight in treated animals compared to controls, but it was not significant (5.7 +/- 2.5 vs. 7.5 +/- 3.2 g). Twenty eight out of 31 litters from treated animals were viable (90%), versus 100% of controls (no significant difference). Treatment did not have any significant effect on the number of live (8.5 +/- 2.9 in treated vs. 9.5 +/- 2.0 in control) pups/litter at birth, pup postnatal survival (83.9 +/- 28.0 in

treated vs. 99.4 +/- 2.5 in control), pup weight gain (0.5 +/- 0.1 g vs. 0.5 +/- 0.1 g in control), or pup birth weight (1.5 +/- 0.1 g vs. 1.7 +/- 0.1 g in control).

Test condition : A preliminary range-finding study was conducted to find the dose to use in the developmental study (the LD10 if achieved at an attainable dose). Based on the findings in this study, time-mated CD-1 female mice (6-8 weeks of age, 50/group) were dosed orally with 2000 mg/kg test material or water on days 6-13 of gestation (at 10 ml/kg). Maternal body weights were taken on Days 6 and 17 of gestation and on postnatal day 3. Mice were observed twice daily during treatment and once daily on gestation days 14-17. Signs of toxicity were recorded and dead mice were necropsied to determine if they died from dosing error. The number of live and stillborn pups was recorded as soon as possible after delivery (within 12 hr). Weights of dams and pups (as a litter) were taken at this time. The number of live pups, their total weight and maternal body weight were also measured 48 hours after the initial weighing. Females that failed to deliver a litter by presumed gestation day 22 were killed and uteri were examined.

Mortality data were analyzed by the 2-tail Fisher's exact test. The proportion of surviving pregnant mice that gave birth to viable litters (one or more live-born pups) was compared to the control by a 1-tail Fisher-Irwin exact test. For mice that delivered a viable litter, maternal body weight change from gestation day 6 to postnatal day 3 (pd3), the number of liveborn pups per litter, percent neonatal survival to pd3, average pup weight at birth, and average pup weight gain by pd3 were analyzed by pairwise multiple comparisons of control and treated groups, using a 2-tail Mann-Whitney U-test.

Reliability : (2) valid with restrictions. Acceptable, well-documented publication which meets basic scientific principles. Purity was not stated. The fetuses were not examined for defects.

(14)

5.10 OTHER RELEVANT INFORMATION

Type : Biochemical or cellular interactions

Result : The effects of the various alkoxyacetic acids on rat erythrocytes were qualitatively similar and consisted of early swelling followed by hemolysis. These effects were associated with a parallel decrease in blood ATP levels. The order of toxicity was as follows: butoxyacetic acid > propoxyacetic acid ≈ pentoxyacetic acid > ethoxyacetic acid > methoxyacetic acid. At equimolar concentrations, neither heptanoic, butoxypropionic nor propoxypropionic acids caused any significant effect on rat erythrocytes. Studies with butoxyacetic acid (BAA) showed that while the concentration of BAA in plasma remained relatively constant, the concentration of BAA in erythrocytes increased with time. Incubation of BAA with rat blood for 30 minutes followed by washing reduced (but did no eliminate) the ability of BAA to cause swelling. BAA in saline was more effective than BAA in Emulphor/saline in causing hemolysis.

Test condition : After at least a 1-week acclimation period, blood was collected from male Fisher 344 rats (9-13 weeks old) by cardiac puncture using EDTA as anticoagulant. Blood from individual rats was pooled. Alkoxyacetic acids were dissolved in Emulphor/saline (1:0) such that 10 microliters/ml of blood gave the desired final concentration of acid (1-4 mM). In one experiment, butoxyacetic acid (BAA) was dissolved in saline without Emulphor to determine the effect of the solubilizer. Blood chemical mixtures were incubated in a 37 degree shaking water bath. After 0.5 – 4.0 hours, aliquots were removed from each test tube and the hematocrit was determined. The

remaining blood was spun in a centrifuge and plasma was aspirated. Free plasma hemoglobin was quantified colorimetrically using Drabkin's Reagent Kit. Each concentration of test material was tested in triplicate and was accompanied by a matching control at each time point. Each study was repeated 2-3 times on different dates with freshly collected blood. The data from all experiments were pooled and analyzed.

To determine the effect of the materials on blood ATP, blood was collected from 9-13 week old rats (as described above) using acetate-citrate-dextrose as the anticoagulant. After incubation with the test materials, the hematocrit was determined and 1 ml of the remaining treated blood was immediately mixed with 1 ml of 12% tricholoroacetic acid. The tubes were placed on ice for 5 min and then spun in a centrifuge at 3000 x g for 10 min. The clear supernatant was tested for ATP using Sigma assay kit No 366A.

To assess the effect of BAA preincubation on erythrocyte swelling, BAA (1.0 or 2.0 mM) was dissolved in physiological saline and incubated with rat blood. A matching control was incubated with saline and similarly processed. Each concentration and control was tested in sextuplet. After a 30-min incubation period, the hematocrit was determined and all samples were spun in a centrifuge at low speed. Plasma in 3 samples from each test condition was aspirated, discarded and replaced with the same volume of fresh plasma. Plasma from the other 3 samples was not removed. Erythrocytes were then resuspended, spun in a centrifuge again, and resuspended in either new or the original plasma. All samples were then incubated for up to 4 hours. Samples were taken for analysis of hematocrit at 1,2 and 4 hours.

To determine the distribution of BAA between erythrocytes and plasma, rat blood was incubated at 37 degrees C with [14C]BAA at 2.0 mM. Aliquots ().5 ml each) of the blood plus BAA mixtures were removed at 0, 1, 2, and 4 hours after incubation. Hematocrit was determined and the rest of the blood was spun in a centrifuge. Erythrocytes were oxidized in triplicate using a Packard tissue oxidizer. The plasma was aspirated and the amount of radioactivity in both plasma and erythrocytes was determined by liquid scintillation counting (in triplicate). The concentration of radioactivity was calculated per ml of erythrocytes or plasma. The total amount of radioactivity was determined using the hematocrit value in the calculation of the volume of erythrocytes and plasma. The remaining plasma was filtered and analyzed by HPLC.

Test substance : propoxyacetic acid, butoxyacetic acid, pentoxyacetic acid, ethoxyacetic acid methoxyacetic acid, 14C labeled butoxyethanol, heptanoic, butoxypropionic and propoxypropionic acid. Purity of all materials was at least 95%.

Reliability : (1) valid without restriction. Acceptable, well documented study.
11.02.2002 (11)

Type : absorption

Result : The absorption rates (mean +/- SD) were 0.58 +/- 0.39 (human) and 2.30 +/- 0.79 (rat) milligrams/cm2/hr. The corresponding permeability constants were 6.43 +/- 4.34 x 10E4 and 2.52 +/- 0.86 x 10E-3 cm/hr, respectively. This indicates that the rate of absorption of the test material is about 4 times faster in full thickness rat skin than human stratum corneum.

For human skin, contact with undiluted test material for 8 hours produced a mean damage ratio of 2.38 (mean of 4 cells) versus 1.10 in the control (mean of 3 cells). For rat skin, contact with undiluted test material for 8 hours produced a mean damage ratio of 10.18 versus 1.81 in the control. These damage ratios indicate that undiluted test material caused a greater degree of damage to rat skin than human stratum corneum.

Test condition : The percutaneous absorption rates of 2-propoxyethanol (EP) through human stratum corneum and full thickness skin from Sprague-Dawley rats

were measured in vitro using Franz-type diffusion cells. The test was conducted according to GLP regulations. The integrity of each skin sample was determined by measuring its permeability to tritiated water (approximately 1 microcurie per skin sample) before and after (on Days 1 and 3) the permeability to 14C-EP was determined (on Day 2). The donor solution (tritiated water or 14C-EP) was added in excess to the donor cell to ensure steady -state absorption kinetics. A control cell contained saline (rather than 14C-EP) on Day 2. Duplicate samples (50 microliters) were taken from the receptor chambers hourly for 8 hours in all tests and assayed for radioactivity by liquid scintillation counting. Donor and receptor chambers were washed three times with saline, refilled with saline containing antibiotics and an antimycotic and were allowed to stir overnight between exposures. Nine cells were used in each experiment: one control cell and two test cells from each of three human or rat skin donors.

The permeability constant and absorption rate were calculated for each cell by dividing the slope of the linear portion of the concentration of radioactivity versus time curve by the donor count (DPM/ml) times the skin area (in cm2). The absorption rate was calculated by dividing the permeability constant (cm/hr) by the concentration of material in the donor solution. The ratio of tritiated water permeation after exposure to [14C-EP]/ tritiated water permeation before exposure to [14C-EP] was used to derive a damage ratio.

Test substance : The purity of the unlabeled 2-propoxyethanol was 98.94 +/- 0.94 % and the purity of [1,2-ethanol 14C]-labeled 2-propoxyethanol [14C-EP] was > 99%.

Reliability : (1) valid without restriction. Acceptable, well documented study
11.02.2002 (2)

Type : Biochemical or cellular interactions

Remark : Absolute values of bound radioactivity in plasma, protein or lipid were too small (low pmole/mg range) for the data to be interpreted. Butoxyacetic acid (the major metabolite of ethylene glycol monobutyl ether) also was tested and was found to be approximately twice as potent in causing hemolysis of rat red blood cells as propoxyacetic acid. This material also had no significant effect on human red blood cells at 5.0 mM.

Result : Rat blood: Propoxyacetic acid (a major metabolite of ethylene glycol propyl ether) caused nearly complete hemolysis of washed red blood cells within 3 hr at a concentration of 5 mM. Whole rat blood incubated with 2.0 or 5.0 mM propoxyacetic acid (PAA) had an increased hematocrit and mean corpuscular volume (MCV) and decreased mean corpuscular hemoglobin concentration (MCHC). The changes in MCV and MCHC mirrored changes in hematocrit. The plasma level of the radiolabeled test material exceeded that of the red blood cells. No components other than the radiolabeled test materials were detected by HPLC analysis of red blood cells or plasma.

Human blood: Human washed red blood cells were not hemolyzed by a concentration of 5 mM. The plasma level of the radiolabeled test material exceeded that of the red blood cells. The ratio of test material in plasma/red blood cell was greater in human blood than rat blood (2.42 vs. 1.53 microcuries/g), indicating less accumulation of test material in human than rat red blood cells. No components other than the radiolabeled test materials were detected by HPLC analysis of red blood cells or plasma.

Test condition : The effect of test material on blood cell integrity was determined by incubating washed red blood cells from male, Sprague Dawley rats and humans (in triplicate) with 0, 0.5, 1.0, 2.0 and 5.0 mM test material in phosphate buffered saline. Samples were incubated at 37 degrees C and assayed at 30 min, 1, 2, 3, and 4 hr. The absorbance (540 nm) of the supernatants was determined. Red blood cell suspensions added to

distilled water served as controls (for 100% hemolysis).

The effect of test material on whole blood indices was determined by incubating samples of whole blood from male, Sprague Dawley rats and humans with test material at 1, 2, and 5 mM. Samples were removed immediately (t=0) and at 0.5, 1, 2, 3, and 4 hr. Aliquots were analyzed for white blood cell and red blood cell counts, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin and mean corpuscular hemoglobin concentration.

To determine the effect of test material on permeability and if the material could bind to red blood cells, rat and human blood were spiked with radiolabeled test material (2 microcuries/g). An aliquot was removed after mixing (t=0) and at 2 and 4 hrs. Samples of plasma and packed red blood cells were analyzed by liquid scintillation spectrometry (LSS). Concentrations of 14C-labeled propoxyacetic acid in samples of filtered plasma and supernatant from lysed red blood cells were determined by reversed-phase HPLC. Red blood cells were also extracted with chloroform to obtain lipid. Radioactivity in the final extract was analyzed using LSS. Plasma and red blood cell proteins were precipitated and washed with methanol:water until washes contained only background levels of radioactivity. The final washed proteins were dissolved in tissue solubilizing agent and aliquots were assayed for radioactivity (LSS) and protein.

Test substance : The test material for the hemolysis experiments was n-propoxyacetic acid (purity > 98 %). The test material for the permeability and binding experiment was [1.2-14C]-n-propoxyacetic acid. The chemical and radiochemical purities of this material were > 98.6% and >99 %, respectively.

Reliability : (1) valid without restriction. Acceptable, well documented study
11.02.2002 (6)

Type : Biochemical or cellular interactions

Remark : Ethylene glycol, ethylene glycol monomethyl ether, ethylene glycol monoethyl ether and ethylene glycol monobutyl ether were also tested. Ethylene glycol and ethylene glycol monomethyl ether behaved differently than the other materials in that they effectively blocked intercellular communication over a much broader concentration range than the other materials (10-60 mg/ml and 5-30 mg/l, respectively).

Result : Test material caused an increase in recovery of colonies over the narrow concentration range of 2-5 mg/ml. Cytotoxicity was observed at 8 mg/ml.

Test condition : Ethylene glycol monopropyl ether (0.5, 1, 2, 3, 5 and 8 mg/ml) was incubated with a mixture of 4 x 10E5 Wild-type Chinese hamster V9 cells and 100 mutant V79 cells that lacked HGPRT for 30 minutes, followed by 50 microliters of 6-thioguanine. There were 10 plates per dose. Negative and positive controls consisted of plates incubated without any test material and with TPA (1 ng/ml). Cytotoxicity was monitored by plating 100 mutant V79 cells that lacked HGPRT in separate dishes. Fresh medium containing 10 g/ml was added to the plates every three days. Plates were incubated for a total of 8 days, stained and scored for the number of colonies per plate. An increased number of recovered colonies over background reflected blockage of junction- mediated intercellular communication.

Reliability : (1) valid without restrictions. Acceptable, well documented study
17.02.2002 (25)

Type : other: pharmacokinetics

Result : Regardless of the route of administration, absorbed radioactivity was eliminated rapidly with the majority eliminated by 12 hours. Following oral administration of either 15 or 150 mg/kg [14C]-ethylene glycol monopropyl ether (EGPE), 97% and 96%, of the administered doses were recovered by 72 hours, respectively. Urinary elimination accounted for 75-81% of the activity recovered after oral administration. A similar pattern was observed after inhalation of either 25 or 175 ppm. Less than 27% of dermally administered radioactivity was absorbed during a 6-hr exposure period. The majority (74%) of the radioactivity was recovered either as unabsorbed liquid or in washings of application sites. Propoxyacetic acid (PAA) and its glycine conjugate N-(2-propoxyacetyl)glycine were the principal urinary metabolites identified regardless of the route of administration. PAA and the glycine conjugate accounted for 42-61% and 24-38% of the total urinary radioactivity after administration by any route, respectively. Ethylene glycol accounted for up to 14% of the radioactivity in urine (regardless of route of administration). Glucuronidase treatment of urine revealed the presence of 2-6% EGPE glucuronide.

The half-lives for the first order elimination of EGPE and PAA from rat blood were 0.12 and 0.77 hr, respectively (iv administration). The apparent volume of distribution and clearance rate for EGPE following iv administration were 98.7% and 1.3 kg/hr. A similar pharmacokinetic profile was observed following oral administration of 15 mg/kg EGPE. At an oral dose of 150 mg/kg, EGPE had an elimination half-life of 0.20 hr, suggesting saturation of metabolism or excretion. Elimination of PAA also appeared to be saturated at this dose.

Test condition : Male Sprague-Dawley rats (193-255 g, 6-7 weeks of age) were used in all studies. Test animals were selected from a population of healthy rats and were randomly assigned to a treatment group. Five animals were administered the test material by each route (iv, oral, dermal and nose-only inhalation) and were immediately housed individually in all glass-metabolism chambers. Indwelling jugular cannulae were inserted under anesthesia to animals used in pharmacokinetic studies. These animals were allowed to recover for 3 days before being used.

The dorsal region of rats designated for dermal exposure was shaved approximately 24 hours prior to dermal application. The following day, a custom-made glass containment cell was attached to the dorsal midline of each rat. A polyethylene disc with a central needle hole (for test material application) was adhered to the upper surface of the cells.

Dose formulations were prepared one day prior to treatment. The specific radioactivity of [14C]EGPE in each dose formulation was calculated based on the amount of radioactivity in the dose formulation (by scintillation spectrometry) and the mass of EGPE (labeled and unlabeled) added to the solution. Dosing solutions were also analyzed for chemical purity and concentration by capillary- or packed-column GC and for radiochemical purity by packed-column GC or reversed-phase HPLC with radiochemical flow detection on or prior to the day of treatment.

For intravenous dosing, formulations were prepared by dissolving known weights of unlabeled and radiolabeled test material in sterile physiological saline so that 15 mg/kg ethylene glycol monopropyl ether (EGPE) and 50 microcuries/kg were delivered in a volume of 1.0 ml/kg. Material was given as a bolus injection into the lateral tail vein. Oral doses were formulated with distilled water such that doses of 15 mg/kg and 150 mg/kg EGPE and 100 microcuries/kg were delivered by intragastric intubation in a volume of 5 ml/kg. For the dermal studies, known weights of unlabeled and radiolabeled EGPE were combined such that 50 mg/cm2 (approximately 450 mg/kg) and 350 microcuries/kg of undiluted [14C]-EGPE were applied

to the test animals through the hole in the cover of the glass containment cell. A small drop of adhesive, a polyethylene patch and a piece of heavy tape were placed over the hole. Test material was allowed to remain on the skin for 6 hours, at which time the patches were removed and excess test material was recovered. The skin and interior of the cells were washed and dried with swabs. Swabs and washes were kept for analysis.

Inhalation exposures were conducted using a 24-port anodized nose-only chamber. The entire apparatus was housed within a fume hood. Conditioned room air was provided to the vapor generator and then to the individual nose ports using vacuum pumps to maintain a constant negative pressure. During exposure of a group of ten animals, the total inlet flow rate was approximately 5 l/min. EGPE was metered by a syringe pump at a constant rate into the top of the heated glass column. The delivery rate of EGPE and air flow were balanced to assure complete vaporization and no accumulation of test material in the column. Rats were housed during exposure in adjustable plastic restraints and were exposed to 25 or 175 ppm test material for 6 hr through stainless steel nose ports. All animals were acclimated to the chamber restraints (2-6 hr/day) for a minimum of 6 days before treatment. Five rats were exposed for metabolism and disposition data and 5 were exposed for pharmacokinetic data. Vapor concentrations were monitored continuously.

Radiolabelled compounds exhaled in breath were collected from animals in the oral, dermal and inhalation studies by passing air maintained at 500 ml/min from the metabolism chambers through 2 parallel series of traps. Volatile components were recovered with 2 traps containing activated charcoal and 14CO2 was collected with 2 traps containing potassium hydroxide. Traps were changed at 12, 24, 48 and 72 hr after oral dosing and the start of inhalation and dermal exposures. The respired air trap contents were weighed at the time of collection.

Venous blood samples (100-200 microliters) were obtained from the jugular vein cannulae in inhalation-exposed animals or from the retro-orbital sinus in animals exposed by other routes at intervals of from 5 min up to 24 hours after the start of exposure. Urine samples were collected 12, 24, 48 and 72 hours after oral dosing and the start of inhalation and dermal exposures. Feces were collected 24, 48 and 72 hours after the start of exposures. The weight of urine or feces was determined at the time of collection. Urine and fecal samples were stored frozen and in the dark until analyzed.

Rats were killed at the end of exposures and blood samples (approximately 3 ml) were collected from the abdominal aorta. The samples were analyzed for complete blood counts and blood smears were prepared and examined. The spleen, liver and kidneys were removed, weighed and stored frozen for later analysis. The carcasses were weighed and placed into a container for immediate solubilization prior to liquid scintillation analysis. Skin from the exposure site of dermally exposed rats was excised and stored frozen for later analysis.

All biological samples collected were analyzed for total 14C by liquid scintillation spectrometry (LSS). Specimens of tissues were assayed in duplicate (except the spleen, which was assayed in duplicate or triplicate). Small aliquots of blood and urine were analyzed for radioactivity and the remainder was analyzed by GC/MS. Blood and fecal samples and internal tissues were combusted prior to analysis. Liver, kidneys and feces were homogenized prior to combustion. The activated charcoal used to trap expired volatile organics was extracted with methanol and 1 ml aliquots were analyzed by LSS. The radioactivity in the potassium hydroxide traps

was assayed directly. Washes from cages and restraints (inhalation exposure) and the containment cell cap, swabs used for washing and drying the skin, and cell and skin rinsings (dermal exposure) also were analyzed for radioactivity.

Urine was filtered and analyzed by HPLC with radioisotope detection. Blood was extracted with toluene and the extracts were assayed for concentrations of EGPE and propoxyacetic acid (PAA) by GC/MS. Derivatized samples of plasma also were analyzed for EGPE and PAA by GC/MS.

All compartmental pharmacokinetic parameters were determined using SAS NLIN (Version 6). Concentrations of EGPE and PAA in blood were analyzed for individual rats at each collection time. Model parameters for individual animals were averaged within studies. Estimates for the area under the blood concentration-time curve, blood half-life, rate of clearance, and rate constants for absorption and elimination were determined following the selection and optimization of an appropriate model. All calculated half-lives were based on simple first-order elimination. The concentrations of EGPE and PAA in blood after administration by the various routes were fit to exponential equations. The area under the concentration vs. time curve, clearance and apparent volume of distribution were calculated from the fitted parameters. The dermal absorption rate was based on total recovered activity from urine, cage washes, feces, expired air, tissues, and carcasses. The amount recovered as volatile organics was assumed to arise from unabsorbed EGPE and was not included in the total. All data were summarized using descriptive statistics including calculations of means and standard deviations. None of the protocol deviations had a significant bearing on the outcome.

Test substance : The purity of unlabeled test material was 99.9%. The radiochemical purity of 14C labeled ethylene glycol propyl ether was 97.9%. Specific activities of two samples that were used were 8.7 and 15.3 millicuries/mmole. [1-14C]propoxyacetic acid that had a specific activity of 8.9 microcuries/g also was used.

Reliability : (1) valid without restriction. Acceptable, well documented study
15.02.2002 (7)

Type : other: testicular toxicity
Test substance : n-propoxyacetic acid.
Result : Test material was toxic to cultured cells at a concentration of 20 mM and was slightly toxic at 10 mM. Changes observed at 10 mM included a slightly higher incidence of degenerate pachytene spermatocytes than normal and a decrease in the carnitine acetyltransferase activity of the attached germ cell fraction. At 20 mM, PAA produced changes qualitatively similar to, but less severe than 5 mM MAA.

There was no effect of test material on testicular weights or morphology in rats treated with 776 mg/kg/day for 4 days.

Remark : The toxicity of ethylene glycol monomethyl and monoethyl ethers, and methoxy-, ethoxy- and butoxy- acetic acids also was tested in this study. Addition of ethylene glycol monomethyl or monoethyl ether at up to 50 mM had no effect on the cultured cells. Metabolism studies showed no metabolism of these glycol ethers in the cultured cells. Butoxyacetic acid had no effect on cultured cells at 20 mM and did not produce toxicity in vivo at 868 mg/kg/day. In contrast, 5 mM methoxyacetic acid (MAA) produced toxicity to pachytene spermatocytes (reduced numbers and degeneration) and reductions in carnitine acetyltransferase and lactate dehydrogenase activity in attached germ cells. Treatment with 592 mg/kg/day MAA for 4 days produced testicular toxicity (mainly localized to the pachytene spermatocytes) in rats. Similar toxicity (although less severe) was noted in

cells treated with 5 mM ethoxyacetic acid and rats treated with 684 mg/kg/day ethoxyacetic acid for 4 days.

These results suggest that alkoxyacetic acid metabolites are responsible for testicular toxicity of the ethylene glycol ethers and that the ability of the glycol ethers to cause testicular toxicity decreases with increasing chain length.

Test condition : Mixed cultures of Sertoli and germ cells were prepared from testes of 28-day old male Sprague Dawley rats. After 24 hr in medium containing 10% fetal calf serum, treatment was started by replacing the medium with serum-free medium containing 10 or 20 mM test material. Medium changes were made every 24 hours. pH was adjusted to 7.2 before test material was added. Osmolality was measured. The test was terminated at 72 hours. Some cultures were fixed, stained and examined microscopically. Activities of carnitine acetyltransferase and lactate dehydrogenase in Sertoli and germ cells were determined.

Male Sprague-Dawley rats (31 days old) were treated by gastric intubation with 776 mg/kg/day test material for 4 days. Test material was dissolved in water and adjusted to ph 6. Control rats received an equal amount of water (5 ml/kg). The rats were killed 24 hours after the last dose and the testes were removed, fixed, stained and examined by light microscopy.

All data were evaluated by Dunnett's test for multiple comparisons.

Reliability : (2) valid with restrictions. Acceptable, well documented study, with the exception that the purity was not listed.

15.02.2002 (12)

Type : Metabolism
Remark : EGBE and EGHE also were tested in this study.
Result : A single isozyme of rat liver alcohol dehydrogenase (ADH-3) was responsible for oxidizing the test material and other glycol ethers. A Vmax of 3.04 nmol NADH/min/mg protein and a Km value of 0.23 mM were reported for the test material. These values were lower than those of EGBE and higher than those for EGHE, suggesting that at equivalent concentrations, metabolism of ethylene glycol propyl ether will be less rapid than EGBE and more rapid than EGHE.

Test condition : Livers from male (247-317 g) Wistar rats were homogenized. The 1000,000 g supernatant was used for the assay after dialysis overnight. The activity of alcohol dehydrogenase following incubation with 0.05 - 10 mM test material was determined. Two isozymes were isolated using gel electrophoresis.

Reliability : (2) valid with restrictions. Basic data given.

(1)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

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SIDS Dossier

and

Robust Study Summaries

for CAS No. 112-07-2

Existing Chemical	:	ID: 112-07-2
CAS No.	:	112-07-2
EINECS Name	:	2-butoxyethyl acetate
EINECS No.	:	203-933-3
TSCA Name	:	Ethanol, 2-butoxy-, acetate
Molecular Formula	:	C8H16O3
Structural Formula	:	O=C(OCCOCCCC)C

Producer Related Part

Company	:	PCA Services, Inc.
Creation date	:	04.03.2002

Substance Related Part

Company	:	PCA Services, Inc.
Creation date	:	04.03.2002
Memo	:	
Printing date	:	10.05.2004
Revision date	:	06.06.2005
Date of last Update	:	06.06.2005
Number of Pages	:	107
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Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD AND COMPANY INFORMATION

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Country	:	Netherlands
Phone	:	31-172-431601
Telefax	:	31-172-432494
Telex	:	
Cedex	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

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

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

Substance type	:	organic
Physical status	:	liquid
Purity	:	$\geq$ 99%
Source	:	Eastman Chemical Company

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

2-Butoxy-ethylacetaat
Source : VOS B.V. Alphen aan den Rijn
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

2-Butoxyethyl acetate

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

BUTHYLGLYCOL ACETATE
Source : CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA"
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Butoxyethyl acetate
Source : Eastman Chemical B.V. The Hague
BASF AG Ludwigshafen
Huels AG Marl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

BUTYL CELLOSOLVEACETATE
Source : BP Chemicals Ltd. London
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Butyl cellosolve acetate
Source : Eastman Chemical B.V. The Hague
BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Butyl Cellusolve Acetate (UNION CARBIDE Trade Name)
Source : Courtaulds Chemicals(L) Leek,Staffs.
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

BUTYL ETHOXOL ACETATE
Source : BP Chemicals Ltd. London
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Butyl Ethoxyl Acetate (ICI Trade Name)
Source : Courtaulds Chemicals(L) Leek,Staffs.
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Butyl glycol acetate
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Butyl Glycol Acetate(or BGA)
Source : Courtaulds Chemicals(L) Leek,Staffs.
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Butyl Oxitol Acetate (SHELL Trade Name)
Source : Courtaulds Chemicals(L) Leek,Staffs.
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

BUTYLGLYCOL ACETATE
Source : BP Chemicals Ltd. London
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Butylglycol acetate
Source : Huels AG Marl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Butylglykolacetat
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Butylglykolaectat
Source : BRENNTAG Chemiepartner GmbH Mülheim

EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

EGBEA
Source : BP Chemicals Ltd. London
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Ethanol, 2-butoxy, acetate
Source : Eastman Chemical B.V. The Hague
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Ethanol, 2-butoxy-, acetate
Source : Huels AG Marl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Ethanol, 2-butoxy-, acetate (6CI, 7CI, 8CI, 9CI)
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

ETHANOL, 2-BUTOXYACETATE
Source : BP Chemicals Ltd. London
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

ethyleenglycolmonobutyletheracetaat
Source : VOS B.V. Alphen aan den Rijn
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Ethylene glycol butyl ether acetate
Source : Eastman Chemical B.V. The Hague
BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

ETHYLENE GLYCOL BUTYL ETHER ACETATE
Source : BP Chemicals Ltd. London
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

ETHYLENE GLYCOL MONOBUTHYL ETHER ACETATE
Source : CHEMIAL DIVISIONE DI SISAS SPA CAVAGLIA"
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Ethylene glycol monobutyl ether acetate
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Ethyleneglycolbutylether acetate
Source : Huels AG Marl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Glycol monobutyl ether acetate
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Glycolmonobutylether acetate
Source : Huels AG Marl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Eastman® EB Acetate
Source : Eastman Chemical Company

1.3 IMPURITIES

CAS-No : 111-55-7
EINECS-Name : Ethylene glycol diacetate
Molecular formula : C6H10O4
Value : Maximum 0.25%
Source : Eastman Chemical Company

CAS-No : 111-76-2
EINECS-Name : Ethylene glycol monobutyl ether
Molecular formula : C6H14O2
Value : Maximum 0.25%
Source : Eastman Chemical Company

CAS-No :
EINECS-Name : Water
Value : 0.05% maximum
Source : Eastman Chemical Company

1.4 ADDITIVES

Remark : No additives typically

1.5 QUANTITY

Quantity : 4,540 – 22,700 metric tons in the U.S.
Source : 2002 US TSCA Inventory Update Report
Reliability : (1) valid without restriction. Up to date reference.

:
Quantity : 10 000 - 50 000 tonnes in
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.

1.6.1 LABELLING

Labelling : as in Directive 67/548/EEC
Symbols : Xn
Nota : D
Specific limits : yes
R-Phrases : (20/21) Harmful by inhalation and in contact with skin
S-Phrases : (2) Keep out of reach of children
(24) Avoid contact with skin
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.

1.6.2 CLASSIFICATION

Classification	:	as in Directive 67/548/EEC
Class of danger	:	corrosive
R-Phrases	:	(20/21) Harmful by inhalation and in contact with skin
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark	:	(4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.

1.7 USE PATTERN

Type	:	Type
Category	:	Wide Dispersive Use
Source	:	Chinn H, Anderson E and Yoneyama M, Glycol Ethers, CEH Marketing Research Report,SRI International. 2000.
Reliability	:	(1) valid without restriction. Up to date reference.
Type	:	Use
Category	:	Solvent in surface coatings and plasticizer in latex adhesive formulations.
Source	:	Chinn H, Anderson E and Yoneyama M, Glycol Ethers, CEH Marketing Research Report, SRI International. 2000.
Reliability	:	(1) valid without restriction. Up to date reference.
Type	:	type
Category	:	Non dispersive use
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark	:	(4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.
Type	:	type
Category	:	Wide dispersive use
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark	:	(4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.
Type	:	industrial
Category	:	Basic industry: basic chemicals
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark	:	(4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Type	:	industrial
Category	:	Paints, lacquers and varnishes industry
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark	:	(4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.
Type	:	use
Category	:	Solvents
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark	:	(4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.

Type : use
Category : Surface-active agents
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit : MAK (DE)
Limit value : 20 ml/m3
Short term exposure
Limit value : 40 ml/m3
Schedule : 30 minute(s)
Frequency : 4 times
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. The study was not available for review. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. (73)

Type of limit : MAK (DE)
Limit value : 135 mg/m3
Remark : hautresorptiv
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. The study was not available for review. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. (73)

Type of limit : MAK (DE)
Limit value : 20 ml/m3
Short term exposure
Limit value : 80 ml/m3
Schedule : 15 minute(s)
Frequency : 4 times
Country : Germany
Remark : labelled with H (skin resorption)
Source : Huels AG Marl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.

Type of limit : MAK (DE)
Limit value : 135 mg/m3
Short term exposure
Limit value : 540 mg/m3
Schedule : 15 minute(s)
Frequency : 4 times
Country : Germany

Source : Huels AG Marl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.

Type of limit : MEL (UK)
Limit value : 54 mg/m3
Remark : Skin notation.
Source : BP Chemicals Ltd. London
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.

Type of limit : other
Limit value :
Remark : Eastman Chemical Company occupational exposure limit:
25 ppm TWA
Source : Eastman Chemical B.V. The Hague
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.

Type of limit : other: Company Exposure Standard (CES)
Limit value : 140 mg/m3
Short term exposure
Limit value : 140 mg/m3
Schedule : 10 minute(s)
Frequency : times
Remark : No recent data.
Product not made for 3 Years approx.
Normal exposure on an 8hr. basis
Short term exposure on a 10min. basis.
Source : Courtaulds Chemicals(L) Leek,Staffs.
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.

1.9 SOURCE OF EXPOSURE

Memo : Emissionserklaerung [Emissions report] Huels 1992
Remark : Release into the atmosphere on production site in 1992: less than 25 kg/a
Source : Huels AG Marl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. The study was not available for review. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

(47)

Remark : Thought to be used as a solvent mainly in emulsion paints.
Source : Courtaulds Chemicals(L) Leek,Staffs.
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European

Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.

Remark : Release into the atmosphere on production site in 1992: less than 25 kg/a
Source : Huels AG Marl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. The study was not available for review. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

(47)

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 : KBwS (DE)
Labelled by : KBwS (DE)
Class of danger : 1 (weakly water polluting)
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.

Classified by : other: Huels AG
Labelled by : other: Huels AG
Class of danger : 1 (weakly water polluting)
Country : Germany
Source : Huels AG Marl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. The study was not available for review. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

(48)

Classified by :
Labelled by :
Class of danger : 1 (weakly water polluting)
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. All data (except the reliability rating) came from an

IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. A reference was not listed.

Country : Germany
Source : Huels AG Marl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. The study was not available for review. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

(48)

1.14.2 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung [Accident regulation] (DE)
Substance listed : No
No. in directive :
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. The study was not available for review. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

(70)

1.14.3 AIR POLLUTION

Classified by : other: VCI (Butylglykolacetat)
Labelled by : other: VCI (Butylglykolacetat)
Number : 3.1.7 (organic substances)
Class of danger : II
Country : Germany
Source : Huels AG Marl
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : (4) not assignable. The study was not available for review. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

(48)

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	-64 ° C
Decomposition	:	
Sublimation	:	
Method	:	other: unknown
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Reliability	:	(2) valid with restrictions. Published in a peer-reviewed reference book.
Flag	:	Critical study for SIDS endpoint.

(82)

Value	:	= -64.6 ° C
Decomposition	:	no at ° C
Sublimation	:	no
Method	:	other
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 – 1.4
Reliability	:	(2) valid with restrictions. Data came from a MSDS

(28)

Value	:	= -64 ° C
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	The study was not available for review (4) not assignable. The study was not available for review. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

(15)

2.2 BOILING POINT

Value	:	= 184 - 195 ° C at 1013 hPa
Decomposition	:	
Method	:	other: DIN 53 171
Year	:	
GLP	:	
Test substance	:	as prescribed by 1.1 -1.4
Reliability	:	(2) valid with restrictions. Published in a peer-reviewed reference book.

(15) (82)

2.3 DENSITY

Type	:	density
Value	:	0.94 at 20° C
Test substance	:	as prescribed by 1.1 -1.4
Reliability	:	(2) valid with restrictions. Published in a peer-reviewed reference book.

(82)

Type	:	density
Value	:	= .935 - .942 g/cm3 at 20° C
Remark	:	Data came from an IUCLID document for CAS No. 112-07-2 published by

the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review. The study was given a reliability rating of 2 (valid with restrictions) in the original IUCLID document.

(15)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value : 0.4 hPa at 20° C
Decomposition : no data
Method : other: unknown
Year :
GLP : no data
Test substance : as prescribed by 1.1 -1.4
Reliability : (2) valid with restrictions. Published in a peer-reviewed reference book.
Flag : Critical study for SIDS endpoint

(82)

Value : = .38 hPa at 20° C
Decomposition : no
Method other (measured)
Year :
GLP : no
Test substance : as prescribed by 1.1 – 1.4
Reliability : (2) valid with restrictions. Data came from a MSDS
Flag : Critical study for SIDS endpoint

(28)

Value : = .31 hPa at 20° C
Remark : Data came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review. The study was given a reliability rating of 2 (valid with restrictions) in the original IUCLID document.

(15)

Value : = .39 hPa at 20° C
Remark : Data came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review. The study was given a reliability rating of 2 (valid with restrictions) in the original IUCLID document.

(15)

Value : = 1.4 hPa at 40° C
Remark : Data came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen

EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review. The study was given a reliability rating of 2 (valid with restrictions) in the original IUCLID document.

(16)

2.5 PARTITION COEFFICIENT

Log pow : = 1.51 at ° C
Method : OECD Guide-line 107 "Partition Coefficient (n-octanol/water), Flask-shaking Method"
Year :
GLP : no data
Test substance : as prescribed by 1.1 -1.4
Remark : Method came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Reliability : (2) valid with restrictions. Published in a peer-reviewed reference book.
Flag : Critical value for SIDS endpoint.

(11) (82)

Log pow : = 1.57 at 20° C
Method : other: calculated using the EPIWIN KOWWIN (v1.66) program
Year : 2001
GLP : no
Test substance : as prescribed by 1.1 –1.4
Remark : The input for this model run was CAS No. 112-07-2.
Reliability : (2) valid with restrictions. Data were obtained by modeling.

2.6.1 WATER SOLUBILITY

Value : = 15 g/l at 20 ° C
Qualitative :
Method : other: unknown
Year :
GLP : no data
Test substance : as prescribed by 1.1 –1.4
Reliability : (2) valid with restrictions. Published in a peer-reviewed reference book.
Flag : Critical value for SIDS endpoin

(82)

Value : = 1.1 g/l at 20 ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Method : other
Year :
GLP : no
Test substance : as prescribed by 1.1 –1.4
Reliability : (2) valid with restrictions. Data came from a MSDS.

(28)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	= 71 ° C
Type	:	
Method	:	other
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 –1.4
Remark	:	Tag Closed Cup method
Source	:	Eastman Chemical Company unpublished data
Reliability	:	(2) valid with restrictions. Methodological information was not available.
Value	:	= 78 ° C
Type	:	closed cup
Method	:	other: DIN 51 758
Year	:	
GLP	:	
Test substance	:	
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(15)

2.8 AUTO FLAMMABILITY

Value	:	= 280 ° C at
Method	:	other: DIN 51 794
Year	:	
GLP	:	
Test substance	:	
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(15)

2.9 FLAMMABILITY

2.10 EXPLOSIVE PROPERTIES

Remark	:	Explosionsgrenzen in Luft [Explosive limits in air]: 1,7-8,4 Vol.% All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(16)

2.11 OXIDIZING PROPERTIES

2.12 ADDITIONAL REMARKS

Remark	:	Gefaehrliche Reaktionen: Zutritt von Luft/Sauerstoff verhindern (Peroxidbildung) [Hazardous reactions: avoid contact with air/oxygen (forms peroxides)] All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(15)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	Sun light
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Direct photolysis		
Halflife t1/2	:	= 6 hour(s) (12-hour day)
Degradation	:	% after
Quantum yield	:	
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	1.5E6 OH/cm3
Rate constant	:	= .0000000000212328 cm3/(molecule*sec)
Degradation	:	50 % after 6.045 hours
Deg. Product	:	
Method	:	other: calculated using the EPIWIN AOP (v1.90) program
Year	:	2003
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The input to the EPIWIN Aop program was the SMILES code provided by CAS No. 112-07-2. No other variables influence this calculation.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint

09.03.2002

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	
Rate constant	:	cm3/(molecule*sec)
Degradation	:	% after
Deg. Product	:	
Method	:	other (calculated)
Year	:	
GLP	:	
Test substance	:	
Remark	:	Rate Constant: 1.8*10^-11 cm^3/molecule*sec Data came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review. The study was given a reliability rating of 2 (valid with restrictions) in the original IUCLID document.

(2)

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	500000 molecule/cm3

Rate constant	:	cm3/(molecule*sec)
Degradation	:	= 50 % after 18.4 hour(s)
Remark	:	Rate Constant: 20.9*10^-12 cm^3/molecule*sec Data came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review. The study was given a reliability rating of 2 (valid with restrictions) in the original IUCLID document.

(3)

3.1.2 STABILITY IN WATER

Type	:	abiotic
t1/2 pH4	:	at degree C
t1/2 pH7	:	305 days at room temperature
t1/2 pH8	:	30.5 days at room temperature
Deg. Product	:	
Method	:	other: calculated using EPIWIN Hydrowin (v1.67) program with CAS No. 112-07-2 as the input. No other variables influence this calculation.
Year	:	2001
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	A reliability rating of 2 is assigned. EPIWIN HYDROWIN provided half lives for hydrolysis for the ester bond, using methoxyethyl acetate as the model compound. The EPIWIN program does not estimate a contribution for hydrolysis for ether linkages. It is general knowledge that ether bonds do not hydrolyze readily under neutral ambient conditions.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint

09.03.2002

3.1.3 STABILITY IN SOIL

Type	:	other
Radiolabel	:	
Concentration	:	
Soil temp.	:	degree C
Soil humidity	:	
Soil classif.	:	
Year	:	
Remark	:	Based upon an estimated Koc of 26, ethylene glycol monobutyl ether acetate is expected to leach readily in soil. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(55)

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	fugacity model level III
Media	:	water - air
Air (level III)	:	11.1
Water (level III)	:	87.4
Soil (level III)	:	1.37
Biota (level II / III)	:	0.162
Method	:	other: EPIWIN
Year	:	2003
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Measured inputs to the EPIWIN program were melting point (-64 degrees C), boiling point (190 degrees C), vapor pressure (0.3 mm Hg), Log Pow (1.51) and water solubility (15 g/l). Emission rates of 1000 kg/hr to air, 500 kg/hr to water, and 0 kg/hr to soil, and sediment were used, based on the production and use patterns that would predict that emissions are primarily to air and water. The EPIWIN HENRY (v3.10) program estimates a Henry's Law Constant of 6.38 E-6 atm-m3/mole at 25 degrees C (Bond Estimate). The EPIWIN PCKOC (v1.66) program estimates a Koc (soil-sediment partition coefficient) of 10. EPIWIN Fugacity Level III estimated half-lives are: air = 12.1 hours, water = 208 hours, soil = 208 hours, and sediment = 832.3 hours.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint.

09.03.2002

Type	:	volatility
Media	:	water - air
Air (level I)	:	
Water (level I)	:	
Soil (level I)	:	
Biota (level II / III)	:	
Soil (level II / III)	:	
Method	:	
Year	:	
Remark	:	The volatilization half-lives from a model environmental river (1 meter deep) and model pond have been estimated to be 6.6 and 74 days, respectively. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(55) (81)

3.3.2 DISTRIBUTION

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type	:	aerobic
Inoculum	:	other:non-acclimated sewage organisms
Contact time	:	
Degradation	:	= 72 % after 20 day
Result	:	
Kinetic of test substance	:	5 day = 53 **%** 10 day = 69 **%** 20 day = 72 **%** **%** **%**
Deg. Product	:	not measured
Method	:	other: as described in "Standard Methods for the Examination of Water and Wastewater", 16th ed., USPHA, Washington, D.C., 1985
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The calculated theoretical oxygen demand was 2.10 mg/mg. After 5, 10 and 20 days of incubation, the percent biooxidation was 53, 69 and 72% (respectively).
Test condition	:	A modified version of the biochemical oxygen demand (BOD) method published in "Standard Methods for the Examination of Water and Wastewater", 16th edition, Am. Public Health Association, 1985 was used. A discussion of these modifications appears in Price et al., "Brine shrimp bioassay and seawater BOD of petrochemicals", J. Water Poll. Control Fed., Jan. 1974. Nonacclimated domestic sewage organisms were used as seed in the test. Domestic wastewater was filtered through glass wool and added (3 ml/bottle) as seed material to clean BOD bottles. A buffered, aerated solution containing minerals was then added. Small amounts of test material were added from a 0.1 % stock solution to yield concentrations of 3, 7 and 10 mg/l. A control with no test material also was run. At least two of the concentrations were tested in duplicate. Dissolved oxygen (DO) was monitored five times during the course of the 20-day test. The solution was reaerated when the DO dropped below 4.0 mg/l. Reaeration (if needed) was accomplished by dividing the BOD bottle contents between 2 BOD bottles, sealing, shaking them twenty times, returning contents to the original BOD bottle, recording the oxygen level, resealing, and returning the BOD bottle to the incubator. Samples were analyzed routinely for nitrites and nitrates. Results of the tests were expressed in terms of % biooxidation calculated as the cumulative oxygen uptake for the test material minus a control x 100 / initial concentration of test material x theoretical oxygen demand.
Test substance	:	Test material was butyl CELLOSOLVE® acetate.
Reliability	:	(2) valid with restrictions. Comparable to guideline study with acceptable restrictions. Purity was not stated.
Flag	:	Critical study for SIDS endpoint

(84)

Type	:	aerobic
Inoculum	:	activated sludge, non-adapted
Concentration	:	1000mg/l related to COD (Chemical Oxygen Demand) related to
Contact time	:	
Degradation	:	> 90 % after 6.5 day
Result	:	

Deg. Product	:	
Method	:	OECD Guide-line 302 B "Inherent biodegradability: Modified Zahn-Wellens Test"
Year	:	
GLP	:	
Test substance	:	
Remark	:	Lag-Phase = 0 Tage[days] All data (except where noted) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. Additional data obtained from a IUCLID document published by INERIS (dated 22-MAY-2003) is as follows: Concentration related to DOC is 400 mg/l, concentration of inoculum was 1 g/l, origin of inoculum was industrial STP, and measured biodegradation rate was 12% / day. It also was stated that preadaptation was possible due to the origin of inoculum. The reliability rating listed in the INERIS document was (2) valid with restrictions.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(2) valid with restrictions. Guideline study that was not available for review. Enough information from the INERIS document was obtained to support this assignment. Purity was not stated. (85)
Type	:	aerobic
Inoculum	:	activated sludge, domestic, non-adapted
Concentration	:	5mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	
Degradation	:	= 96.7 % after 3 hour(s)
Result	:	
Deg. Product	:	
Method	:	OECD Guide-line 303 A "Simulation Test - Aerobic Sewage Treatment: Coupled Unit Test"
Year	:	1981
GLP	:	no
Test substance	:	other TS: Huels AG
Remark	:	Mean retention time: 3 hours All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review. (46)
Type	:	aerobic
Inoculum	:	
Contact time	:	
Degradation	:	= 51 % after 5 day
Result	:	
Deg. Product	:	
Method	:	other: BSB-Test
Year	:	

GLP	:	
Test substance	:	
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review. (12)
Type	:	aerobic
Inoculum	:	other bacteria: Klaeranlagenablauf (KA Edenkoben)
Concentration	:	20mg/l related to DOC (Dissolved Organic Carbon) related to
Contact time	:	
Degradation	:	= 96 % after 14 day
Result	:	
Deg. Product	:	
Method	:	other: ISO-Test 7827
Year	:	
GLP	:	
Test substance	:	
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review. (17)
	:	
Type	:	aerobic
Inoculum	:	domestic sewage
Concentration	:	20 mg/l related to DOC (Dissolved Organic Carbon)
Degradation	:	= 96 % after 14 day(s)
Kinetic	:	1 day(s) 0 % 3 day(s) 26 % 7 day(s) 97 % 14 day(s) 96 %
Method	:	ISO 7827 "Evaluation in an aqueous medium of the 'ultimate' aerobic biodegradability of organic compounds - method by analysis of dissolved organic carbon (DOC)"
Year	:	1989
Remark	:	Concentration of inoculum = 0.5 ml/l; Inoculum comes from the Edenkolben STP (activated sludge) All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by INERIS, dated 22-MAY-2003. The reliability rating listed on that document was (2) valid with restrictions. This appears to describe the same study as summarized in the previous record, but is in more detail.
Reliability:	:	(2) valid with restrictions. Basic data given. (5)
Type	:	aerobic
Inoculum	:	other bacteria: Belebtschlamm, communal [Community activated sludge treatment plant]
Contact time	:	
Degradation	:	= 88 % after 28 day
Result	:	

Kinetic of test substance	:	1 day = 3 **%** 5 day = 31 **%** 10 day = 58 **%** 15 day = 73 **%** 20 day = 82 **%**
Deg. Product	:	
Method	:	other: Respirometrischer [Respirometer] Test (OECD 301 C)
Year	:	
GLP	:	
Test substance	:	
Remark	:	BSB des THSB Gut biologisch abbaubar [Readily biodegradable] All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated. This same study was described similarly in a IUCLID document published by INERIS, dated 22-MAY-2003. The reliability rating listed in that document was (2) valid with restrictions.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The information obtained from the INERIS document is not detailed enough to support an assignment of (2) valid with restrictions.

(14)

3.6 BOD5, COD OR BOD5/COD RATIO

BOD5		
Method	:	other: BSB-Test
Year	:	
GLP	:	
Concentration	:	related to
BOD5	:	mgO2/l
COD		
Method	:	other: CSB-Test
Year	:	
GLP	:	
COD	:	= 2071 mg/g substance
RATIO BOD5 / COD		
BOD5/COD	:	= .51
Remark	:	BSB5 =1065 mg/g All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(12)

3.7 BIOACCUMULATION

BCF	:	2.902
Elimination	:	
Method	:	BCFwin v2.15
Year	:	2004
GLP	:	
Test substance	:	as prescribed by 1.1- 1.4

Remark	:	The estimated Log BCF = 0.463. Measured inputs to the EPIWIN program were melting point (-64 degrees C), boiling point (190 degrees C), vapor pressure (0.3 mm Hg), Log Pow (1.51) and water solubility (15 g/l).
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
BCF	:	= 3.2
Elimination	:	
Method	:	other: estimated value
Year	:	
GLP	:	
Test substance	:	
Remark	:	Based upon a water solubility of 11000 mg/l the BCF for ethylene glycol monobutyl ether acetate can be estimated to be 3.2 from a regression-derived equation. This BCF value suggests that ethylene glycol monobutyl ether acetate will not bioconcentrate significantly in aquatic organisms. All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(56) (63)

3.8 ADDITIONAL REMARKS

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Oncorhynchus mykiss
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
LC50	:	= 20-40
Method	:	OECD guideline 203
Year	:	2002
GLP	:	no data
Test substance	:	as prescribed by 1.1 -1.4
Remark	:	The authors noted that it was impossible to calculate an accurate LC50 value because the mortality rate changed from 0-100% over two successive concentrations. However, an LC50 value can be obtained from the two successive concentrations which caused 0% (20 mg/l) and 100% (40 mg/L) mortality by calculating the geometrical mean (28.3 mg/l). Methodological information was obtained from: Devillers J et al. 2002. Ecotoxicity of ethylene glycol monomethyl ether and its acetate. Toxicol Mech Methods 12:241-254.
Result	:	None of the fish exposed to 20 mg/l died. Mortality at the next concentration (40 mg/l) was 100%. No other results were given.
Test condition	:	A LC50 can be obtained from the two successive concentrations which caused 0% (20mg/L) and 100% (40 mg/L) mortality by calculating the geometrical mean: 28.3 mg/L. Groups of seven young fish were disposed in 15L of reconstituted water and exposed to a serial dilution of eight concentrations of the test substance and controls (in duplicate). Other test conditions were as follow: pH = 8 +/- 0.3, water hardness = 250 +/- 25 mg/L $CaCO_3$, T = 16 +/- 1°C with a 12-hour light/dark photo period. The number of dead animals was registered after 24, 48, 72 and 96 hours. We can also noticed that $K_2Cr_2O_7$ was used as the toxic reference chemical. Moreover, chemical analyses were made to verify that real concentrations corresponded with the nominal concentrations. A LC50 can be obtained from the two successive concentrations which caused 0% (20mg/L) and 100% (40 mg/L) mortality by calculating the geometrical mean: 28.3 mg/L. Groups of seven young fish were disposed in 15L of reconstituted water and exposed to a serial dilution of eight concentrations of the test substance and controls (in duplicate). Other test conditions were as follow: pH = 8 +/- 0.3, water hardness = 250 +/- 25 mg/L $CaCO_3$, T = 16 +/- 1°C with a 12-hour light/dark photo period. The number of dead animals was registered after 24, 48, 72 and 96 hours. We can also noticed that $K_2Cr_2O_7$ was used as the toxic reference chemical. Moreover, chemical analyses were made to verify that real concentrations corresponded with the nominal concentrations. Groups of seven young fish were disposed in 15 liters of reconstituted water and exposed to a serial dilution of eight concentrations of the test substance and controls (in duplicate). Concentrations tested were not listed. Other test conditions were as follows: pH = 8 +/- 0.3, water hardness = 250 +/- 25 mg/l $CaCO_3$, temperature = 16 +/- 1°C, 12-hour light/dark photo period. The number of dead animals was registered after 24, 48, 72 and 96 hours. $K_2Cr_2O_7$ was used as a positive control. Concentrations were verified analytically. The 96-hour LC50 value was calculated by probit analysis. No other information about the test conditions was given.
Test substance	:	Purity of the test material was 99%.
Reliability	:	(1) valid without restriction Guideline study.

Flag : Critical study for SIDS endpoint

(23)

Type : static
Species : Pimephales promelas (Fish, fresh water)
Exposure period : 96 hour(s)
Unit : mg/l
Analytical monitoring : no
LC50 : m = 31
Method : other: as described in "Standard Methods for the Examination of Water and Wastewater", 16th ed., USPHA, Washington, D.C., 1985
Year : 1974
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Result : The 24-hr, 48-hr and 96-hr LD50 values were 56, 39 and 31 mg/l.
Remark : The source of the dilution water, how stock and test solutions were prepared, size of vessels used, final pH, biological observations, cumulative mortality, mortality of controls, abnormal responses, method of calculating the LC50 value, solubility/insolubility of test material and purity of test material were not listed.
Test condition : An initial range-finding test was conducted using 2 fish exposed to concentrations ranging from 10 to 10000 mg/l. Definitive tests were performed with 10 fish (2.5 to 5 cm) per test concentration in vessels containing 18.5 liters of dilution water under minimal controlled aeration (after the first four hours of the test). Fish were exposed for up to 96 hours. The temperature of the water ranged from 71 to 76 degrees F, the total alkalinity from 30-40 mg/l, the total hardness from 30 to 60 mg/l, the dissolved oxygen from 7.5 to 9.0 mg/l throughout the study. The initial pH was 7.8.
Test substance : Test material was butyl CELLOSOLVE® acetate.
Reliability : (2) valid with restrictions. Basic data given.

(83)

Type : static
Species : Leuciscus idus (Fish, fresh water)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : no
LC50 : = 80
Method : other: DIN 38412 part 15
Year :
GLP : no
Test substance : other TS
Remark : All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. It is not known what is meant by “other TS”.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance : Huels AG
Reliability : (4) not assignable. The study was not available for review.

(49)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type : static
Species : Daphnia magna (Crustacea)

Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	m = 143
Method	:	other: test procedures followed those recommended by EPA and ASTM
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Lighting conditions, method of calculating the LC50 value, numbers of deaths at each concentration, condition of controls and purity and solubility/insolubility of the test material were not listed. Data were listed as LC50 values, rather than EC50 values.
Result	:	The LC50 value (and 95% confidence limits) was 143 (117-173) mg/l.
Test condition	:	Daphnia magna stocks were originally obtained from the EPA laboratory at Duluth, MN. They were maintained at 20-22 degrees C in a series of 600 ml beakers filled with Kanawha River water obtained from the South Side Boat Ramp (Charleston, SC). Daphnia were fed three times a week with a laboratory-prepared food consisting of trout food, yeast and alfalfa powder. Daphnia used in the test were offspring of 20-50 gravid females isolated for 24 hours. A series of from 5-10 equidistant concentrations based on results of fish toxicity studies (plus control) were tested. Tests were conducted in 250 ml beakers containing 100 ml of test solution (in Kanawha River water) and 5 Daphnia (less than 24 hours old). Tests were run in duplicate. Dissolved oxygen and pH were determined initially and at 48 hours for all test solutions (dissolved oxygen values were not listed). Total hardness, alkalinity, pH and conductivity of the test and holding water were 55 mg/l as CaCO3, 36 mg/l as CaCO3, 6.7, and 250 micromhos/cm. Mortalities were recorded at 24 and 48 hours.
Test substance	:	Test material was butyl CELLOSOLVE® acetate.
Reliability	:	(2) valid with restrictions. Basic data given.
Flag	:	Critical study for SIDS endpoint.

(84)

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC50	:	= 81.9
Method	:	other: DIN 38412/11
Year	:	
GLP	:	no
Test substance	:	other TS: Huels AG
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000. It is not known what is meant by “other TS: Huels AG”.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(46)

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	24 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC0	:	= 58

EC50	:	= 150
EC100	:	= 320
Method	:	other: Daphnien-Kurzzeittest [Daphnia short-time test], DIN 38412 Teil [Part] 11, Bestimmung der Wirkung von Wasserinhaltsstoffen auf Kleinkrebse [Determination of the effect of water contaminants on small crustaceans]
Year	:	
GLP	:	
Test substance	:	
Remark	:	All information was reproduced from IUCLID documents for CAS No. 112-07-2 prepared by the European Chemicals Bureau, (dated 11-FEB-2000) and INERIS, (dated 22-MAY-2003) pH between 5.8 and 8.1, O_2 between 2.9 and 8.1 mg/l and T = 21°C. Four replicates were performed for each concentration (0, 10, 18, 32, 58, 100, 180, 320 mg//). The percentages of deaths in each group were as follows: 0, 0, 5, 0, 5, 40, 45 and 100, respectively). Three different endpoints were calculated after 24 hours: EC0, EC50 and EC100. After 24h, an EC0 of 10 mg/l, an EC50 of 145 mg/l (95% confidence interval = 120-174 mg/l) and an EC100 of 320 mg/l were obtained. The EC50 value reported in the INERIS IUCLID document (145 mg/l) was different from that reported in the European Chemicals Bureau IUCLID document (150 mg/l). No reliability rating was listed in the European Chemicals Bureau IUCLID document. The reliability rating listed in the INERIS IUCLID document was 2 (valid with restrictions). The source and supplier and age of the Daphnia at study initiation were not listed. No information was listed about preparation of stock and test solutions, purity and solubility of test material, size of vessels and volume of test solution, source of the dilution water, lighting, criterion for effect, and method of calculating the EC50 value.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(2) valid with restrictions. Basic information given.

(12)

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC0	:	= 10
EC50	:	= 37
EC100	:	= 320
Method	:	other: Daphnien-Kurzzeittest [Daphnia short-time test], DIN 38412 Teil [Part] 11, Bestimmung der Wirkung von Wasserinhaltsstoffen auf Kleinkrebse [Determination of the effect of water contaminants on small crustaceans]
Year	:	
GLP	:	
Test substance	:	
Remark	:	All information was reproduced from IUCLID documents for CAS No. 112-07-2 prepared by the European Chemicals Bureau, (dated 11-FEB-2000) and INERIS, (dated 22-MAY-2003) pH between 5.8 and 8.1, O_2 between 2.9 and 8.1 mg/l and T = 21°C. Four replicates were performed for each concentration (0, 10, 18, 32, 58, 100, 180, 320 mg//). The percentages of deaths in each group were as follows: 5, 5, 30, 40, 75, 75, 95 and 100. Three different endpoints were calculated

after 48 hours: EC0, EC50 and EC100. After 48h, an EC0 of 10 mg/l, an EC50 of 37 mg/l (95% confidence interval = 29-48 mg/l) and an EC100 of 320 mg/l were obtained. No reliability rating was listed in the European Chemicals Bureau IUCLID document. The reliability rating listed in the INERIS IUCLID document was 2 (valid with restrictions).

The source and supplier and age of the Daphnia at study initiation were not listed. No information was listed about preparation of stock and test solutions, purity and solubility of test material, size of vessels and volume of test solution, source of the dilution water, lighting, criterion for effect, and method of calculating the EC50 value.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (2) valid with restrictions. Basic data given.

(12)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : yes
EC50 : = 67.5
Method : other:ISO Guideline 6341 (ISO 1996)
Year : 2002
GLP : no data
Test substance : as prescribed by 1.1 -1.4
Remark : The source and supplier and age of the Daphnia at study initiation were not listed. No information was listed about preparation of stock and test solutions, solubility of test material, size of vessels and volume of test solution, source of the dilution water, lighting, or numbers of organisms affected at each concentration.

Methodological information was obtained from: Devillers J et al. 2002. Ecotoxicity of ethylene glycol monomethyl ether and its acetate. Toxicol Mech Methods 12:241-254.

Result : A 48-hour EC50 of 67.5 mg/l was calculated by probit analysis. No other results were listed.

Test condition : During this assay groups of neonates were exposed in darkness to a serial dilution of BGA. Four replicates of five animals were used for each concentration. Other test conditions included a pH of 7.8 +/- 0.2, a water hardness of 250 +/- 20 mg/L ($CaCO_3$) and a temperature of 20+/- 2°C. $K_2Cr_2O_7$ has been used as the toxic material of reference. A 48-hour EC50 of 67.5 mg/L was calculated by probit analysis. Chemical analyses were made to verify that the actual concentrations corresponded with the nominal ones.
During this assay groups of neonates were exposed in darkness to a serial dilution of BGA. Four replicates of five animals were used for each concentration. Other test conditions included a pH of 7.8 +/- 0.2, a water hardness of 250 +/- 20 mg/L ($CaCO_3$) and a temperature of 20+/- 2°C. $K_2Cr_2O_7$ has been used as the toxic material of reference. A 48-hour EC50 of 67.5 mg/L was calculated by probit analysis. Chemical analyses were made to verify that the actual concentrations corresponded with the nominal ones.
Groups of neonates were exposed in darkness to a serial dilution of test material (concentrations were not listed). Four replicates of five animals were used for each concentration. Other test conditions included a pH of 7.8 +/- 0.2, a water hardness of 250 +/- 20 mg/l ($CaCO_3$) and a temperature of 20 +/- 2°C. $K_2Cr_2O_7$ was used as a positive control. Concentrations of test material were analytically confirmed. The number of

immobile animals was registered after 48 hours of exposure. No other test conditions were listed.

Test substance : Purity of the test material was 99%.

Reliability : (2) valid with restrictions. Basic data given.

(23)

Type	:	static
Species	:	Brachionus calyciflorus (rotifer)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC10	:	= 6.9
EC20	:	= 13.7
EC50	:	= 303
Method	:	other:AFNOR NFT 90-377
Year	:	2002
GLP	:	no data
Test substance	:	as prescribed by 1.1 -1.4
Remark	:	The source and supplier of the rotifers were not listed. No information was listed about preparation of stock and test solutions, solubility of test material, volume of test solution, source of the dilution water, criterion for effect, or numbers of organisms affected at each concentration. Methodological information was obtained from: Devillers J et al. 2002. Ecotoxicity of ethylene glycol monomethyl ether and its acetate. Toxicol Mech Methods 12:241-254.
Result	:	The EC10, EC20 and EC50 values (with their respective confidence intervals) were as follows: 6.9 (5.4 – 23.2), 13.7 (9.9 – 16.4) and 303 (229-343) mg/l. No other results were given.
Test condition	:	Cyst hatching was initiated in moderately hard water about 20 hours before the beginning of the test (at 25°C under a light intensity of 3000 lux.). pH was adjusted to 7.5. After 18 hours of incubation cysts were regularly checked to ensure the removal of test organisms within two hours of hatching. The assay was performed in a 48-well microplate (five concentrations plus one control with eight replicates). Test media consisted in synthetic fresh water solution with a suspension of the green alga *Chlorella vulgaris* as food source. One rotifer was disposed per well (newly hatched rotifer) and the incubation occurred at 25°C in darkness. After 48 hours, the total number of rotifers per well was counted and EC10 and EC20 were determined by non-linear regression using a log logistic model (test conditions seem to have been adapted for the determination of an EC10). The respective confidence intervals for these endpoints were as follow: EC10 = 5.4-23.2 mg/L and EC20 = 9.9-16.4 mg/L. No analytical monitoring was performed during the test. Cyst hatching was initiated in moderately hard water about 20 hours before the beginning of the test (at 25°C under a light intensity of 3000 lux.). pH was adjusted to 7.5. After 18 hours of incubation cysts were regularly checked to ensure the removal of test organisms within two hours of hatching. The assay was performed in a 48-well microplate (five concentrations plus one control with eight replicates). Test media consisted in synthetic fresh water solution with a suspension of the green alga *Chlorella vulgaris* as food source. One rotifer was disposed per well (newly hatched rotifer) and the incubation occurred at 25°C in darkness. After 48 hours, the total number of rotifers per well was counted and EC10 and EC20 were determined by non-linear regression using a log logistic model (test conditions seem to have been adapted for the determination of an EC10). The respective confidence intervals for these endpoints were as follow: EC10 = 5.4-23.2 mg/L and EC20 = 9.9-16.4 mg/L. No analytical monitoring was performed during the test. Cyst hatching was initiated in moderately hard water about 20 hours before

the beginning of the test (at 25°C under a light intensity of 3000 lux.). pH was adjusted to 7.5. After 18 hours of incubation cysts were regularly checked to ensure the removal of test organisms within two hours of hatching. The assay was performed in a 48-well microplate (five concentrations plus one control with eight replicates). Test media consisted in synthetic fresh water solution with a suspension of the green alga *Chlorella vulgaris* as food source. One rotifer was disposed per well (newly hatched rotifer) and the incubation occurred at 25°C in darkness. After 48 hours, the total number of rotifers per well was counted and EC10 and EC20 were determined by non-linear regression using a log logistic model (test conditions seem to have been adapted for the determination of an EC10). The respective confidence intervals for these endpoints were as follow: EC10 = 5.4-23.2 mg/L and EC20 = 9.9-16.4 mg/L. No analytical monitoring was performed during the test.
Cyst hatching was initiated in moderately hard water about 20 hours before the beginning of the test (at 25°C under a light intensity of 3000 lux). pH was adjusted to 7.5. Hatching took place at 25 degrees C under a light intensity of 3000 lux. After 18 hours of incubation, cysts were regularly checked to ensure the removal of test organisms within two hours of hatching. The assay was performed in a 48-well microplate (five concentrations plus one control with eight replicates). Test media consisted of synthetic fresh water solution with a suspension of the green alga *Chlorella vulgaris* as food source. One newly hatched rotifer was disposed per well. The transfer was completed under a microscope (magnification x 10) using a micropipette. The incubation occurred at 25°C in darkness. After 48 hours, the total number of rotifers per well was counted, and the EC10, EC20 and EC50 were determined by non-linear regression using a log logistic model. No analytical monitoring was performed during the test. No other test condition information was listed.

Test substance : Purity of the test material was 99%.
Reliability : (2) valid with restrictions. Basic data given.

(23)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no data
EC10	:	> 500
EC50	:	> 500
Method	:	other: Scenedesmus-cell reproduction inhibition test DIN 38412 L 9
Year	:	1989
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Remark	:	The original record in the IUCLID database has been replaced with a more robust version. The study was translated into English from German by the reviewer. The results indicated that the test material may have had a slight stimulatory effect on cell biomass; however, the results were not significantly different from control. The only water parameter mentioned was pH. The source of the dilution water, size of exposure vessels and volumes of solution, method of preparation of test solutions, light conditions and purity of the test material were not described. Fluorescence measures chlorophyll content, and chlorophyll content is a measure of biomass. In a study described by Herman et al. (Aquatic

Toxicol 18:87-100, 1990), 4 different ways of measuring biomass were checked for sensitivity (cell number, absorbance, chlorophyll content and dry weight). Measuring cell number was the most sensitive means of assessing algal cell growth, followed by absorbance and chlorophyll content, which were of equal utility. Since most test methods use absorbance for calculating biomass, and results of tests measuring chlorophyll content and absorbance are similar, tests employing fluorescence to measure chlorophyll content should be as sensitive as those employing absorbance as a means of assessing algal biomass.

Result : Fluorescence of blank vials was zero for all concentrations of test material at all time points. Average fluorescence of controls at 0, 24, 48, 72 and 96 hours was 36, 98, 313, 794 and 1795 units. Values for the two lowest concentrations were lower than control at 72 and 96 hours (694 and 1619 units at these times for 25 mg/l and 704 and 1671units for 50 mg/l), and slightly greater than control at 24 and 48 hours (121 and 337 units at these times for 25 mg/l and 125 and 338 units for 50 mg/l). Initial values were 37 and 38 for 25 mg/l and 50 mg/l, respectively (not different from control). For concentrations of 100, 250 or 500 mg/l, values at all time points (with the exception of time 0) were slightly greater than control. For 100 mg/l, the values at 0, 24, 48, 72 and 96 hours were 38, 151, 363, 816 and 1769; for 250 mg/l the values at the same time points were 38, 158, 400, 854 and 1887; and for 500 mg/l the values were 38, 153, 722, 1089 and 1949. None of the values were designated as being significantly greater than control. Values for the 4 replicates at each concentration varied by <= 7.68%. pH of the control medium increased from 7.85 to 7.98, but pH of all other media did not differ significantly from the initial value (7.62 to 7.70). Temperature of all media remained constant at 24.8 degrees C.

Test condition : A SAG 86.81 culture of Scenedesmus subspicatus (10,000 to 15,000 cells/ml) was maintained at 21 to degrees C. Cells in suspension were treated with 0 (control), 25, 50, 100, 250 or 500 mg/l test material in quadruplicate. Test concentrations were chosen based on the results of a preliminary test. Fluorescence of vials containing treated cells was determined 0, 24, 48, 72 and 96 hours after treatment in a fluorimeter (at wavelengths from 300 to 780 nm). Fluorescence of 2 blank vials containing test material (at each concentration) and medium without cells was subtracted from values obtained for test vials. The values for the four tests were averaged and a standard deviation was calculated. Fluorescence was converted to cell number (N) using the equation fluorescence = N/ml – 4748.47/220.024. The pH of solutions was determined before and at the end of the test.

Reliability : (2) valid with restrictions. Basic data given.

Flag : Critical study for SIDS endpoint

(13)

Type : static
Species : Pseudokirchneriella subcapitata
Exposure period : 72 hour(s)
Unit : mg/l
Analytical monitoring : yes
NOEC : = 300 (growth and biomass)
EC50 : = 520 (biomass), 1570 (growth)
Method : other:ISO Guideline 8692 (ISO, 1993)
Year : 2002
GLP : no data
Test substance : as prescribed by 1.1 -1.4
Remark : The only water parameter mentioned was temperature. The source of the dilution water, size of exposure vessels and volumes of solution, method of preparation of test solutions, and light conditions were not described.

Methodological information was obtained from: Devillers J et al. 2002. Ecotoxicity of ethylene glycol monomethyl ether and its acetate. Toxicol Mech Methods 12:241-254.

Result : The NOECs for growth and biomass were both 300 mg/l. The EC50 values for biomass and growth were 520 and 1570 mg/l, respectively.

Test condition : This test was performed according to the norm ISO 8692: "Water quality – fresh water and algal growth inhibition test with *Scenedesmus subspicatus* and *Selenestrum capricornutum*". Test conditions were as follow: incubation occurred on a shaking table under constant temperature (ca. 23°C) and light. Each test was performed on three replicate batches at each concentration and at each control batch. The cell densities were determined using an electronic particle counter after 24, 48 and 72 hours and the inhibition of growth was estimated as the average growth rate expressed as a percentage of the control growth rate. EC50 was calculated by means of probit analysis and NOEC was determined by using a software (TOXSTAT). It can also be noticed that although the solutions were analysed, toxicity results were based on nominal concentrations. This test was performed according to the norm ISO 8692: "Water quality – fresh water and algal growth inhibition test with *Scenedesmus subspicatus* and *Selenestrum capricornutum*". Exponentially growing batch cultures of algae were exposed to a serial dilution of test material. Each test was performed on three replicate batches at each concentration and on 6 control batches. Incubation took place on a shaking table under constant temperature (ca. 23°C) and light. The cell densities were determined using an electronic particle counter after 24, 48 and 72 hours and the inhibition of growth was estimated as the average growth rate expressed as a percentage of the control growth rate. The EC50 was calculated by means of probit analysis and the NOEC was determined using a software (TOXSTAT). Although the solutions were analyzed for concentration of test material, toxicity results were based on nominal concentrations. No other information about test conditions was given.

Test substance : Purity of the test material was 99%.

Reliability : (2) valid with restrictions. Guideline study with acceptable restrictions.

(23)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : aquatic
Species : other bacteria
Exposure period : 16 hour(s)
Unit :
Analytical monitoring :
IC50 : m > 500
Method : other
Year : 1987
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Test condition : Selected concentrations (not listed) were incubated for 16 hours at 23 degrees C on a shaker table in the presence of nutrients, buffer, growth substrate, and sewer microorganisms. Toxicity was indicated when the resulting turbidity was at (or less than) 50% of the control (IC50). Details of the test are published in: Alsop et al., "Bacterial Growth Inhibition Tests", J. Water Pollution Control Federation, Vol 52: No. 10, October, 1980.
Test substance : Test material was butyl CELLOSOLVE ®acetate.
Reliability : (2) valid with restrictions. Basic data given.

(84)

Type	:	
Species	:	activated sludge, domestic
Exposure period	:	30 minute(s)
Unit	:	mg/l
Analytical monitoring	:	
EC20	:	= 900
Method	:	other: Test for Inhibition of Oxygen Consumption by Activated Sludge, ISO 8192
Year	:	
GLP	:	
Test substance	:	
Remark	:	Stoerungen der Abbauaktivitaet von Belebtschlamm sind nicht zu erwarten. [Disruption of the breakdown activity of activated sludge is not anticipated]. All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(14)

Type	:	
Species	:	activated sludge, domestic
Exposure period	:	180 minute(s)
Unit	:	mg/l
Analytical monitoring	:	
EC20	:	900
Method	:	other: Test for Inhibition of Oxygen Consumption by Activated Sludge, ISO 8192
Year	:	
GLP	:	
Test substance	:	
Remark	:	All data (unless listed otherwise) came from IUCLID documents for CAS No. 112-07-2 published by the European Chemicals Bureau, (dated 11-FEB-2000) and INERIS (dated 22-MAY-2003). The test was conducted on activated sludge from a domestic waste water treatment plant according to OECD Guideline 209. Concentrations of material tested were 0.02, 0.05, 0.2, 0.5 and 1 g/l. The EC20s at 30 (900 mg/l) and 180 minutes (> 1000 mg/l) were calculated. A positive control (3,5-dichlorophenol) was tested. The EC50 value for this chemical at 30 minutes was 22 mg/l.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(3) invalid. The result obtained from the 180 minute test performed does not conform with that of the 30-minute test. The same conclusion was stated in the INERIS document.

(14)

Type	:	
Species	:	Pseudomonas putida (Bacteria)
Exposure period	:	17 hour(s)
Unit	:	mg/l
Analytical monitoring	:	
EC10	:	= 722
EC50	:	= 964

EC90	:	= 1206
Method	:	other: Pseudomonas-Zellvermehrungs-Hemmtest [Pseudomonas cell reproduction inhibition test], DIN 38412 Teil [Part] 8, zum Gelbdruck verabschiedet [retired to the yellow page section], Bestimmung der Hemmwirkung von Wasserinhaltsstoffen auf Bakterien [Determination of the inhibitory effect of water contaminants on bacteria] European reference method: EN ISO 10712:1995
Year	:	1990
GLP	:	no
Test substance	:	
Remark	:	All data were obtained from a IUCLID document published by INERIS on 22-MAY-2003. The assay was conducted at 24 +/- 1 degrees C. Nine concentrations were tested: 0 (control), 39, 78, 156, 312, 625, 1250, 2500, 5000 and 10000 mg/l. Cell multiplication of treated cells was compared to the control. The EC10, EC50 and EC90 values after 17 hours were 722, 964 and 1206 mg/l, respectively. The reliability rating stated in the INERIS document was (2) valid with restrictions.
Reliability	:	(2) valid with restrictions. Basic data given.

(12)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

Species	:	Ceriodaphnia dubia
Endpoint	:	EC10
Exposure period	:	7 days
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	16.4
EC10	:	30.40
EC20	:	30.7
Method	:	AFNOR NF T 90-376
Year	:	2000
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Result	:	Parental toxicity (based on measured concentrations):

Conc (mg/l)	0	0.4	1.1	2.6	5.3	16.4	43.3
Mortality (%)	0	0	0	0	20	0	10

The average number of offspring per alive parent was:

Conc (mg/l)	0	0.4	1.1	2.6	5.3	16.4	43.3
Offspring (n)	24.3	24.3	25.6	24.0	27.6	25.0	16.6

The 7 day EC10 value and its confidence interval was 30.40 (9.89-37.73) mg/l. The EC20 value and its confidence interval was 30.7 (22.6 -39.7) mg/l. The NOEC was 16.4 mg/l.

Test condition	:	Young organisms (< 24 hours old) and from the second to fifth brood of healthy adults reared in the laboratory were individually introduced in 100 ml glass vials containing 50 ml of test solution (mineral water with Ca = 78 mg/l, Mg = 24 mg/l, Na = 5 mg/l, K = 1 mg/l, SO4 = 10 mg/l and Cl = 4.5 mg/l). Hardness and pH of the test solutions were measured daily (except weekends). Values were within the guidelines of pH = 8.0 +/- 0.3 and

hardness = 150 +/- 20 mg/l as CO3. Daily measurements of dissolved oxygen ranged between 8.6 and 9.2 mg/l. Temperature was monitored continuously. The test was conducted at 20 +/- 1 degrees C. A 16:8 light:dark photoperiod was employed. Light intensity at the air/water interface ranged between 300 and 500 lx. Test solutions were changed daily (with the exception of weekends). The organisms were fed with Chorella vulgaris (6 x 10E6 cells/50 ml), Raphidocelis subcapitata (3 x 10E6 cells/50 ml) and 25 microliters/50 ml of a stock solution (5 g/l) of commercial fish food.

Ten replicates (one individual per each) were used per treatment and control. A range of 5 concentrations spanning those causing 0-100% inhibition of reproduction were used (0.51, 1.28, 3.2, 8.3, 20.0 and 50.0 mg/l). Flasks were closed and were not aerated. Analytically determined concentrations during actual exposure were 0.4, 1.1, 2.6, 5.3, 16.4 and 43.3 mg/l).

The criterion for estimating the effect of the material on the reproduction of the organism was the EC10 at 7 days. The EC10 value was calculated according to the method of Hill (Garrie et al., Water Res. 24:59-65, 1990 and Vindimian et al., J Appl Biochem 5:261-268, 1983). The following criteria had to be met in order for the test to be considered valid: control survival of > 80%, < 20% of males at Day 7 in each batch, > 60% of control females having three broods, and control females having at least 15 offspring in 7 days.

Concentrations of test material in each renewal solution were measured when they were first used and when they were replaced. The test material was first extracted from the water by solid-phase microextraction with a carboxen-polydimethylsiloxane fiber and then analyzed by capillary gas chromatography on a Carbox column.

Test substance : Purity of the test material was 99%.
Reliability : (1) valid without restrictions
Guideline study

(24) (50)

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	
Vehicle	:	other: pure neutralized olive oil
Value	:	= 2400 mg/kg bw
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The LD50 value for butylglycol acetate (BGA) was 3000 +/- 300 mg/kg for male rats and 2400 +/- 200 mg/kg for female rats. The LD50 values for ethylglycol acetate (EGA) in both sexes were slightly higher. No animals died after Day 3 following administration. The numbers and times of deaths for each sex at each dose were not mentioned. Hemoglobinuria and/or hematuria were noted in animals treated with BGA or EGA (more severe with BGA). This decreased over the course of the experiment but sometimes persisted for over 1 week. Doses at which these effects were noted were not listed. Kidneys and bladders of rats that died were dilated with blood. Tubular nephrosis and dilation were noted in kidneys of rats treated with all doses of BGA. Kidneys of rats treated with the highest doses of BGA also showed glomerulo-tubular necrosis and hyaline droplet degeneration. The numbers and sexes of animals exhibiting lesions were not stated. Necropsies of animals that survived to 2 weeks were normal.
Test condition	:	Rats (220-240 g) were randomly divided into 10 animals/group/sex and were acclimated for 2 weeks prior to treatment. Butylglycol acetate (BGA) and ethylglycol acetate (EGA) diluted in pure, neutralized olive oil were administered to rats by gastric intubation using 10 ml of solution/kg. Animals were fasted overnight (16-24 hr) prior to dosing. Weights were recorded before dosing and at the end of the 14-day observation period. All deaths occurring during the observation period were recorded. LD50 values were determined by the graphic method of Miller and Tainter (Proc Soc Exp Biol Med 57: 261-264, 1944) and Bartlett (Suppl J Roy Stat Soc 4:137-170, 1937). The presence of blood, protein, glucose, ketone bodies and nitrites in the urine and urine pH was measured with test strips (times not indicated). Red and white blood cells in urine were counted with a Coulter counter. Hemoglobin was also measured. All animals were necropsied upon death. Heart, lungs, liver, spleen, pancreas, kidneys, adrenals, ovaries, bladder, skin, brain, eyes, stomach and testes were fixed and examined histologically.
Test substance	:	Butylglycol acetate came from Pfaltz & Bauer, Flushing, New York. Purity was not noted. Purity of ethylglycol acetate was >= 99%.
Reliability	:	(2) valid with restrictions. Basic data given.
Flag	:	Critical study for SIDS endpoint

(74)

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	

Vehicle :
Value : = 1600 mg/kg bw
Remark : All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.
(61)

Type : LD50
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Value : = 7000 mg/kg bw
Remark : All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.
(69)

Type : LD50
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Value : = 2360 mg/kg bw
Method : other: BASF-Test
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.
(6)

Type : LD50
Species : mouse
Strain :
Sex :
Number of animals :
Vehicle :
Value : = 3200 mg/kg bw
Remark : All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.
(67)

Type : LD50

Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	= 2830 mg/kg bw
Method	:	other: BASF-Test
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(6)

Type	:	
Species	:	rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Method	:	other: BASF-Test
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Orale Gabe [Oral dose] (Sonde) von [probe of] 938 mg/kg Letalitaet bei 2/3 der Kaninchen. [Lethality in 2/3 of the rabbits]. All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(9)

Type	:	
Species	:	rabbit
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Method	:	other: BASF-Test
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Orale Gabe (Sonde) von 980 mg/kg bzw. 1960 mg/kg Letalitaet bei 6/6 der Kaninchen. Tiere verendeten unter Anzeichen von Atonie, Rollkraempfen, beschleunigter Atmung; Hyperaemie und Blutfarbstoffausscheidung in die vordere Augenkammer lagen vor. Blutbefund: Hburie , Hct sinkt unter 10 %, Absinken der Lymphozyten bei Gesamtleukozytose, Degeneration bei allen Blutzellfraktionen.Harn: Nierenepithelien, sowie Erythrozyten u. Hb Path. Anatomie: Hb-Urie, Nephrosen, geschaedigte Lymphopoese, Lungenoedem, Verfettung von Leber und Herzmuskel. Beurteilung: Haemolyse (massiv) beding haemoglobinurische Nephrose, die zum Tod fuehrt.

[Oral dose (probe) of 980 mg/kg and 1960 mg/kg respectively. Lethality in 6/6 rabbits. Animals died with signs of atony (languor, listlessness), convulsions, rapid breathing, hyperemia and blood pigment separation in the front eye chamber (porphyrin tears). Blood analysis: hemoglobin, hematocrit levels under 10%, reduction of lymphocytes, general leukocytosis, and degeneration of all blood fractions. Urinary: changes in kidney epithelium as well as erythrocytes and hemoglobin. Anatomy: Hemoglobinuria, nephrosis, damaged lymphopoesis, lung edema, fat deposits in the liver and heart muscle. Evaluation: Massive hemolysis and hemoglobin nephropathy leading to death.]

All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(10)(76)

Type :
Species : cat
Strain :
Sex :
Number of animals :
Vehicle :
Method : other: BASF-Test
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : Orale Gabe (Sonde) von 938 mg/kg Letalitaet bei 0/2 der Katzen. [Oral dose (probe) of 938 mg/kg. Lethality with 0/2 of the cats].

All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(9)

5.1.2 ACUTE INHALATION TOXICITY

Type : LC0
Species : other: rat and rabbit
Strain : Wistar (rat), New Zealand (rabbit)
Sex : male/female
Number of animals : 10
Vehicle :
Exposure time : 4 hour(s)
Value : >= 400 ppm
Method : other
Year : 1979
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Result : All rats and rabbits survived a 4-hr exposure to saturated vapor-air mixtures of butylglycol acetate (BGA) or ethylglycol acetate (EGA). A slight and transient hemoglobinuria and/or hematuria (not lasting over 24 to 48 hours) was noted in rabbits (numbers and sexes of animals affected

were not listed). No gross pathological lesions were found in animals upon necropsy.

Test condition : Male and female rats (N= 10/sex/group, 220 to 240 g) and four rabbits (2 of each sex, 2.2 to 2.5 kg) were exposed for 4 hours to saturated air-vapor mixtures of butylglycol acetate (BGA; approximately 400 ppm) or ethylglycol acetate (EGA; approximately 2000 ppm) in gas chambers. Test material was placed in a bubbler having a scintered-glass plate in its lower part and compressed air (1000 liters/hr) flowed through a lateral inlet pipe under the glass plate. The air was saturated with BGA or EGA by bubbling through the solvent and was brought into the chamber through a glass tube.

Body weights were recorded before dosing and at the end of the 14-day observation period. All deaths occurring during the observation period were recorded. LD50 values were determined by the graphic method of Miller and Tainter (Proc Soc Exp Biol Med 57: 261-264, 1944) and Bartlett (Suppl J Roy Stat Soc 4:137-170, 1937). The presence of blood, protein, glucose, ketone bodies and nitrites in the urine and urine pH was measured with test strips (times not indicated). Red and white blood cells in urine were counted with a Coulter counter. Hemoglobin was also measured. All animals were necropsied after the observation period.

Test substance : Butylglycol acetate came from Pfaltz & Bauer, Flushing, New York. Purity was not noted. Purity of ethylglycol acetate was >= 99%.

Reliability : (2) valid with restrictions. Basic data given.

Flag : Critical study for SIDS endpoint

(74)

Type : other: IRT
Species : rat
Strain :
Sex :
Number of animals :
4Vehicle :
Exposure time : 8 hour(s)
Method : other: BASF-Test
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : Keine Letalitaet nach 3 h Exposition in einer bei 20 Grad C angereicherten bzw. gesaettigten Atmosphaere (Dampf); spaeter Letalitaet. [No lethality after 3 hours exposure in an enriched namely saturated atmosphere (vapor) at 20 degrees C; subsequent lethality].

All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(6)

Type : other: IRT
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Exposure time : 8 hour(s)
Remark : Keine Letalitaet nach 8 Stunden Exposition (Dampf).
[No lethality after 8 hours exposure (vapor)].

All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(69)

Type : other: IRT
Species : mammal
Strain :
Sex :
Number of animals :
Vehicle :
Exposure time : 6 hour(s)
Method : other: BASF-Test
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : Keine Letalitaet nach Exposition in einer bei 20 Grad C angereicherten bzw. gesaettigten Atmosphaere (Dampf). Spezies: Ratte, Katze, Kaninchen, Meerschweinchen, Maus [No lethality after exposure to an enriched, saturated atmosphere (vapor) at 20 degrees C. Species: rat, cat, rabbit, guinea pig, mouse].

All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(7)

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Species : rabbit
Strain : other: New Zealand (color not specified)
Sex : no data
Number of animals : 6
Vehicle : no data
Value : = 1500 mg/kg bw
Method : other: modified Draize sleeve technique
Year : 1979
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Result : The LD50 value for rabbits was approximately 1500 mg/kg for butylglycol acetate (BGA) and 10500 mg/kg for ethylglycol acetate (EGA). Animals generally died between 24 to 48 hours, and no later than 4 days. The numbers and sexes of animals that died and the doses at which deaths occurred were not listed. Hemoglobinuria and/or hematuria, and decreases in red blood cells and blood hemoglobin were observed in animals treated with EGA or BGA.

In some animals treated with BGA, red blood cells fell to less than 10E12/liter and hemoglobin to 480-650 mmol/liter blood (20-25% of normal). The lowest values were reached after 48 to 72 hours and returned to normal in animals who survived treatment. The numbers and sexes of

animals exhibiting these hematological changes and dose levels at which they were observed were not listed.

For both solvents, necropsy of animals that died revealed bloody kidneys and the presence of high quantities of blood in the bladder. Closer examination of the bladders of these animals revealed a necrotizing, hemorrhagic, and atrophic acute tubular necrosis with occasional glomerular lesions. Kidneys of animals who survived the 2-week observation period appeared normal.

Test condition : Clipped skin of rabbits (6 animals per group weighing 2.2 to 2.5 kg)) was treated with various concentrations of butylglycol acetate (BGA) or ethylglycol acetate (EGA). Test materials were held in contact with skin for 24 hours using successive layers of gauze, cotton-wool, a sheet of rubber, and a bandage. An additional sheet of rubber was fastened around the trunk of the animals to prevent leakage. The weight difference between these elements before and after skin contact was used to calculate the amount of test material absorbed. Since approximately 10% of the applied BGA (7500 to 23500 mg) was absorbed, groups of rats were actually administered 610 +/- 310 mg/kg, 910 +/- 140 mg/kg, 1130 +/- 390 mg/kg, 1830 +/- 290 mg/kg and 2200 +/- 530 mg/kg.

Weights were recorded before dosing and at the end of the 14-day observation period. All deaths occurring during the observation period were recorded. LD50 values were determined by the graphic method of Miller and Tainter (Proc Soc Exp Biol Med 57: 261-264, 1944) and Bartlett (Suppl J Roy Stat Soc 4:137-170, 1937). The presence of blood, protein, glucose, ketone bodies and nitrites in the urine and urine pH was measured with test strips (times were not indicated). Red and white blood cells in urine were counted with a Coulter counter. Hemoglobin was also measured. All animals were necropsied upon death or at the end of the 14-day observation period. Heart, lungs, liver, spleen, pancreas, kidneys, adrenals, ovaries, bladder, skin, brain, eyes, stomach and testes were fixed and examined histologically.

Test substance : Butylglycol acetate came from Pfaltz & Bauer, Flushing, New York. Purity was not noted. Purity of ethylglycol acetate was >= 99%.

Reliability : (2) valid with restrictions. Basic data given.

Flag : Critical study for SIDS endpoint

(74)

Type : LD50
Species : rabbit
Strain :
Sex :
Number of animals :
Vehicle :
Value : ca. 1480 mg/kg bw
Remark : All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.

(69)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : LD50
Species : mouse

Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Route of admin.	:	i.p.
Exposure time	:	
Value	:	= 754 mg/kg bw
Method	:	other: BASF-Test
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(6)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	6
PDII	:	
Result	:	slightly irritating
EC classification	:	
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The primary irritation index of butylglycol acetate (BGA) was 0.17 and of ethylglycol acetate (EGA) was 0.08. Four out of 6 rabbits treated with BGA showed very slight erythema (Grade 1) at 24 hr and no perceptible irritation at 72 hr.
Test condition	:	Ethylglycol acetate and butylglycol acetate were tested for primary irritation on intact and abraded skin of six rabbits each according to French regulations (1971), derived from the method of Draize.
Test substance	:	Butylglycol acetate came from Pfaltz & Bauer, Flushing, New York. Purity was not noted. Purity of ethylglycol acetate was >= 99%.
Reliability	:	(2) valid with restrictions. Basic data given.

(74)

Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
PDII	:	
Result	:	not irritating
EC classification	:	
Method	:	other: BASF-Test
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	All data (except the reliability rating) came from an IUCLID document for

CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(6)

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
PDII :
Result : not irritating
EC classification :
Method : other: Smyth Carpenter
Year :
GLP :
Test substance :
Remark : (Grade 1)

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(69)

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
PDII :
Result : not irritating
EC classification :
Method : Draize Test
Year :
GLP :
Test substance :
Remark : (4 Stunden Einwirkzeit) [4 hours effective time]

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(51)

Species : rabbit
Concentration :
Exposure :
Exposure time :
Number of animals :
PDII :
Result :
EC classification :
Method : other: 4 hour covered patch application

Year	:	
GLP	:	no data
Test substance	:	other TS
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Result	:	No significant erythema in rabbits after 4 h covered patch application.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance	:	2-butoxyethyl acetate
Reliability	:	(4) not assignable. The study was not available for review. (32) (52)
Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
PDII	:	
Result	:	not irritating
EC classification	:	not irritating
Method	:	Directive 84/449/EEC, B.4 "Acute toxicity (skin irritation)"
Year	:	
GLP	:	no data
Test substance	:	other TS
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance	:	2-butoxyethyl acetate
Reliability	:	(4) not assignable. The study was not available for review. (87)
Species	:	rabbit
Concentration	:	
Exposure	:	
Exposure time	:	
Number of animals	:	
PDII	:	
Result	:	irritating
EC classification	:	
Method	:	Draize Test
Year	:	
GLP	:	no data
Test substance	:	other TS
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance	:	2-butoxyethyl acetate
Reliability	:	(4) not assignable. The study was not available for review. (87)

5.2.2 EYE IRRITATION

Species	:	rabbit

Concentration	:	
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	6
Result	:	not irritating
EC classification	:	
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	This test was described in the original IUCLID document prepared by the European Chemicals Bureau. Additional information has been added for this submission.
Result	:	The mean irritation score for BGA was 0.67. Two out of 6 rabbits had slight conjunctival redness and discharge within 24 hours of exposure. Irritation resolved by 48 hours. EGA was not irritating.
Test condition	:	Ethylglycol acetate (EGA) and butylglycol acetate (BGA) were tested for in six rabbits each according to French regulations (1971), derived from the method of Draize.
Test substance	:	Butylglycol acetate came from Pfaltz & Bauer, Flushing, New York. Purity was not noted. Purity of ethylglycol acetate was >= 99%.
Reliability	:	(2) valid with restrictions. Basic data given.

(74)

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	not irritating
EC classification	:	
Method	:	other: BASF-Test
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(6)

Species	:	rabbit
Concentration	:	
Dose	:	
Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	not irritating
EC classification	:	
Method	:	other: Smyth Carpenter
Year	:	
GLP	:	
Test substance	:	
Remark	:	(Grad 2) All data (except the reliability rating) came from an IUCLID document for

CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(69)

5.3 SENSITIZATION

Type : Guinea pig maximization test
Species : guinea pig
Number of animals :
Vehicle :
Result : not sensitizing
Classification : not sensitizing
Method : other: no data
Year : 1989
GLP : no data
Test substance : other TS: ethylene glycol butyl ether
Remark : Animals were induced with injection (route not stated) of 0.5% test material or application of 25% test material and challenged with 10% test material.
Reliability : (4) not assignable. The primary reference was not available for review

(80)

Type : Patch-Test
Species : human
Method : HRIPT
Reliability : (4) not assignable. The primary reference was not available for review.

(39)

5.4 REPEATED DOSE TOXICITY

Species : rats
Sex : male/female
Strain : F344/N
Route of admin. : inhalation
Exposure period : 14 weeks
Frequency of treatment : 6 hrs and 12 minutes per day, 5 days per week
Post obs. period :
Doses : 31, 62.5, 125, 250, 500 ppm
Control group : yes
NOAEL : < 31 ppm
LOAEL : 31 ppm
Method : other
Year : 2000
GLP : yes
Test substance : other TS
Remark : This study is appropriate for EGBEA because glycol ether acetates rapidly hydrolyze to their corresponding glycol ethers in vivo.
Result : Mortality and time to death: Six females were killed moribund during the study. One female in the 250 ppm group was killed moribund during week 8. Four females in the 500 ppm group were killed moribund during week 1 and one during week 5. All other animals survived to the end of the study.

Body weight: The mean final body weights (197 +/- 4 g) and body weight gains (89 +/- 3 g) of females exposed to 500 ppm were significantly less

than controls (217 +/- 5 and 105 +/- 4 g, respectively).

Clinical findings: Clinical findings were most prevalent in rats exposed to 125, 250 or 500 ppm and included abnormal breathing, pallor, red urine stains, nasal and eye discharge, lethargy, and increased salivation and/or lacrimation. All females exposed to 500 ppm had tail lesions consisting of alternating bands of dark purplish-blue with blanched white bands in approximately the distal one-third of the tail. This progressed to self-mutilation (chewing off) and /or sloughing of this portion of the tail. These findings were most prevalent during the first two weeks. However, all females exposed to 500 ppm lost the distal portion of the tail.

Hematology findings: A dose-dependent anemia, characterized by decreases in hematocrit, hemoglobin and erythrocyte counts occurred in males exposed to > = 125 ppm and all groups of exposed females. The anemia was characterized as macrocytic, normochromic and responsive. Evidence of macrocytosis was demonstrated by increases in mean cell volumes (in females exposed to > = 62.5 ppm and males exposed to > = 125 ppm). There was no effect of treatment on mean cell hemoglobin concentrations. An erythropoetic response was demonstrated by increases in the reticulocyte counts in males and females exposed to > = 125 ppm and increases in nucleated erythrocyte counts in males and females exposed to > = 250 ppm. Microscopic evaluation of blood smears of rats in the 50 ppm groups revealed increased numbers of polychromatophilic erythrocytes. Decreases in leukocyte counts, characterized by decreased lymphocyte and monocyte counts, occurred in males exposed to > = 125 ppm . Platelet counts increased in females exposed to 125 or 500 ppm.

Organ weights: Kidney weights of males exposed to 500 ppm and females exposed to > = 125 ppm and liver weights of males exposed to > = 250 ppm and females exposed to > = 125 ppm were significantly greater than controls. Thymus weights of females exposed to 500 ppm were significantly less than controls.

Histopathologic changes: Female rats that were killed moribund exhibited a number of histopathologic changes. Thrombosis occurred in a number of tissues in high dose females. Thromboses were associated with areas of infarction in the tail and necrosis in the incisors and liver. Thrombosis was present in the atrium of the heart, in the nasal septum, in central veins of the liver associated with large foci of necrosis, in the lung, the femur, tail, and dental pulp. There were areas of necrosis within bone marrow. Affected marrow was infiltrated by macrophages. In the most severely affected vertebrae in the tail, there was growth plate degeneration with no evidence of renewed longitudinal growth. Atrophy of the spleen and thymus; inflammation, necrosis, ulceration and hyperplasia of the forestomach; centrilobular degeneration of the liver; and renal tubule degeneration were also observed in rats killed moribund.

Similar effects were seen in animals that survived to study termination. Bone marrow necrosis and infarcts were found in the tails of all surviving females exposed to 500 ppm. Minimal hematopoetic cell proliferation of the spleen was noted in females exposed to > = 62.5 ppm (N = 1, 10, 8 and all 5 survivors in 62.5, 125, 250 and 500 ppm groups) and all males exposed to > = 250 ppm. Bone marrow hyperplasia was increased in all males exposed to > = 250 ppm and females exposed to > = 62.5 ppm (N = 8, 10, all 9 survivors and all 5 survivors in 62.5, 125, 250 and 500 ppm groups). Increased pigmentation of Kupffer cells in the liver was also noted in males exposed to > = 125 ppm (N = 7, 10 and 10 at 125, 250 and 500 ppm) and all surviving females exposed to > = 62.5 ppm. Renal tubule pigmentation was noted in 8/10 males exposed to 250 ppm, all males exposed to 500

ppm, and all surviving females exposed to > = 125 ppm. Minimal forestomach inflammation and hyperplasia were noted in 2 or 3 males exposed to > = 250 ppm. Epithelial hyperplasia of the forestomach were noted in 1 female each in the 250 and 500 ppm groups.

The NOAELs were 62.5 ppm in male rats and < 31 ppm in female rats.

Test condition : Animals: The rats were approximately 4 weeks old on receipt from the supplier (Taconic Laboratory Animals and Service, Germantown, NY). They were quarantined for 11-12 days before use. Five animals per sex were randomly selected for parasite evaluation and gross examination for evidence of disease. At the end of the study, serologic analyses were performed on 5 sentinel rats/sex. Water and food were available ad libitum (except during exposure, when food was withheld).

Vapor generation: The test material was held in a stainless-steel reservoir under a nitrogen blanket. The material was pumped into a glass column filled with glass beads and heated by a flexible electric heat tape encircling the column. Vapor temperature was monitored at the top of the condenser column by a temperature sensor. The vapor-laden air was transferred through a heated Teflon distribution line and diluted with HEPA- and charcoal-filtered air. Three-way valves in the chamber inlet ducts allowed vapors to be diverted to the exhaust until a stable concentration of test material was built up in the distribution line. At each chamber, vapor moving through the inlet duct was further diluted with filtered air to the appropriate concentration of test material. The total active mixing volume of each chamber was 1.7 m3. A small particle detector was placed in the chambers to measure concentrations of aerosol. No particle counts above the minimum resolvable level (200 particles/cm3) were detected.

Chamber concentrations were monitored with an on-line gas chromatograph (GC). The monitor was coupled with the inhalation chambers by a computer-controlled 12-port stream select valve. The GC was calibrated by comparing chamber concentration data to data from grab samples analyzed by an off-line GC. The grab samples were collected in bubblers containing water. The off-line GC was calibrated with gravimetrically prepared standards. Chamber concentration uniformity was maintained throughout the study.

Buildup and decay rates for chamber concentrations were determined with and without animals in the chambers. The time to achieve 90% of the target concentration and the time for decay to 10% of the target concentration was 12.5 minutes. Studies of 2-butoxyethanol degradation and monitoring for impurities were conducted throughout the studies by comparing bubbler samples to a reference sample. No significant degradation was observed during the studies.

Chambers were maintained at 23.9 – 24.3 degrees C, at a relative humidity of 55-56%, and under a 12 hour light/dark cycle. There were 15 air changes per hour.

Study conduct: Groups of 10 animals/sex were exposed to 0, 31, 62.5, 125, 250 or 500 ppm test material by inhalation, 6 hours and 12 minutes per day, 5 days per week for 14 weeks. Clinical observations were recorded weekly. Animals were weighed initially, weekly, and at the end of the study.

At the end of 14 weeks, rats were anesthetized and blood was withdrawn from the retroorbital plexus. Blood for hematology determinations [erythrocyte, platelet and total and differential leukocyte counts, hematocrit, hemoglobin concentration, mean cell volume, mean cell hemoglobin (and

hemoglobin concentration), morphological assessment of erythrocytes, platelets and leukocytes and nucleated erythrocyte counts was placed in tubes containing the anticoagulant potassium EDTA. Smears made from preparations of equal volumes of new methylene blue and whole blood were incubated to 20 minutes and examined microscopically for numbers of reticulocytes.

Necropsies were performed on all animals. The heart, right kidney, liver, lungs, right testis, and thymus were weighed. These tissues plus the adrenal gland, bone and marrow, brain, clitoral gland, esophagus, kidney, large intestine (cecum, colon, rectum), larynx, lymph nodes (mandibular, mesenteric, bronchial, and mediastinal), mammary gland, nose, ovary, pancreas, parathyroid, pituitary gland, preputial gland, prostate, salivary gland, small intestine (duodenum, jejunum, ileum), spleen, stomach (forestomach and glandular), testis (with epididymis and seminal vesicle), thyroid gland, trachea, urinary bladder, uterus and all gross lesions and tissue masses were fixed and preserved in 10% neutral buffered formalin. All tissues collected from rats in the control, 250 ppm (females) and 500 ppm (males and females) were processed for microscopic examination. In addition, the bone marrow, forestomach, kidney, liver, and spleen of male rats and nose, salivary gland, tail and thymus of female rats from other exposure groups were examined. Target organs were identified and a no observable adverse effect level was identified.

Statistical analyses: Organ and body weight and neurobehavioral data were analyzed using the parametric multiple comparison procedures of Dunnett (J Am Stat Assoc 50:1096-1121, 1955) and Williams (Biometrics 27:103-117, 1971 and Biometrics 28:519-531, 1972). Hematology data were analyzed with the nonparametric multiple comparison methods of Shirley (Biometrics 33:386-389, 1977) and Dunn (Technometrics 6:241-252, 1964). Jonckheere's test (Biometrika 41:133-145, 1954) was used to assess the significance of dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to analysis, extreme values were identified by the outlier test of Dixon and Massey (Introduction to Statistical Analysis, McGraw-Hill, 1951, p. 145-147), and implausible values were eliminated from the analyses. Average severity values were analyzed for significance with the Mann-Whitney U test (Nonparametric Statistical Methods, John Wiley and Sons, 1973, p.120-123). Treatment effects were determined by applying a multivariate analysis of variance to the transformed data. The Fisher's exact test was used to analyze histopathological data. The critical values for significance were $p < 0.05$ for body weight data, $p < 0.01$ or 0.05 for hematology data and $p < 0.01$ for histopathology data.

Conclusion : The NOAEL was 62.5 ppm in male rats and < 31 ppm in female rats. Higher concentrations were associated with red blood cell toxicity. Increases in kidney and or liver weights were observed in rats exposed to 125 ppm or more test material. Histological lesions in the liver, forestomach, bone marrow, kidneys and/or spleen were noted in rats exposed to 62.5 ppm or more test material.

Test substance : The purity of the test material (ethylene glycol butyl ether, CAS No. 111-76-2) was > 99%.

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

Flag : Critical study for endpoint.

19.02.2002 (59)(60)

Species : mice

Sex : male/female

Strain	:	B6C3F1
Route of admin.	:	inhalation
Exposure period	:	14 weeks
Frequency of treatment	:	6 hrs and 12 minutes per day, 5 days per week
Post obs. period	:	
Doses	:	31, 62.5, 125, 250, 500 ppm
Control group	:	yes
NOAEL	:	< 31 ppm
LOAEL	:	31 ppm
Method	:	other
Year	:	2000
GLP	:	yes
Test substance	:	other TS
Remark	:	This study is appropriate for EGBEA because glycol ether acetates rapidly hydrolyze to their corresponding glycol ethers in vivo.
Result	:	Survival: Two males and two females exposed to 500 ppm died and two males and two females were killed moribund during the first two weeks of the study. All other mice survived until the end of the study. Body weights: The final mean body weights and body weight gains of males exposed to > = 125 ppm were significantly less than control. Final weights of males exposed to 125, 250 or 500 ppm were 94%, 94% and 88% of control. There was no effect of treatment on female body weight. Clinical signs: Clinical findings were observed only in animals exposed to 500 ppm that died or were killed moribund, and included abnormal breathing, red urine stains and lethargy. Hematological data: A concentration-dependent anemia, evidenced by decreases in hematocrit, hemoglobin and erythrocyte counts occurred in males exposed to > = 125 ppm . All exposed groups of females also had decreased erythrocytes and hemoglobin, and females exposed to > = 125 ppm had decreased hematocrits. Reticulocyte counts were increased in males and females exposed to > = 125 ppm. The morphologic classification was normocytic and normochromic since there was no change in mean cell volume or mean cell hemoglobin concentration. Platelet counts increased in males exposed to 500 ppm and females exposed to >= 250 ppm. Microscopic evaluation of blood smears showed increased numbers of polychromatophilic erythrocytes. Organ weights: Absolute and relative liver weights of males exposed to 500 ppm and relative liver weights of males exposed to 250 ppm and females exposed to 500 ppm were greater than control. Histopathologic changes: Animals that died or were killed moribund exhibited several changes. One to three male mice had ulceration and necrosis of the forestomach. Three female male mice had full wall thickness forestomach necrosis, and one female had an ulcer in the glandular stomach. Acute inflammation surrounded the necrotic or ulcerative lesions. Supprative inflammation was present in the peritoneum of 2 males and on the mediastinal pleura of 2 males and 2 females. These lesions were considered to be secondary to gastric ulceration and/or necrosis. Lymphoid atrophy of the spleen, thymus and lymph nodes occurred in all 2-4 males and 2- 3 of the females. Renal cortical degeneration and some necrosis were noted in all 4 males and 3 out of the four females. The types of lesions found in animals that survived to study termination were similar between males and females. Epithelial hyperplasia and of the

muscularis or serosa of the forestomach occurred in females exposed to > = 125 ppm (N = 9, 10 and 4 survivors of exposure to 125, 250 and 500 ppm). Inflammation of the forestomach was noted in 2, 4, and 4 survivors of exposure to 125, 250 and 500 ppm. Two males exposed to 500 ppm had epithelial hyperplasia of the forestomach, but no inflammation. Hemosiderin pigmentation of the spleen was found in all males exposed to > = 125 ppm and all females exposed to > = 250 ppm. Hematopoetic cell proliferation was found in 2/10, 9/10 and all males exposed to 125, 250 or 500 ppm, and 1/10 and all females exposed to 250 or 500 ppm. Hemosiderin pigmentation was observed in Kupffer cells in the livers of all males exposed to 500 ppm and all females exposed to > = 250 ppm. Hemosiderin pigmentation was increased in 5/6 males and all females exposed to 500 ppm.

The NOAELs in males and females were 62.5 ppm and < 31 ppm, respectively. At 31 and 62.5 ppm, the only changes observed were slight decreases in hemoglobin and erythrocytes ($p < 0.05$) in females.

Test condition : Animals: The mice were approximately 4 weeks old on receipt from the supplier (Taconic Laboratory Animals and Service, Germantown, NY). They were quarantined for 11-12 days before use. Five animals per sex were randomly selected for parasite evaluation and gross examination for evidence of disease. At the end of the study, serologic analyses were performed on 5 sentinel rats/sex. Water and food were available ad libitum (except during exposure, when food was withheld).

Vapor generation: The test material was held in a stainless-steel reservoir under a nitrogen blanket. The material was pumped into a glass column filled with glass beads and heated by a flexible electric heat tape encircling the column. Vapor temperature was monitored at the top of the condenser column by a temperature sensor. The vapor-laden air was transferred through a heated Teflon distribution line and diluted with HEPA- and charcoal-filtered air. Three-way valves in the chamber inlet ducts allowed vapors to be diverted to the exhaust until a stable concentration of test material was built up in the distribution line. At each chamber, vapor moving through the inlet duct was further diluted with filtered air to the appropriate concentration of test material. The total active mixing volume of each chamber was 1.7 m3. A small particle detector was placed in the chambers to measure concentrations of aerosol. No particle counts above the minimum resolvable level (200 particles/cm3) were detected.

Chamber concentrations were monitored with an on-line gas chromatograph (GC). The monitor was coupled with the inhalation chambers by a computer-controlled 12-port stream select valve. The GC was calibrated by comparing chamber concentration data to data from grab samples analyzed by an off-line GC. The grab samples were collected in bubblers containing water. The off-line GC was calibrated with gravimetrically prepared standards. Chamber concentration uniformity was maintained throughout the study.

Buildup and decay rates for chamber concentrations were determined with and without animals in the chambers. The time to achieve 90% of the target concentration and the time for decay to 10% of the target concentration was 12.5 minutes. Studies of 2-butoxyethanol degradation and monitoring for impurities were conducted throughout the studies by comparing bubbler samples to a reference sample. No significant degradation was observed during the studies.

Chambers were maintained at 23.9 – 24.3 degrees C, at a relative humidity of 55-56%, and under a 12 hour light/dark cycle. There were 15

air changes per hour.

Study conduct: Groups of 10 animals/sex were exposed to 0, 31, 62.5, 125, 250 or 500 ppm test material by inhalation, 6 hours and 12 minutes per day, 5 days per week for 14 weeks. Clinical observations were recorded weekly. Animals were weighed initially, weekly, and at the end of the study.

At the end of 14 weeks, mice were anesthetized and blood was withdrawn from the retroorbital plexus. Blood for hematology determinations [erythrocyte, platelet and total and differential leukocyte counts, hematocrit, hemoglobin concentration, mean cell volume, mean cell hemoglobin (and hemoglobin concentration), morphological assessment of erythrocytes, platelets and leukocytes and nucleated erythrocyte counts was placed in tubes containing the anticoagulant potassium EDTA. Smears made from preparations of equal volumes of new methylene blue and whole blood were incubated to 20 minutes and examined microscopically for numbers of reticulocytes.

Necropsies were performed on all animals. The heart, right kidney, liver, lungs, right testis, and thymus were weighed. These tissues plus the adrenal gland, bone and marrow, brain, clitoral gland, esophagus, gallbladder, kidney, large intestine (cecum, colon, rectum), larynx, lymph nodes (mandibular, mesenteric, bronchial, and mediastinal), mammary gland, nose, ovary, pancreas, parathyroid, pituitary gland, preputial gland, prostate, salivary gland, small intestine (duodenum, jejunum, ileum), spleen, stomach (forestomach and glandular), testis (with epididymis and seminal vesicle), thyroid gland, trachea, urinary bladder, uterus and all gross lesions and tissue masses were fixed and preserved in 10% neutral buffered formalin. All tissues collected from rats in the control and 500 ppm animals were processed for microscopic examination. In addition, the kidney, liver, lung, lymph nodes (mandibular and mesenteric), stomach, testis and thymus of low and mid-dose animals were examined. Target organs were identified and a no observable adverse effect level was identified.

Statistical analyses: Organ and body weight and neurobehavioral data were analyzed using the parametric multiple comparison procedures of Dunnett (J Am Stat Assoc 50:1096-1121, 1955) and Williams (Biometrics 27:103-117, 1971 and Biometrics 28:519-531, 1972). Hematology data were analyzed with the nonparametric multiple comparison methods of Shirley (Biometrics 33:386-389, 1977) and Dunn (Technometrics 6:241-252, 1964). Jonckheere's test (Biometrika 41:133-145, 1954) was used to assess the significance of dose-related trends and to determine whether a trend-sensitive test (Williams' or Shirley's test) was more appropriate for pairwise comparisons than a test that does not assume a monotonic dose-related trend (Dunnett's or Dunn's test). Prior to analysis, extreme values were identified by the outlier test of Dixon and Massey (Introduction to Statistical Analysis, McGraw-Hill, 1951, p. 145-147), and implausible values were eliminated from the analyses. Average severity values were analyzed for significance with the Mann-Whitney U test (Nonparametric Statistical Methods, John Wiley and Sons, 1973, p.120-123). Treatment effects were determined by applying a multivariate analysis of variance to the transformed data. The Fisher's exact test was used to analyze histopathological data. The critical values for significance were $p < 0.05$ for body weight data, $p < 0.01$ or 0.05 for hematology data and histopatholgy data.

Conclusion : The NOAELs were 62.5 ppm in males and < 31 ppm in females. Higher concentrations were associated with red blood cell toxicity in mice. Increases in kidney and or liver weights were observed in mice exposed to

250 ppm or more test material. Histological lesions in the liver, forestomach, bone marrow, kidneys and/or spleen were noted in mice exposed to 125 ppm or more test material.

Test substance : The purity of the test material (ethylene glycol butyl ether, CAS No. 111-76-2) was > 99%.

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

Flag : Critical study for endpoint.

19.02.2002 (59)(60)

Species	:	other: rat and rabbit
Sex	:	male/female
Strain	:	other: Wistar (rat) and New Zealand (rabbit)
Route of admin.	:	inhalation
Exposure period	:	10 months
Frequency of treatment	:	4 hr/day, 5 days week
Post obs. period	:	
Doses	:	100 ppm
Control group	:	yes
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	as prescribed by 1.1 –1.4
Remark	:	The results of the study were written to encompass effects noted in both the rat and rabbit. It is appropriate to discuss the effects noted in both species together in one summary since the effects in both species were compared.
Result	:	There was no effect of treatment with butylglycol acetate (BGA) or ethylglycol acetate (EGA) on body weight gain, and no abnormalities were found in urine. No gross pathological lesions were observed in treated animals. Very discrete renal lesions (characterized by a few areas of tubular nephritis with tubular enlargement or atrophy in the cortical zone, inflammatory fibrosis were noted in treated rabbits of the loop of Henle and distal convoluted tubules was observed in both treated rabbits and controls (although less pronounced). Similar changes were noted in the male rat (although even more discrete) along with tubular enlargement with hyaline casts. Some areas of tubular nephrosis were observed in female rats and controls. The numbers of animals affected with any of these lesions were not stated.
Test condition	:	Forty male and female rats (220 to 240 g), divided into 4 groups of either 10 males or 10 females, and four rabbits (2 of each sex, 2.2 to 2.5 kg) were exposed for 4 hours/day, 5 days/week, for 10 months to butylglycol acetate (100 ppm) or ethylglycol acetate 200 ppm) in gas chambers. Test material was placed in a bubbler having a scintered-glass plate in its lower part and diluted to the desired concentration with compressed air which flowed through a lateral inlet pipe under the glass plate. Concentrations were verified daily by weighing the remaining amount of solvent. Ten male and ten female rats and two male and two female rabbits were exposed to air only (controls). Weights were recorded before dosing and weekly. The presence of blood, protein, glucose, ketone bodies and nitrites in the urine and urine pH was measured with test strips (times not indicated). Red and white blood cells in urine were counted with a Coulter counter. Hemoglobin was also measured. All animals were necropsied following death or termination. Heart, lungs, liver, spleen, pancreas, kidneys, adrenals, ovaries, bladder, skin, brain, eyes, stomach and testes were fixed and examined histologically.
Test substance	:	Butylglycol acetate came from Pfaltz & Bauer, Flushing, New York. Purity

was not noted. Purity of ethylglycol acetate was >= 99%.

Reliability : (4) not assignable. Endpoints measured are not up to current standards for repeated dose studies. Only one concentration was tested. No statistical analyses were performed on data for kidney lesions. It is difficult to discern from the data whether the doses of BGA or EGA administered had any significant effect.

(74)

Species : other: rat and rabbit
Sex : male/female
Strain : other: Wistar (rat), New Zealand (rabbit)
Route of admin. : inhalation
Exposure period : 1 month
Frequency of treatment : 4 hr/day, 5 days/week
Post obs. period : 1 week
Doses : 400 ppm
Control group : yes
NOAEL : < 400 ppm
Method : other
Year : 1979
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : The results of the study were written to encompass effects noted in both the rat and rabbit. It is appropriate to discuss the effects noted in both species together in one summary since the effects in both species were compared.
Result : There were no differences in body weight gain between treated and untreated animals. From Week 2 of exposure onwards, animals started showing hemoglobinuria and/or hematuria (slight in rats and more pronounced in rabbits). Red blood cell counts decreased in rabbits after 3 weeks of exposure. The two rabbits with the lowest red blood cell counts (avg. 2.5E 12 /liter) and hemoglobin values (avg. 3.4 mmol/liter) died during week 4. At necropsy, their kidneys were hypertrophic and swollen with blood. Kidneys of exposed female rats exhibited tubular nephrosis ranging from a simple cellular cloudy swelling to hemorrhagic necrosis. The numbers of animals affected with kidney lesions were not stated. No significant findings were noted in kidneys of exposed male rats or females allowed to recover for 1 week. All rabbits showed necrotizing tubular nephrosis, atrophic tubular dilation and luminar granular deposits.
Test condition : Forty male and female rats (220 to 240 g), divided into 4 groups of either 10 males or 10 females, and four rabbits (2 of each sex, 2.2 to 2.5 kg) were exposed for 4 hours/day, 5 days/week, for 1 month to a saturated air-vapor mixture of butylglycol acetate (BGA; approximately 400 ppm) in gas chambers. Test material was placed in a bubbler having a scintered-glass plate in its lower part and compressed air (1000 liters/hr) flowed through a lateral inlet pipe under the glass plate. The air was saturated with BGA or EGA by bubbling through the solvent and was brought into the chamber through a glass tube. Ten male and ten female rats and two male and two female rabbits were exposed to air only (controls).

Weights were recorded before dosing and weekly. The presence of blood, protein, glucose, ketone bodies and nitrites in the urine and urine pH was measured with test strips (times not indicated). Red and white blood cells in urine were counted with a Coulter counter. Hemoglobin was also measured. Two-thirds of the rats were euthanized at the end of the experiment. The other animals were allowed to recover 1 week before euthanization. All animals were necropsied following death or termination. Heart, lungs, liver, spleen, pancreas, kidneys, adrenals, ovaries, bladder, skin, brain, eyes, stomach and testes were fixed and examined

histologically.

Test substance : Butylglycol acetate came from Pfaltz & Bauer, Flushing, New York. Purity was not noted.

Reliability : (4) not assignable. Endpoints measured are not up to current standards for repeated dose studies. Only one concentration was tested.

(74)

Species : rat
Sex : no data
Strain : no data
Route of admin. : inhalation
Exposure period : 4 Wochen [4 weeks]
Frequency of treatment : 5 Appl. pro Woche [per week] / 6 Std. Taeglich [daily]
Post obs. period : keine Angabe [no results]
Doses : 2,3 mg/l; 10 Tiere [animals]
Control group : no data specified
Method :
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Result : Von den 10 eingesetzten Ratten starben bis zur 10. Inhalation vier Tiere. Apathie, Seitenlage, beschleunigte Atmung und Anaemie lagen vor. Haemoglobinabfall und Hb-urie waren zunaechst deutlich normalisierten sich in der 2. Haelfte des Versuchs wieder, wobei weibliche Tiere einen staerkeren initialen Haemoglobinabfall aufwiesen als maennliche. Die Sektion ergab keinen charakteristischen Befund. [Of the 10 dosed rats, 4 animals died up to the 10^{th} exposure by inhalation. Apathy, laying on the side, rapid breathing and anemia were observed. Reduced hemoglobin and hemoglobin in the urine were initially clearly observed, but were normalized in the 2^{nd} half of the experiment. Female animals demonstrated a stronger initial hemoglobin decrease than male animals. Autopsy gave no characteristic result].
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.

(7)

Species : Mouse
Sex : no data
Strain : no data
Route of admin. : Inhalation
Exposure period : 4 Wochen [weeks]
Frequency of treatment : 5 Appl. pro Woche [per week], 6 Std. Taeglich [hours daily]
Post obs. period : keine Angabe [no findings]
Doses : 2,3 mg/l; Es waren je 20 Maeuse im Versuch. [20 Mice were used in the study].
Control group : other: Luft [air]
Method :
Year :
GLP : No
Test substance : as prescribed by 1.1 – 1.4
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Result : Klinische Symptome waren nicht zu sehen, Haemoglobinurie lag nicht vor.

Von der 4. bis zur 15. Exposition starben 6 von 20 Maeusen der exponierten Gruppe, in der Kontrollgruppe starben ebenfalls 8 von 20 Maeusen. Die Sektion ergab keine Besonderheiten. [Clinical symptoms were not observed. Hemoglobin in the urine was not observed. From the 4th to the 15th exposure, 6 of 20 mice of the exposed group died. Eight of 20 controls died. Autopsy gave no particular observations].

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(7)

Species : rabbit
Sex : no data
Strain : no data
Route of admin. : Inhalation
Exposure period : 4 Wochen [weeks]
Frequency of treatment : 5 Appl. pro Woche [per week], 6 Std. Taeglich [daily]
Post obs. period : keine Angabe
Doses : 2,3 mg/l; 3 Tiere [animals]
Control group : no data specified
Method :
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Result : Die 3 Kaninchen stammten aus einem akuten Inhalationsversuch mit einmaliger Exposition von 3 mg/l ueber 6 Std. Die Tier starben nach 4 bzw. 11 Expositionen. Zunaechst trat starke Haemoglobinurie auf. Nach mehreren Inhalationstagen sanken Haemoglobin und Haematokrit stark ab. Neben einem haemolytischen Ikterus zeigte die patholog. Untersuchung vielfaeltigste Befunde. [The 3 rabbits came from an acute inhalation study with one-time exposure of 3 mg/l over 6 hours. The animals died after 4-11 exposures. At first pronounced hemoglobinuria was observed. After several inhalation sessions hemoglobin and hematocrit decreased strongly. Beside a hemolytic icterus, the pathological examination showed multifold remarkable findings].
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.

(7)

Species : rabbit
Sex : no data
Strain : no data
Route of admin. : gavage
Exposure period : 5 Wochen weeks
Frequency of treatment : max. 5 Appl. pro Woche (insgesamt 25 mal) [5 applications per week (25 applications in all)]
Post obs. period : Keine [none]
Doses : 0,2 ml/kg entspr. 186 mg/kg [0.2 ml/kg, corresponding to 186 mg/kg; 3 animals]
Control group : no data specified
Method :
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : All information (except the reliability rating) came from an IUCLID

document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Result : Es waren 3 Tiere im Versuch, die im akuten Toxizitaetsversuch bereits 0,2 ml/kg erhalten hatten. Klinische und klinisch- chemische Parameter waren nicht veraendert, die Bestimmung der osmotischen Resistenz der Erythrozyten war normal. Gegen Ende des Versuchs war der Haematokrit geringfuegig erniedrigt. Pathologische Veraenderungen waren weder in der Sektion noch bei der Histologie zu sehen. [Three animals in the study had already been exposed to 0.2 ml/kg in a prior acute toxicity study. Clinical and clinical/chemical parameters were not changed. Osmotic resistance of the erythrocytes were normal. Toward the end of the study the hematocrit was insignificantly reduced. Pathological changes were seen neither in the autopsy nor the histology].

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(9)

Species : cat
Sex : no data
Strain : no data
Route of admin. : inhalation
Exposure period : 4 Wochen [weeks]
Frequency of treatment : 5 Appl. pro Woche [per week], 6 Std. taeglich [daily]
Post obs. period : keine Angabe [no data]
Doses : 2,3 mg/l; 3 Tiere [animals]
Control group : no data specified
Method :
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Result : Es waren 3 Katzen im Versuch, die bereits vorher im akuten Versuch einer einmaligen Exposition von 6 Std. und 3 mg/l unterzogen worden waren. Zunaechst traten Speichelfluss, Brechreiz und beschleunigte Atmung auf. Der vorruebergehende Haemoglobinabfall von bis zu 45 % normalisierte sich nach der 9.Inhalationsexposition. Haemoglobinurie oder gestoerte Leberfunktion war nicht festzustellen. [Three cats in the study had already been exposed in a prior acute study one time for six hours at 3 mg/l. Soon after exposure began salivation, nausea and rapid breathing occurred. The decrease in hemoglobin count was up to 45% but then normalized toward the 9^{th} exposure session. Hemoglobin in the urine or disturbed liver function was not observed].

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(7)

Species : cat
Sex : no data
Strain : no data
Route of admin. : gavage
Exposure period : 5 Wochen [weeks]
Frequency of treatment : max. 5 Appl. pro Woche (insgesamt 25 Appl.) [max. 5 Appl per week (25 total exposure sessions)]
Post obs. period : 2 - 3 Wochen weeks

Doses	:	0,2 ml/kg entspr. 186 mg/kg; 2 Tiere [0.2 ml/kg corresponding to 186 mg/kg; 2 animals]
Control group	:	no data specified
Method	:	
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Result	:	Es waren 2 Katzen, die im akuten Versuch bereits einmalig 0,2 ml/kg erhalten hatten, im Versuch. Es wurde zeitweilig Erbrechen sowie Stoerung des Gleichgewichtes beobachtet. Gegen Ende der Behandlung war ein Absinken der Erythrozytenzahl sowie des Haemoglobins um etwa 30 - 50 % zu sehen. Nach zwei bis drei Wochen normalisierten sich die Blutparameter. Die osmotische Resistenz der Erythrozyten war normal. [Two cats in this study had already been exposed one time in a prior acute study to 0.2 mg/kg. Nausia as well as disturbance of the equilibrium were observed. Toward the end of the treatment a reduction of the erythrocyte count as well as hemoglobin count of about 30-50% was observed. After 2-3 weeks the blood parameters normalized. The osmotic resistance of the erythrocytes was normal].
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(9)

Species	:	guinea pig
Sex	:	no data
Strain	:	no data
Route of admin.	:	Inhalation
Exposure period	:	4 Wochen [weeks]
Frequency of treatment	:	5 Applikationen pro Woche, 6 Std. taeglich [5 applications per week, six hours daily]
Post obs. period	:	keine Angabe [no data]
Doses	:	2,3 mg/l; 10 Tiere [animals]
Control group	:	no data specified
Method	:	
Year	:	
GLP	:	No
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Result	:	Von den 10 eingesetzten Meerschweinchen waren 8 bereits im akuten Inhalationsversuch 3 mg/l ueber 6 Std. Exponiert gewesen. Es trat keine toxische Wirkung bezueglich klinischer, klinisch-chemischer Parameter sowie in der patholog. Untersuchung zutage. [Eight of the 10 guinea pigs used in this study had already been exposed in a prior acute inhalation study to 3 mg/l over 6 hours. No toxic effects or clinical chemical changes were seen in this four week study].
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(7)

5.5 GENETIC TOXICITY 'IN VITRO'

Type	:	Ames test
System of testing	:	S. typhimurium strains TA100, TA1535, TA1537, TA97, TA98.
Concentration	:	0, 100, 333, 1000, 3333 or 10000 micrograms/plate
Cytotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	OECD Guide-line 471 "Genetic Toxicology: Salmonella typhimurium Reverse Mutation Assay"
Year	:	1993
GLP	:	yes
Test substance	:	other TS: ethylene glycol monobutyl ether (CAS No. 111-76-2), purity > 99%
Result	:	The numbers of mutant colonies in controls in the absence of S-9 were 164 +/- 5.5 for TA 100, 30 +/- 4.9 for TA1535, 11 +/- 3.2 for 1537, 180 +/- 15.1 for TA97 and 25 +/- 2.3 for TA98. Addition of S-9 had no significant effect on control mutation indices (with the exception of a decrease from 30 +/- 4.9 to 12-14 in TA1535 with 10-30% rat or hamster S-9 and an increase from 25 +/- 2.3 to 40 +/- 0.6 in TA98 with 30% rat S-9). Treatment with test material had no effect on the number of mutant colonies in the presence or absence of S-9. The number of mutant colonies ranged from 112-169 for TA 100 with or without S-9, from 22-39 for TA1535 without S-9 and from 7-14 for TA1535 with S-9, from 9-14 for 1537 with or without S-9, from 130-215 for TA97 with or without S-9, and from 11-33 for TA98 with or without hamster S-9 or 10% rat S-9 and from 34-42 for TA98 with 30% rat S-9. Positive controls induced at least a 2-fold increase in the number of mutant colonies.
Test condition	:	Testing was performed according to the method of Zeiger et al. Environ. Mol. Mutagen. 19:2, 1992. Test material was incubated with S. typhimurium strains TA97, TA98, TA100, TA1535 and TA1537 either in buffer or S9 mix from Aroclor 1254-induced male Sprague Dawley rat or Syrian hamster liver for 20 minutes at 37 degrees C. Top agar supplemented with L-histidine and d-biotin was added, and the contents were mixed and poured onto the surfaces of minimal glucose agar plated. Histidine-independent mutant colonies were counted following incubation for 2 days at 37 degrees C. Each trial consisted of triplicate plates of concurrent positive and negative (solvent) controls and 5 concentrations (100, 333, 1000, 3333, 10000 micrograms/plate) of test material. The positive controls were sodium azide (for TA100 and TA1535), 9-aminoacridine (for TA97 and TA1537), and 4-nitro-o-phenylenediamine (TA98) in the absence of S9 and 2-aminoanthracene for all strains in the presence of S9. Concentrations of positive controls were not listed. A positive response was defined as a reproducible, dose-dependent increase in colonies in any one strain. An equivocal response was an increase that was not dose-related, reproducible or was not of sufficient magnitude to support a determination of mutagenicity. There was no minimum percentage or fold increase required for a chemical to be judged positive or weakly positive.
Test substance	:	Aldrich Chemical Co, >99% pure
Reliability	:	(2) valid with restrictions. Guideline study with acceptable restrictions.
Flag	:	Supporting study for mutagenicity endpoint

(59)(60)(86)

Type	:	Ames test
System of testing	:	S. typhimurium strains TA97a, TA98, TA100, TA102
Concentration	:	up to 14,000 micrograms/plate
Cytotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	positive
Method	:	other
Year	:	1995
GLP	:	
Test substance	:	other TS: ethylene glycol monobutyl ether (CAS No. 111-76-2), purity = 99%.
Remark	:	The material was positive in TA97a at 2200 micrograms/plate without rat liver S9 and at 4400 micrograms/plate with S9, and negative in all other strains
Reliability	:	(4) not assignable. The primary reference was not available for review. (45)

Type	:	Ames test
System of testing	:	S. typhimurium strains TA97a, TA100, E. coli WP2uvrA
Concentration	:	up to 10,000 micrograms/plate
Cytotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1996
GLP	:	
Test substance	:	other TS: ethylene glycol monobutyl ether (CAS No. 111-76-2), purity = 99.04%.
Remark	:	The material was negative in all strains with and without S9.
Reliability	:	(4) not assignable. The primary reference was not available for review. (38)

Type	:	Ames test
System of testing	:	S. typhimurium strains TA98, TA100, TA1535, TA1537, TA1538
Concentration	:	0.3 to 15 micrograms/plate
Cytotoxic conc.	:	10 mg/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1985
GLP	:	yes
Test substance	:	other TS: ethylene glycol monohexyl ether (CAS No. 112-25-4)
Result	:	Test concentrations did not deviate more than 2.5% from stated concentrations. In the tests without metabolic activation, toxicity was observed at 15 and 10 mg/plate in all strains. In the tests without metabolic activation, toxicity was found at 15 mg/plate with all strains, and at 10 mg/plate in strains TA98, TA1537 and TA1538. The number of mutant colonies in negative controls ranged from an average of 6 (TA1537 without activation) to 140 (TA100 without activation). Tests were valid, as positive controls induced anywhere from 83 (TA1535 with activation) to 1847 colonies (TA1535 without activation). The number of colonies observed in cultures treated with nontoxic concentrations of test material ranged from 4 (in TA1537 without metabolic activation) to 139 (TA100 with activation). No concentration of test material induced a 2-fold increase in the number of mutant colonies (with respect to control) in any

system.

Test condition : The test substance was dissolved in ethanol to a concentration of 300 mg/ml. All subsequent dilutions were made in ethanol on each day of testing. Dilutions were made so that 50 microliters would deliver the required dose. All dilutions were gravimetrically analyzed.

A preliminary toxicity test was performed with strain TA100 to determine concentrations to use in the test. Test chemical was added at five doses chosen to span a range that included nontoxic to moderately toxic concentrations (0.3, 1, 3, 10 and 15 mg/plate). All concentrations were tested in triplicate. Since this test showed that 100 microliters of ethanol vehicle was toxic, test material (and vehicle) was added in 50 microliter aliquots. The following positive controls (0.01 mg) were tested: 4-nitro-o-phenylenediamine (TA98 and TA 1538 without activation), sodium azide (TA100 and TA1535 without activation), 9-aminoacridine (TA1537 without activation), and 2-aminoanthracene (all strains with activation). Sterility checks were run concurrently.

S-9 liver homogenate was prepared from Aroclor 1254-induced Sprague-Dawley male rats. For tests with metabolic activation, 0.5 ml of S-9 mix containing 50 microliters of S9 was added per plate. For tests without metabolic activation, 50 microliters of phosphate buffered saline were added.

Treated cultures were incubated for 48-72 hours (temperature not stated). Colonies were counted using standard methods. The criterion for a positive result was at least a 2-fold, dose-dependent increase in the number of mutant colonies compared to the control.

Test substance : Purity of test substance was 98.4% (by weight).
Reliability : (1) valid without restriction. The study is comparable to a guideline study.
Flag : Supporting study for mutagenicity endpoint

(57)

Type : HGPRT assay
System of testing : CHO cells
Concentration : up to 1% (v/v) without S9 and 0.5% (v/v) with S9
Cytotoxic conc. :
Metabolic activation : with and without
Method : other
Year : 1989
GLP :
Test substance : other TS: ethylene glycol monobutyl ether (CAS No. 111-76-2), purity = 99.44%.
Remark : The material was negative with and without S9.
Reliability : (4) not assignable. The primary reference was not available for review.

(68)

Type : HGPRT assay
System of testing : V79 cells
Method : other
Year : 1996
Test substance : other TS: ethylene glycol monobutyl ether (CAS No. 111-76-2), purity = 99%.
Remark : Using the same cells, these investigators reported an increase in sister chromatid exchanges at 15-25 mM, a small increase in micronuclei (2-fold) at 8 and 16 mM, increases in mitotic division and aneuploidy at 8 and 16 mM, inhibition of cellular communication at 8-34 mM, but no increase in chromosomal aberrations. In the same reference the investigators report a negative cell transformation test in Syrian hamster embryo cells at up to 8 mM, and a negative bone marrow micronucleus test in CD-1 mice at up to

800 mg/kg.
Result : The result was positive over a concentration of 20-75 mM.
Reliability : (4) not assignable. The primary reference was not available for review. (33)

Type :
System of testing : CHO AS52 cells
Concentration : up to 0.1% (v/v), 7.6 mM
Cytotoxic conc. :
Metabolic activation :
Method : other
Year : 1989
GLP :
Test substance : other TS: ethylene glycol monobutyl ether (CAS No. 111-76-2), purity was not listed
Remark : The cell line was constructed to detect gene mutation and clastogenic events.
Result : The material was negative. The concentration tested produced cell toxicity.
Reliability : (4) not assignable. The primary reference was not available for review. (21)

Type : Cytogenetic assay
System of testing : Chinese hamster ovary (CHO) cells
Concentration : 2513, 3750 and 5000 micrograms/ml (21.2 to 42 mM based on a MW of 118.17)
Cytotoxic conc. :
Metabolic activation : with and without
Result : negative
Method : other: Galloway, S.M. et al. (1987). Environ. Mol. Mutagen. 10(Suppl10), 1-175
Year : 1987
GLP : yes
Test substance : other TS: ethylene glycol monobutyl ether (CAS No. 111-76-2)
Remark : Butoxyethanol induced cell cycle delay but not chromosomal aberration.
Result : The results of the first experiment (with a 10.5 hour harvest time) were negative. Since the test material caused a significant cell cycle delay, there was not a sufficient number of first-division metaphase cells at harvest. Therefore, the experiment was repeated with an increased incubation time prior to the addition of colcemid. The results of this experiment (20.5 hour harvest time) were positive at 5000 micrograms/ml (7 % of cells with aberrations vs. 0 % in controls) but did not show a dose response relationship. An additional test with a similar harvest time (20.7) as the second test was negative.

Mitomycin C caused a dose-dependent increase in the percentage of cells with aberrations all tests without S-9 (with the exception of test 2, which showed an inverse relationship of aberrations with dose). It was thought that the doses of mitomycin C were mislabeled in this experiment. Cyclophosphamide induced a dose-dependent increase cells with aberrations in the experiment with S-9. Therefore, the test was valid.

The types of aberrations observed were not listed.
Test condition : Testing was performed as reported by Galloway et al. Environ Mol Mutagen 10(Suppl 10):1-175, 1987. Test material was tested in cultured Chinese hamster ovary cells for induction of chromosomal aberrations in the presence and absence of Aroclor 1254-induced male Sprague Dawley rat liver S9 and cofactor mix. Each test consisted of concurrent solvent and positive controls [mitomycin C without S-9 (0.25 and 0.75 micrograms/ml in trial 1 and 0.05 and 0.08 micrograms/ml in trials 2 and 3) and cyclophosphamide with S-9 (7.5 and 37.5 micrograms/ml)] and three

concentrations of test material (2513, 3750 and 5000 micrograms/ml). The highest dose used was one that produced some cytotoxicity (% lethality was not listed). One test per dose was conducted, and tests yielding equivocal or positive results were repeated.

In the tests without S-9, cells were incubated with test material for 8.5 hours. Colcemid was then added and the incubation was continued for 2 hours. For the test with S-9, cells were treated with test material and S9 for 2 hours, after which the medium was removed. Cells were then incubated for 8.5 hours in fresh medium, with colcemid present for the last 2 hours. All cells were harvested by mitotic shake-off, fixed and stained with Giemsa. The incubation period was extended if cell cycle delay was anticipated.

Cells were selected for scoring based on good morphology and completeness of karyotype (21 +/- 2 chromosomes). All slides were scored blind and those from a single test were read by the same person. One or two hundred first-division metaphase cells were scored at each dose level. Classes of aberrations included simple (breaks and terminal deletions), complex (rearrangements and translocations), and other (pulverized cells, despiralized chromosomes, and cells containing 10 or more aberrations).

Statistical analyses were conducted on both the dose response curve and individual dose points. A linear regression trend test vs. the log of the dose was used. For a single trial, a significant difference for one dose point ($p < 0.05$) and a significant trend ($p < 0.015$) were considered weak evidence for a positive response. Significant differences for 2 or more doses indicated a positive response. A positive trend test in the absence of a significant increase at any one dose was considered equivocal.

Reliability : (2) valid with restrictions. Purity of the test material was not given.
Flag : Supporting study for chromosomal aberration endpoint
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Type : Cytogenetic assay
System of testing : Chinese Hamster Ovary Cell
Concentration : 0.1 to 0.4 mg/ml (without activation); 0.08 to 0.4 mg/ml (with activation)
Cytotoxic conc. : 0.8 mg/ml
Metabolic activation : with and without
Result : negative
Method : other
Year : 1985
GLP : yes
Test substance : other TS: ethylene glycol monohexyl ether (CAS No. 112-25-4)
Result : The percentage of aberrant cells in cultures treated with vehicle, 0.1, 0.2 or 0.4 mg/ml test material for 6 hours in the absence of activation was 4 +/- 0, 2 +/- 0, 4 +/- 2.83, and 5 +/- 1.41, respectively (no significant difference). The values obtained after 10 hours of incubation were 1+/- 1.41, 2 +/- 2.83, 4 +/- 0 , and 4 +/- 2.83, respectively (no significant difference). The positive control (TEM) induced 26% of cells to be aberrant after a 6-hour incubation period (tests at 10 hours were not performed).

The percentage of aberrant cells in cultures treated with vehicle, 0.08, 0.1 or 0.2 mg/ml test material for 6 hours in the presence of activation was 5 +/- 1.41, 2 +/- 2.83, 4 +/- 2.83, and 3 +/- 4.24 respectively (no significant difference). The values obtained after 10 hours of incubation with vehicle, S-9 homogenate and 0.2, 0.3 or 0.4 mg/ml test material were 4 +/- 0, 2 +/- 2.83, 3 +/- 4.24, and 3 +/- 1.41, respectively (no significant difference). The positive control (cyclophosphamide) induced 26% of cells to be aberrant after a 6 -hour incubation period (tests at 10 hours were not

performed).

There also was no significant difference in the types of aberrations found between treated and negative control cells. Most aberrations were chromatid breaks or gaps.

Test material did not induce an increase in aberrations. The test was valid, as control incidences were within historical limits, and the positive controls induced a significantly greater percentage of aberrants than controls.

Test condition : S-9 liver homogenate was prepared from Aroclor 1254-induced, male Sprague-Dawley rats and was screened for metabolic activity by the supplier. Typically, 1.0 of a complete metabolic activation system (including S-9 and cofactors) was added to each 4.0 ml of culture medium.

CHO-K1-BH4 (subclone D1) cells were passed once after receipt and were frozen in liquid nitrogen. Stock cultures were prepared from cells thawed at approximately 1- to 2-month intervals. Cells used in tests without S-9 were from passage 7 after thawing, and cells used with S-9 were from passage 3.

Dilutions of test chemical were made in ethanol immediately prior to testing and were verified by gravimetric analyses. Cells (5 x 10E5) were exposed to the highest 3 concentrations of test material that were shown in a preliminary experiment not to produce excessive mitotic inhibition (0.1, 0.2 or 0.4 mg/ml without S-9 or 0.08, 0.1 or 0.2 mg/ml with S-9 in 6 hr experiment or 0.2, 0.3, and 0.4 mg/ml with S-9 in 10-hour experiment) or appropriate positive (15 micrograms/ml cyclophosphamide and triethylenemelamine) and negative (0.5% ethanol) controls for 6 or 10 hours, and harvested. For experiments with metabolic activation, cells were preexposed to test chemical and S-9 for two hours, rinsed, and incubated for an additional 4 or 8 hours. Colchicine was added during the last two hours. Tests were duplicated. The incubation temperature was not listed.

Chromosomes were prepared using standard procedures. A total of 50 cells/culture/harvest interval was examined for chromosome damage. The incidence of chromosome damage was determined for the highest 3 doses that did not produce excessive inhibition of cell division. The number of chromatid and chromosome aberrations, and the total number of aberrations per 50 cells examined (with and without including gaps in the total) were determined.

The Fisher's Exact Test (one-tailed) was used to analyze data. A test was considered positive if a value for at least one test concentration was different from control at the $p < 0.05$ level, and there was evidence of a concentration-dependent effect or reproducibility between duplicate cultures.

A positive effect of treatment was one that caused a statistically significant, dose-related increase in the frequency of structural chromosomal aberrations. A statistically significant effect for at least one dose level that is reproduced in both cultures was considered to be equivocal. A single positive effect in 1 of 2 cultures per dose level was evaluated with respect to the historical control data to help determine possible biological significance.

Test substance : Test sample was 98.4% pure (by weight). Impurities were 0.045% water, 0.62% N-hexanol and 0.68% N-octanol.

Reliability : (1) valid without restriction. The study is comparable to a guideline study.

Flag : Supporting study for chromosomal aberration endpoint

(42)

Type	:	Sister chromatid exchange assay
System of testing	:	Chinese hamster ovary (CHO) cells
Concentration	:	500-5000 micrograms/ml (4.2 to 43.1 mM based on MW of 118.7)
Cytotoxic conc.	:	
Metabolic activation	:	with and without
Result	:	negative
Method	:	other: Galloway, S.M. et al. (1987). Environ. Mol. Mutagen. 10(Suppl 10) 1-175.
Year	:	1987
GLP	:	yes
Test substance	:	other TS: ethylene glycol monobutyl ether (CAS No. 111-76-2)
Remark	:	The highest test concentrations were toxic in systems without metabolic activation but not in the presence of S9.
Result	:	The time in BrdU was lengthened to 31 (test 1) and 36 hours (test 2) for cells incubated with test material in the absence of S-9, because the test material induced a delay in cell cycle. The medium and positive control cultures without S-9 and all cultures containing S-9 were incubated for 26 hours. The first test was considered equivocal. Concentrations of 1,510, 2,220 and 3,000 micrograms/ml induced a 0.74 % decrease and 10.33 and 19.01 % increases in sister chromatid exchanges (SCEs) with respect to control. An additional test repeated at higher concentrations was negative. In this test, treatment with 2,500, 3,000 and 3,500 micrograms/ml induced an 11.66, 13.54 and 15.86 % increase in SCEs. The test with S-9 also was negative. The positive controls induced more than a 20%, dose-dependent increase in the number of SCEs. Therefore, the test was valid.
Test condition	:	Test material was tested for induction of sister chromatid exchanges in the presence and absence of Aroclor 1254-induced male Sprague-Dawley rat liver S-9. Cultures were handled under gold lights to prevent photolysis of bromodeoxyuridine-substituted DNA. Each test consisted of concurrent solvent and positive (0.001 and 0.010 micrograms/ml mitomycin C in the 2 tests without S-9 and 0.4 and 2.0 micrograms/ml cyclophosphamide with S-9) controls and three concentrations of test material (1510, 2,220 and 3,000 micrograms/ml in test 1; 2,500, 3,000 and 3,500 micrograms/ml in test 2 and 500, 1,670 and 5,000 micrograms/ml in the test with S-9). The highest test concentrations were toxic in systems without metabolic activation (% lethality was not listed) but not in the presence of S9. A single flask per dose was used, and tests yielding equivocal or positive results were repeated. In the test without S-9, cells were incubated for 26 hours with test material. Bromodeoxyuridine (BrDdU) was added 2 hours after treatment. After 26 hours, the medium was removed and replaced with fresh medium containing BrdU and colcemid (but not test material). After 2 hrs incubation in this medium, cells were harvested by mitotic shake-off, fixed and stained. In the test with S-9, cells were incubated with test material, serum-free medium and S-9 for 2 hours. The medium was then removed and replaced with medium containing serum and BrdU and no test material. Incubation proceeded for an additional 26 hours, with colcemid present for the final 2 hours. Cells were then harvested as previously described. All slides were scored blind and those from a single test were read by the same person. Fifty second-division metaphase cells per dose were scored for sister chromatid exchanges (SCEs). Statistical analyses were conducted on the slopes of the dose-response curves and the individual dose points. A SCE frequency 20% greater than

the solvent control was chosen as a positive response. An increase at only one dose was considered weak evidence of activity and increases at 2 or more doses was considered a positive response. A statistically significant trend ($p < 0.005$) in the absence of any single values being 20% greater than control was considered equivocal.

Reliability : (2) valid with restrictions. The purity of the test material was not listed.
Flag : Supporting study for chromosomal aberration endpoint
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5.6 GENETIC TOXICITY 'IN VIVO'

Type : Micronucleus assay
Species : other: mouse and rat
Sex : male
Strain : other: F344/N (rat) and B6C3F1 (mouse)
Route of admin. : i.p.
Exposure period : 72 hours
Doses : Three doses of 7.03, 14.06, 28.12, 56.25, 112.5, 225, 450 mg/kg (rats) and 17.19, 34.38, 68.78, 137.5, 275, 550 and 1100 mg/kg (mice), separated by 24 hours
Result : negative
Method : other:Shelby et al. 1993. Environ Mol Mutagen 21:160-179.
Year : 2000
GLP : no data
Test substance : other TS: ethylene glycol monobutyl ether (CAS No. 111-76-2)
Result : Two of five rats given 450 mg/kg and all mice given 1,100 mg/kg died. There were no other deaths. No other information about toxicity was given. There was no effect of treatment on the number of micronucleated cells in either rats or mice. The number of micronucleated polychromatic erythrocytes (PCEs)/1000 polychromatic erythrocytes ranged from 1.2-2.2 +/- 0.8 in treated rats (compared to 1.9 +/- 0.2 in controls) and from 2.3-3.8 +/- 0.8 in treated mice (compared to 2.5 +/- 0.2 in controls).

The positive control induced 21.0 +/- 0.4 and 12.9 +/- 1.3 micronucleated PCEs/1000 PCEs in rats and mice, respectively.

Test condition : Published toxicity data were used to select doses. Factors affecting dose selection included solubility, toxicity and the extent of cell cycle delay caused by the material. Male rats and mice (5 animals/group) were injected i.p. 3 times at 24 hours with test material dissolved in phosphate-buffered saline (PBS). Rats were given 7.03, 14.06, 28.12, 56.25, 112.5, 225 or 450 mg/kg and mice were given 17.19, 34.38, 68.78, 137.5, 275, 550 or 1100 mg/kg at each injection). The total dosing volume was 0.4 ml. Negative and positive control animals were injected with the same volume of PBS or cyclophosphamide (7.50 and 10 mg/kg in rats and mice, respectively). The animals were killed 24 hours after the final injection, and blood smears were prepared from bone marrow cells obtained from femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells.

The results were tabulated as the mean of the pooled results from all animals. The frequency of micronucleated cells among PCEs was analyzed by a program that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the solvent control group. In the presence of excess binomial variation (as detected by a binomial dispersion test), the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation.

An individual trial was considered positive if the trend test P value was less than or equal to 0.025 or if the P value for any single dose group was less than or equal to 0.025 divided by the number of dose groups. The magnitude and reproducibility of the effects was taken into consideration when making conclusions about the results.

Reliability : (2) valid with restrictions. Purity of the test material was not listed.
Flag : Supporting study for chromosomal aberration endpoint
19.02.2002 (60)

5.7 CARCINOGENICITY

Species	:	rat
Sex	:	male/female
Strain	:	F344/N
Route of admin.	:	inhalation
Exposure period	:	104 weeks
Frequency of treatment	:	6 hr 12 min per day, 5 days/week
Post. obs. period	:	
Doses	:	31.2, 62.5, 125 ppm
Result	:	
Control group	:	yes
Method	:	other
Year	:	2000
GLP	:	yes
Test substance	:	other TS
Remark	:	This study is appropriate for EGBEA because glycol ether acetates rapidly hydrolyze to their corresponding glycol ethers in vivo. This study was not included in the dossier for EGBE presented at SIAM 6. The changes observed in the respiratory tract were considered to be adaptive. The results from livers from fourteen male mice from the study that were tested for the presence of H. hepaticus were negative. Therefore, it was concluded that the liver lesions were not due to the presence of this pathogen. Reviews and ongoing studies suggest that the findings in this study are of no relevance for human carcinogenic risk. Evidence supporting this conclusion is that 1) ethylene glycol monobutyl ether is not genotoxic and 2) pheochromocytomas in the rat are inducible by a variety of unrelated substances but there are no known chemical inducers of human adrenal medullary tumors (Lynch et al. 1996. Reg Toxicol Pharmacol 23:256-297). The significance of the effects can also be questioned bearing in mind the lack of a clear dose response relationship and the lack of significant difference from the concurrent control. The U.S. EPA in its 1999 IRIS review of EGBE found the tumors in this study "of uncertain relevance" to any human cancer risk (www.epa.gov/iris/subst/0500.htm). Also, a recent reclassification of EGBE under the European Commission process for the reclassification and labeling of dangerous substances confirms a low level of risk for human carcinogenicity and found no support for a category 3 (carcinogen) classification for EGBE (www.esig.org).
Result	:	Survival was not affected by treatment. Mean body weights of females exposed to 125 ppm were generally less than controls. No clinical findings were attributed to treatment. Dose-dependent toxicity to red blood cells was observed (beginning at 31.2 ppm) in males and females, with females being more affected than males. Significant increases in bone marrow cellularity and decreases in the myeloid erythroid ratio relative to

the controls were observed at all time points in females exposed to 125 ppm and a decrease in the myeloid/erythroid ratio was observed in males exposed to 125 ppm at 12 months.

The incidences of combined benign plus malignant pheochromocytomas of the adrenal medulla in females were 3/50 (6%), 4/50 (8%), 1/49 (2%) and 8/49 (16%) in the control, low, medium, and high dose groups, respectively. The incidences of these lesions in the high dose females (16%) was not significantly different from the controls in the study (6%) but exceeded the historical control range (2-13%). A single malignant pheochromocytoma was present at the 125 ppm level. Exposure-related increases in the incidences of hyaline degeneration of the olfactory epithelium were observed in all exposed groups of males and females exposed to 62.5 or 125 ppm. The severity of this lesion was minimal and was not affected by exposure concentration. Two neoplasms were noted in the nose: a chondroma in a 31.2 ppm male and an adenoma in a 62.5 ppm male. These were not considered to be related to treatment. The incidence of Kupffer cell pigmentation was increased in males and females exposed to 62.5 or 125 ppm, and the severity of the lesion was dose dependent. The incidence of splenic fibrosis was increased in males exposed to 62.5 or 125 ppm.

Test condition : Groups of 50 male and 50 female rats (7-8 weeks old) were exposed to test material (0, 31.2, 62.5 or 125 ppm) by inhalation, 6 hours 12 minutes per day, 5 days per week for 104 weeks. Additional groups of 27 animals/sex were exposed to 0, 62.5 or 125 ppm, and 9 animals/sex were exposed to 31.2 ppm for hematology and bone marrow analyses. The rats exposed to 31.2 ppm were evaluated at 3 (hematology only) and 6 months. Nine male and female rats from each of the other exposure groups were evaluated at 3, 6 or 12 months.

All animals were observed twice daily. Body weights and clinical findings were recorded monthly from week 5 through week 89 and every 2 weeks from week 92 until the end of the study.

Complete necropsies and microscopic examinations were performed on all core animals. All organs and tissues were examined for grossly visible lesions. All major tissues (adrenal, bone with marrow, brain, clitoral gland, esophagus, heart, large intestine, small intestine, kidney, larynx, liver, lung, lymph nodes, mammary gland, nose, ovary, pancreas, parathyroid, pituitary, preputial gland, prostate, salivary gland, spleen, stomach, testis, thymus, thyroid, trachea, urinary bladder and uterus) were preserved, sectioned and examined microscopically (blinded).

The probability of survival was estimated by a product-limit procedure. Animals found dead from other than natural causes were not included. Statistical analyses for possible dose-related effects on survival used Cox's method for testing two groups for equality and Tarone's life table test to identify dose-related trends. The poly-k test was used to assess the prevalence of neoplasms and nonneoplastic lesions. Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Organ and body weight data were analyzed with the parametric multiple comparison procedure of Dunnett and Williams. Blood and bone marrow data were analyzed according to the methods of Shirley and Dunn. Jonckheere's test was used to assess the significance of the dose-related trends. Outliers identified by the test of Dixon and Massey were excluded. Average severity values were analyzed by the Mann-Whitney U test. Treatment effects were investigated using a multivariate analysis of variance to transformed data.

Test substance	:	The purity of the test material (ethylene glycol butyl ether, CAS No. 11-76-2) was > 99%.
Conclusion	:	There was no evidence of carcinogenicity in male rats, and equivocal evidence of carcinogenicity in female rats (based on the increased combined incidences of benign or malignant pheochromocytoma (mainly benign) of the adrenal medulla.
Reliability	:	(1) valid without restriction. The study was conducted according to NTP guidelines.

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Species	:	mouse
Sex	:	male/female
Strain	:	B6C3F1
Route of admin.	:	inhalation
Exposure period	:	104 weeks
Frequency of treatment	:	6 hr 12 min per day, 5 days/week
Post. obs. period	:	
Doses	:	62.5, 125 or 250 ppm
Result	:	
Control group	:	yes
Method	:	other
Year	:	2000
GLP	:	yes
Test substance	:	other TS
Remark	:	This study is appropriate for EGBEA because glycol ether acetates rapidly hydrolyze to their corresponding glycol ethers in vivo. This study was not included in the dossier for EGBE presented at SIAM 6. The changes observed in the respiratory tract were considered to be adaptive. The results from livers from fourteen male mice from the study that were tested for the presence of H. hepaticus were negative. Therefore, it was concluded that the liver lesions were not due to the presence of this pathogen. Reviews and ongoing studies suggest that the findings in this study are of no relevance for human carcinogenic risk. Evidence supporting this conclusion is that 1) ethylene glycol monobutyl ether is not genotoxic; 2) the fact that liver neoplasms were only observed in male mice (and not female mice or rats, see above) correlates with the greater sensitivity of male mouse cells to oxidative damage caused by red blood cell hemolysis and hemosiderin (iron) deposition in the liver (Xue et al.1999. Toxicologist 48: Abstract 1084). Because humans are resistant to the hemolytic effects of glycol ethers and have higher liver antioxidant concentrations than mice, they will not develop lesions secondary to the effects on red blood cells and iron deposition in the liver; and 3) the forestomach neoplasms (primarily benign) reported for female mice are most likely the result of chronic irritation. Humans have no organ that is morphologically and functionally comparable to the rodent forestomach, and for nongenotoxic carcinogens, the carcinogenic risk to humans based on forestomach tumor formation is minimal at exposure levels below which irritation of esophageal tissue may occur (Kroes and Wester. 1986. Food Chem Toxicol 24:1083-1089). The U.S. EPA in its 1999 IRIS review of EGBE found the tumors in this study "of uncertain relevance" to any human cancer risk (www.epa.gov/iris/subst/0500.htm). Also, a recent reclassification of EGBE under the European Commission process for the reclassification and labeling of dangerous substances confirms a low level of risk for human carcinogenicity and found no support for a category 3 (carcinogen) classification for EGBE (www.esig.org).

Result : Survival of males exposed to 125 or 250 ppm was significantly less than control. Mean body weights of males and females were generally lower than controls. Exposure to 125 or 250 ppm to males and females was toxic to red blood cells. Effects on red blood cells were also noted at the 6 month time point in females exposed to 62.5 ppm. Increased numbers of platelets were noted in mice exposed to 125 or 250 ppm. Incidences of hemosiderin pigmentation in Kupffer cells were increased in males exposed to 125 or 250 ppm and all exposed groups of females. Incidences of hematopoietic cell proliferation in males exposed to 125 or 250 ppm and females exposed to 250 ppm were increased relative to controls. Hemosiderin pigmentation in the spleen was increased in all groups of exposed males and in females exposed to 125 or 250 ppm. The incidence of bone marrow hyperplasia was increased in males exposed to 125 or 250 ppm. The incidences of hyaline degeneration of the olfactory and respiratory epithelium (but not the degree of severity) were increased in exposed females (but not males). Inflammatory changes observed in the kidney, preputial and prostate glands and prepuce skin in males exposed to 125 or 250 ppm were indicative of urologic syndrome.

The incidences of squamous cell papilloma and squamous cell papilloma or carcinoma (combined) occurred with a positive trend in females, and the incidences in females exposed to 250 ppm (10 and 12 %) were increased relative to study (0%) and historical controls (0-2 % and 0-3%, respectively). The incidences of squamous cell papilloma in male mice exposed to 125 or 250 ppm (2 at each dose) also was greater than historical controls. Incidences of ulcer were significantly increased relative to the study control in males exposed to 125 ppm (9 vs. 1 in controls) and all groups of females. Increased incidences of epithelial cell hyperplasia were increased in all treated groups. A positive trend toward an increase in the incidence of hemangiosarcoma occurred in male mice. The incidence of this lesion was increased ($p = 0.46$) in males exposed to 250 ppm (8%) with regard to chamber (0%) and historical controls. Two of the four high dose males that had hemangiosarcomas in the liver also had them in the bone marrow and heart or spleen. The incidence of hepatocellular carcinoma in males increased in a dose dependent manner and was increased in those exposed to 250 ppm relative to the study control (21 vs. 10). There was no difference in the combined incidence of adenoma and carcinoma between treated (30/49) and control males (30/50). There was a decreased incidence of hepatocellular adenoma in females exposed to 125 or 250 ppm.

Test condition : Groups of 50 male and 50 female mice (7-8 weeks old) were exposed to test material (0, 62.5, 125 or 250 ppm) by inhalation, 6 hours 12 minutes per day, 5 days per week for 104 weeks. Additional groups of 30 male and 30 female mice were exposed to 0, 62.5, or 125 ppm test material for hematology and bone marrow analyses. The rats exposed to 31.2 ppm were evaluated at 3 (hematology only) and 6 months. Ten male and female mice from each of the other exposure groups were evaluated at 3, 6 or 12 months.

All animals were observed twice daily. Body weights and clinical findings were recorded monthly from week 5 through week 93 and every 2 weeks from week 94 until the end of the studies.

Complete necropsies and microscopic examinations were performed on all core animals. All organs and tissues were examined for grossly visible lesions. All major tissues (adrenal, bone with marrow, brain, clitoral gland, esophagus, gallbladder, heart, large intestine, small intestine, kidney, larynx, liver, lung, lymph nodes, mammary gland (females only), nose, ovary, pancreas, parathyroid, pituitary, preputial gland, prostate, salivary

gland, spleen, stomach, testis, thymus, thyroid, trachea, urinary bladder and uterus) were preserved, sectioned and examined microscopically (blinded).

The probability of survival was estimated by a product-limit procedure. Animals found dead from other than natural causes were not included. Statistical analyses for possible dose-related effects on survival used Cox's method for testing two groups for equality and Tarone's life table test to identify dose-related trends. The poly-k test was used to assess the prevalence of neoplasms and nonneoplastic lesions. Unless otherwise specified, a value of k=3 was used in the analysis of site-specific lesions. Tests of significance included pairwise comparisons of each exposed group with controls and a test for an overall exposure-related trend. Organ and body weight data were analyzed with the parametric multiple comparison procedure of Dunnett and Williams. Blood and bone marrow data were analyzed according to the methods of Shirley and Dunn. Jonckheere's test was used to assess the significance of the dose-related trends. Outliers identified by the test of Dixon and Massey were excluded. Average severity values were analyzed by the Mann-Whitney U test. Treatment effects were investigated using a multivariate analysis of variance to transformed data.

Test substance : The purity of the test material (ethylene glycol butyl ether, CAS No. 11-76-2) was > 99%.

Conclusion : There was some evidence of carcinogenic activity in male mice based on increased incidences of hemangiosarcoma of the liver and in female mice based on increased incidences of forestomach squamous cell papilloma or carcinoma (mainly papilloma).

Reliability : (1) valid without restriction. The study was conducted according to NTP guidelines.

19.02.2002 (60)

5.8 TOXICITY TO REPRODUCTION

Type	:	Two generation study
Species	:	mouse
Sex	:	male/female
Strain	:	CD-1
Route of admin.	:	drinking water
Exposure period	:	98 days
Frequency of treatment	:	continuous
Premating exposure period		
Male	:	7 days
Female	:	7 days
Duration of test	:	
Doses	:	0.5, 1.0, 2.0 % (720, 1340, 2050 mg/kg/day)
Control group	:	yes
NOAEL F1 Offspr.	:	= 720 mg/kg bw
Method	:	other:NTP continuous breeding protocol
Year	:	1990
GLP	:	yes
Test substance	:	other TS: ethylene glycol butyl ether
Remark	:	This study is appropriate for EGBEA because glycol ether acetates rapidly hydrolyze to their corresponding glycol ethers in vivo. The summary presented here is different than that submitted for EGBE at SIAM 6. It contains additional information required by new guidelines. No NOAEL for offspring was listed in that dossier. The authors stated that the 0.5% dose

"approaches the NOAEL" for effects on offspring. The writer of this summary agrees with this statement since the only effect observed at this dose was a small (3%) decrease in live pup weight which is of questionable biological significance. Therefore, the NOAEL assigned for toxicity to offspring is 720 mg/kg.
The NOAEL for parental effects was listed as 720 mg/l in the dossier presented at SIAM 6. However, since increases in relative kidney and liver weights occurred at this concentration, the NOEL is < 720 mg/l. It is unclear if these changes were adaptive or adverse, since histopathology of the organs at this concentration was not described.

Result : Live pup weights from animals exposed to 0.5% were significantly reduced (1.56 +/- 0.02 in treated vs. 1.61 +/- 0.01 in control), and parental animals treated with this concentration exhibited significantly increased relative liver (males and females) and kidney (females only) weights. There was no effect of this concentration on fertility.

The test material was toxic to F0 females at 1.0 and 2.0%. Thirteen out of 22 high dose females and 6/20 mid-dose females died during the cohabitation period. Both mid and high dose animals produced significantly fewer litters/pair and fewer pups/litter and had pups with lower weight than controls. Parental animals in these groups exhibited significantly decreased body weight, water consumption and increased kidney weight.

The crossover breeding trial with 1% test material indicated that the female was primarily affected. The mating index was not affected but fertility index and number of live pups/litter were significantly reduced in treated females bred with control males compared to the other groups. Testes and epididymis weights and sperm number and motility of treated males were normal.

Test condition : Each dose of test material was delivered in drinking water available ad libitum. Dosing solutions showed no loss of material over 72 hours and 0.9% loss after 21 days. Dosing solutions were therefore prepared every 2 weeks. Concentrations measured at various times during the test were found to be within 97-104% of target levels.

Animals were 6 weeks old upon receipt and were quarantined for 2-5 weeks. During this period, 2 females and 2 males were killed and their serum was analyzed for 11 viruses. All tests were negative. Mice were allowed free access to food and water. They were randomly assigned to groups by body weight.

Task 1: An initial dose finding study was performed in which 8 animals/sex were exposed to 0, 0.25, 0.5, 1.0, 2.5 and 5% in the water 14 days. Clinical signs, body weight and food consumption were monitored. Animals treated with 2.5 and 5% lost body weight, and 2/8 males and 5/8 females in the 5.0% dose group died. The doses chosen for use in the reproductive study were 0.5, 1.0 and 2.0%.

Task 2: For the reproductive study, eleven-week old mice were allocated into 4 treatment groups. There were 40/sex for untreated controls and 20/sex in each of the following dose groups: 0.5, 1.0, and 2.0% in feed. Separate sexes were group housed for a premating exposure period of 7 days. Females and males from the same dose group were then paired, housed one breeding pair per cage, and cohabitated for 98 days. Test material exposure was continuous. The pairs were separated and the male and female mice were housed individually and exposed continuously. Any litters born after the continuous breeding phase were reared by the dam until weaning, after which the test material was provided to the F1 animals

(offspring) at the same concentration as the F0 animals (parents). The number of pairs producing a litter/number of breeding pairs, the number of litters per pair and live pups per litter, the proportion of pups born alive, sex of live pups, and pup weights within 18 hours of birth were recorded. Food consumption, parental body weights (time not specified), mortality and clinical signs of toxicity of parents also were evaluated.

Task 3: When a positive effect on fertility was detected, a one-week crossover mating trial was performed with F0 animals after the last litter was weaned to determine the affected sex. Three groups of 20 pairs each were mated in the following manner: control males x control females, control females x high-dose females, and control females x high-dose males. The dose used in this study was 1.0%. Pairs were mated for 7 days or until a copulatory plug was detected (whichever came first). Treatment was discontinued during the mating phase and then was reinstated until necropsy (which is assumed to have taken place 98 days after mating). Animals were evaluated for reproductive toxicity (as described in Task 2 above and the body weight and weight of the liver and kidney (with adrenals attached) were obtained. Selected reproductive tissues from males (left testis with epididymis attached, right testis, right epididymis, prostate and seminal vesicles) and females (ovary with oviduct attached, and uterus) were weighed, fixed and embedded in paraffin, stained and evaluated by light microscopy. The sperm concentration, percentage of motile sperm, and percentage of abnormal sperm in the right cauda epididymis were also
evaluated in males and estrous cyclicity (as monitored by vaginal lavage for the preceding 7 days) was measured in females.

Task 4: The final litters of the F0 generation exposed to 0.5% was reared, weaned and exposed to the same concentration of test material as their parents. Concentrations of 1.0 and 2.0% were not tested because there were not enough pups to perform the test. Animals were paired with nonsiblings from the 0.5% or control groups at 74 +/- 10 days. These animals were cohabitated either for 1 week or until a copulatory plug was detected (whichever came first). The F1 parents were euthanized and necropsied. The litters produced and parents were evaluated for reproductive toxicity as previously described (Tasks 2 and 3). Organs and tissues examined upon necropsy were the same as those listed for Task 3.

The Cochran-Armitage test was used to evaluate any dose-related trends in fertility. A chi square test was used to analyze data from Task 3. Pairwise comparisons between the control and dosed groups were made with the Fisher's exact test. The number of litters and the number of live pups per litter were computed on a fertile pair basis and treatment group means were determined. Dose groups means for these variables, the sex ratio and the proportion of live pups were analyzed using a Kruskal-Wallis test. Ordered differences were tested for by Jonckheere's test. The Wilcoxon-Mann-Whitney U test was used to make intergroup pairwise comparisons.

An analysis of covariance was performed to correct for the potential effect of the number of pups per litter on the average pup weight. The covariate used was average litter size, including live and dead pups. Least squares estimated of dose group means, adjusted for litter size, were computed and tested for overall equality using an F test and pairwise equality was tested using a t test. Average organ weights were adjusted for body weight and tested for equality an analysis of covariance. Absolute organ weights were analyzed by the Kruskal-Wallis and Wilcoxon-Mann-Whitney U tests. Dose-related trends were tested for by Jonckheere's test.

Analyses were performed on data for males and females separately and with both sexes combined. The criterion for significance was $p < 0.05$.

Test substance : Purity of the test material (ethylene glycol monobutyl ether, CAS No. 111-76-2) was > 99%.

Reliability : (1) valid without restriction. The study was comparable to a guideline study.

Flag : Critical study for SIDS endpoint.

20.02.2002 (44)

Species	:	other: rat and mouse
Sex	:	male/female
Strain	:	other: F344/N (rat) and B6C3F1 (mouse)
Route of admin.	:	inhalation
Exposure period	:	14 or 104 weeks
Frequency of treatment	:	6 hr 12 min per day, 5 days/week
Post obs. period	:	
Doses	:	14 weeks: 31.2, 62.5, 125, 250 or 500 ppm ; 104 weeks: 31.2, 62.5 or 125 ppm (rat) and 62.5, 125 or 250 ppm (mouse)
Control group	:	yes
Method	:	other
Year	:	2000
GLP	:	yes
Test substance	:	other TS: ethylene glycol butyl ether
Remark	:	This study is appropriate for EGBEA because glycol ether acetates rapidly hydrolyze to their corresponding glycol ethers in vivo. This study was conducted after SIAM 6. Additional results from this study can be found in Sections 5.4 and 5.7.
Result	:	14 week study: There were no statistically significant changes in reproductive organs of exposed animals. Therefore, the NOAEL for reproductive organ toxicity in this study was 500 ppm. 104 week study: There was no significant effect of treatment with any concentration of test material on the histopathology of the uterus, ovaries, seminal vesicles, testes or epididymis of rats. Incidences of testicular atrophy were similar in all treatment groups of rats and mice (including controls). There was a slight, treatment-dependent increase in the incidence of preputial gland inflammation in male mice (4%, 14%, 12%, and 16%) exposed to 0, 62.5, 125 or 250 ppm, respectively. Therefore, the NOAELs for reproductive organ toxicity in this study were the highest concentrations tested (125 ppm in the rat and 250 ppm in the mouse).
Test condition	:	14 week study: Groups of 10 animals/sex were exposed to 0, 31, 62.5, 125, 250 or 500 ppm test material by inhalation, 6 hours and 12 minutes per day, 5 days per week for 14 weeks. The testes (with epididymis and seminal vesicle), preputial gland, prostate, ovaries and uterus from all animals were fixed and preserved in 10% neutral buffered formalin. All tissues collected from rats and mice in the control and high dose animals were processed for microscopic examination. In addition, the testes of low and mid-dose mice were examined. 104 week study: Groups of 10 animals/sex were exposed to 0, 31, 62.5 or 125 ppm (rats) or 62.5, 125 or 250 ppm (mice) test material by inhalation, 6 hours and 12 minutes per day, 5 days per week for 104 weeks. The ovaries, testes (with epididymis and seminal vesicle), preputial gland, prostate and uterus from all animals were examined microscopically. Additional test conditions are provided in sections 5.4 and 5.7.

Test substance	:	The purity of the test material (ethylene glycol butyl ether, CAS No. 11-76-2) was > 99%.
Reliability	:	(1) valid without restriction. The study was conducted according to NTP guidelines.

(60)

Species	:	other: rat and rabbit
Sex	:	male/female
Strain	:	other: Wistar (rat) and New Zealand (rabbit)
Route of admin.	:	inhalation
Exposure period	:	10 months
Frequency of treatment	:	4 hr/day, 5 days week
Post obs. period	:	
Doses	:	100 ppm
Control group	:	yes
Method	:	other
Year	:	1979
GLP	:	no data
Test substance	:	as prescribed by 1.1 –1.4
Remark	:	Additional results from this study can be found in section 5.4. The results of the study were written to encompass effects noted in both the rat and rabbit. It is appropriate to discuss the effects noted in both species together in one summary since the effects in both species were compared.
Result	:	There was no effect of treatment with butylglycol acetate (BGA) or ethylglycol acetate (EGA) on body weight gain, red blood cell numbers or hemoglobin concentration. No abnormalities were found in urine. No lesions were noted in gonads from treated animals.
Test condition	:	Forty male and female rats (220 to 240 g), divided into 4 groups of either 10 males or 10 females, and four rabbits (2 of each sex, 2.2 to 2.5 kg) were exposed for 4 hours/day, 5 days/week, for 10 months to butylglycol acetate (100 ppm) or ethylglycol acetate 200 ppm) in gas chambers. Test material was placed in a bubbler having a scintered-glass plate in its lower part and diluted to the desired concentration with compressed air which flowed through a lateral inlet pipe under the glass plate. Concentrations were verified daily by weighing the remaining amount of solvent. Ten male and ten female rats and two male and two female rabbits were exposed to air only (controls). Weights were recorded before dosing and weekly. The presence of blood, protein, glucose, ketone bodies and nitrites in the urine and urine pH was measured with test strips (times not indicated). Red and white blood cells in urine were counted with a Coulter counter. Hemoglobin was also measured. All animals were necropsied following death or termination. Heart, lungs, liver, spleen, pancreas, kidneys, adrenals, ovaries, bladder, skin, brain, eyes, stomach and testes were fixed and examined histologically.
Test substance	:	Butylglycol acetate came from Pfaltz & Bauer, Flushing, New York. Purity was not noted. Purity of ethylglycol acetate was >= 99%.
Reliability	:	(2) valid with restrictions. Basic data given.

(74)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Fischer 344

Route of admin.	:	inhalation
Exposure period	:	day 6-15 of gestation
Frequency of treatment	:	6 hours/day
Duration of test	:	to day 21 of gestation
Doses	:	25, 50, 100, 200 ppm
Control group	:	yes
NOAEL Maternalt.	:	= 50 ppm
NOAEL Developmental	:	= 50 ppm
NOAEL Teratogenicity	:	= 200 ppm
Method	:	other
Year	:	1984
GLP	:	no data
Test substance	:	other TS: ethylene glycol butyl ether
Remark	:	This study is appropriate for EGBEA because glycol ether acetates rapidly hydrolyze to their corresponding glycol ethers in vivo. The summary presented here is different than that submitted for EGBE at SIAM 6. It contains additional information required by new guidelines. The NOAELs reported above are the same as those reported in the dossier for EGBE submitted at SIAM 6. The author also reports a NOAEL for fetal effects (i.e. developmental) of 50 ppm. However, the only observed effect at the next exposure level of 100 ppm was a small variation in skeletal ossification involving cervical centra. This alteration is considered a transient developmental delay and occurs at high incidences even in control fetuses. This is not a structural change. The effect was not seen in the rangefinder study at 100 ppm. Taking this into account, we believe that the effects seen at 100 ppm are not a true adverse repeatable effect, which would lead to a conclusion that the no observable adverse effect level for fetal effects is 100 ppm. The ECETOC publication "Recognition of, and differentiation between adverse and non-adverse effects in toxicological studies" (TR85, 2002) cites a similar example to this case and concluded that reduced ossification of two centrums was not considered an effect of treatment since there were no correlated effects in other bones." It is not biologically credible that the substance could be such a specific developmental toxicant that it would target one bone only.
Result	:	All analyses of test material were within 10% of target concentrations. Exposure to 100 or 200 ppm resulted in maternal toxicity (clinical signs, decreased body weight and weight gain, and decreased food and water consumption and anemia). Animals exposed to 200 ppm exhibited decreased uterus and relative kidney and spleen weights. Reproductive toxicity also was evident at 200 ppm. There was a decrease in the number of viable implants and live fetuses and an increase in the number of nonviable implants and embryonic resorptions. There was no effect of treatment on the incidences of total, visceral, external or skeletal malformations. There was evidence of retarded skeletal ossification in offspring of rats treated with 100 or 200 ppm. At 200 ppm, there was a significant increase in the number of litters with one or more fetuses exhibiting unossified skeletal elements (e.g. anterior arch of the atlas, cervical centra 5 and 6) or poorly ossified skeletal elements (cervical arches, sternebrae 1,3, 4, and 6, and proximal phalanges of the forelimbs). At 200 ppm there also was a decreased incidence of bilobed thoracic centra at 9 and 13 and of poorly ossified proximal phalanges of the hindlimb. At 100 ppm, there was a significant increase in the incidence of unossified cervical centrum 6. At 100 and 200 ppm, there was a decreased incidence of bilobed cervical centrum 5.

Test condition	:	Virgin male and female rats (100 days old upon arrival) were quarantined for 2 weeks and examined for the presence of pathogens. Food and water were available ad libitum (except during exposures). Rats were mated 1:1 and the paperboard beneath the cages was checked twice daily for dropped copulation plugs. Thirty six plug-positive females were randomly assigned to each treatment group. The day a plug was found was designated as gestation Day 0. The females were exposed on gestation Days 6-15 with 0 (control), 25, 50, 100 or 200 ppm test material for 6 hr/day. Vapor concentrations of test material were analyzed once/hour. The animals were observed daily for clinical signs. Food and water consumption were measured on Days 3, 6, 9, 12, 15, 18 and 21. Animals also were weighed on these days (with the exception of Days 3 and 18). Animals were euthanized on gestation Day 21. Blood samples were taken for analysis of erythrocyte osmotic fragility and hematological examination from the retro-orbital sinus. The gravid uterus, ovaries, cervix, vagina and peritoneal and thoracic cavity of each rat was examined grossly. Corpora lutea were counted. The liver, kidney, thymus, spleen and uterus were weighed. All live and dead fetuses, placentas and resorption sites were recorded. Uteri from females that appeared nongravid were analyzed for early resorptions. All live fetuses were weighed and sexed. All fetuses were examined for external malformations. One-half of the fetuses (randomly selected) were examined for thoracic and peritoneal visceral, and craniofacial abnormalities. The remaining fetuses were examined for skeletal abnormalities. Results of continuous variables were analyzed using Levene's test for equal variances, analysis of variance (ANOVA) and t-tests with Bonferroni probabilities (when appropriate). When Levene's test indicated homogenous variances, the pooled t-test was used for pairwise comparisons. When Levene's test indicated heterogenous variances, all groups were compared by ANOVA for unequal variances followed by the separate variance t-test (when appropriate). Nonparametric data were analyzed by the Kruskal-Wallis test, followed by the Mann-Whitney U test (when appropriate). Incidence data were compared using Fisher's exact test. $p < 0.05$ was the criterion for significance.
Test substance	:	Test material (ethylene glycol monobutyl ether , CAS No. 111-76-2) was 99.6% pure.
Conclusion	:	Test material produced effects on the embryo and fetus only at concentrations that produced maternal toxicity.
Reliability	:	(1) valid without restriction. The study was comparable to a guideline study.
Flag	:	Supporting study for SIDS endpoint
20.02.2002		(77)

Species	:	rabbit
Sex	:	female
Strain	:	New Zealand white
Route of admin.	:	inhalation
Exposure period	:	day 6-18 of gestation
Frequency of treatment	:	6 hours/day
Duration of test	:	up to day 29 of gestation
Doses	:	0, 25, 50, 100 or 200 ppm/day
Control group	:	yes
NOAEL Maternalt.	:	= 100 ppm
NOAEL Fetotoxicity	:	= 200 ppm
NOAEL Embryotoxicity	:	= 100 ppm

NOAEL Teratogen	:	= 200 ppm
Method	:	other
Year	:	1984
GLP	:	no data
Test substance	:	other TS: ethylene glycol butyl ether
Remark	:	This study is appropriate for EGBEA because glycol ether acetates rapidly hydrolyze to their corresponding glycol ethers in vivo. The summary presented here is different than that submitted for EGBE at SIAM 6. It contains additional information required by new guidelines. The NOAELs reported above are the same as those reported in the dossier submitted at SIAM 6. The assignment of a Maternal NOAEL of 100 ppm was made after discounting significant changes in hemoglobin and hematocrit at 100 ppm (since similar changes at 200 ppm were not significant). However, evidence from other studies indicates that the hematological changes at 100 ppm should not be discounted. Repeated dose and in vitro studies show that adverse blood effects would be expected at 100 ppm. This is supported by the fact that red staining on trays (blood in urine) was seen at both the 100 and 200 ppm exposure levels. The lack of significance could be accounted for by the fact that blood samples were not taken until 11 days after treatment ceased, during which time all the dosed animals would have been expected to have recovered significantly. Based on this information, a NOAEL for maternal effects of 50 ppm (not 100 ppm) is indicated.
Result	:	Four rabbits exposed to 200 ppm died. All dead rabbits were pregnant. Rabbits exposed to 200 ppm exhibited decreased body and gravid uterine weights, periocular and perinasal wetness, perinasal discharge, red fluid on cage trays and stained fur. Four rabbits exposed to 200 ppm and 1 exposed to 100 ppm aborted, but these effects were not statistically significant. There was a reduction in the number of total and viable implantations/litter in rabbits exposed to 200 ppm. Significant increases in hemoglobin and hematocrit were observed in animals treated with 100 ppm but not 200 ppm. There was not effect of treatment on the incidence of total, visceral or skeletal malformations. There was an increase in the number of litters (4/19) with one or more fetuses (5) exhibiting fusion of papillary muscles in the left ventricle of in rabbits treated with 100 ppm. This was not considered to be related to treatment as no other fetuses from exposed animals exhibited this condition. There was no increase in the incidences of skeletal variations in treated animals compared to controls. There was a significant reduction in unossified sternebra 6 and in rudimentary rib at the first lumbar vertebra (bilaterally) at 200 ppm.
Test condition	:	Virgin female rabbits (3.0 to 3.5 kg, 5 to 5.5 months old) were quarantined for 2 weeks and examined for the presence of intestinal parasites. Food and water were available ad libitum (except during exposures). Females were bred with in-house males. The date of copulation was designated gestation Day 0. Twenty-four mated females were randomly assigned to each treatment group. The females were exposed on gestation Days 6-18 with 0 (control), 25, 50, 100 or 200 ppm test material for 6 hr/day. Vapor concentrations of test material were analyzed once/hour. The animals were observed daily for clinical signs. Animals were weighed on gestation Day 0, 6, 9, 12, 15, 18, 21 and 29. Animals were euthanized on gestation Day 29. Blood samples were taken for analysis of erythrocyte osmotic fragility and hematological examination by cardiac puncture. The gravid uterus, ovaries, cervix, vagina and peritoneal and thoracic cavity of each rat was examined grossly. Corpora lutea were counted. The liver, kidney, thymus, spleen and uterus were weighed. All live and dead fetuses,

placentas and resorption sites were recorded. Uteri from females that appeared nongravid were analyzed for early resorptions.

Live fetuses were euthanized immediately upon removal from the uterus. All fetuses were weighed, sexed, and examined for external malformations. One-half of the fetuses (randomly selected) were examined for thoracic and peritoneal visceral, and craniofacial abnormalities. The remaining fetuses were examined for skeletal abnormalities.

Results of continuous variables were analyzed using Levene's test for equal variances, analysis of variance (ANOVA) and t-tests with Bonferroni probabilities (when appropriate). When Levene's test indicated homogenous variances, the pooled t-test was used for pairwise comparisons. When Levene's test indicated heterogeneous variances, all groups were compared by ANOVA for unequal variances followed by the separate variance t-test (when appropriate). Nonparametric data were analyzed by the Kruskal-Wallis test, followed by the Mann-Whitney U test (when appropriate). Incidence data were compared using Fisher's exact test. $p < 0.05$ was the criterion for significance.

Test substance : Test material (ethylene glycol monobutyl ether, CAS No. 111-76-2) was 99.6% pure.

Conclusion : The test material was not teratogenic. Embryotoxicity occurred at a dose that was toxic to the mother.

Reliability : (1) valid without restriction. The study is comparable to a guideline study.

Flag : Supporting study for SIDS endpoint

21.02.2002 (77)

5.10 OTHER RELEVANT INFORMATION

Type : Cytotoxicity

Test substance : other TS (ethylene glycol monobutyl ether)

Remark : ECETOC has critically reviewed the health and toxicological properties of butoxyethanol to assist the European Commission in the setting of an exposure standard (Indicative Limit Value) for the material.

Haemolysis during the first few days of exposure is the primary indicator of toxicity in rodents. A NOEL of 25 ppm (equivalent to 121 mg/m^3) has been reported for rats exposed over 90 days (Dodd et al., Toxicol. Appl. Pharmacol., 68: 405-414, 1983) whereas other mammals, including man, are less susceptible. The metabolite 2-butoxyacetic acid is responsible for butoxyethanol-induced haemolysis. This produces lysis of rat red blood cells in vitro at 2 mM whereas only very slight effects (no haemolysis) are seen at 8 mM in red cells from humans susceptible to haemolytic disorders. It was concluded that human erythrocytes are more resistant than blood cells from the rat.

The rat NOEL of 25 ppm was considered by ECETOC as directly relevant to the setting of a workplace exposure standard for butoxyethanol. This NOEL also takes account of concurrent dermal absorption occurring during whole body inhalation exposure. In applying this animal Information, no uncertainty factor is needed for extrapolation from subchronic to chronic exposure since haemolyis is transient, seen only during the first few days of exposure.

A physiologically-based pharmacokinetic model (PBPK model) predicts that the concentration of butoxyacetic acid in blood of humans exposed to 20-25 ppm butoxyethanol will be approximately 0.03 uM. This is 270-fold less than the concentration needed to cause minimal changes in human red blood cells in vitro.

No haemolysis was reported in human volunteers exposed to 50 ppm for 2 hours or 100 or 195 ppm for 8 hours (although irritation of the eyes and respiratory tract were seen at concentrations of 100 ppm and above).

On the basis of the above Information, ECETOC concluded that a long term occupational exposure standard (8 hour TWA) of 20 ppm would be protective of human health.

Information came from an IUCLID document for CAS No. 111-76-2 published by the European Chemicals Bureau on 11-FEB-2000.

Source : BP Chemicals Ltd. London
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. No primary reference was given.
04.04.2005

Type : Cytotoxicity
Test substance : other TS (ethylene glycol monobutyl ether)
Remark : Human red blood cells were obtained from healthy adult volunteers (number was not stated), and male F344 rats (9-11 weeks old). Blood samples were anticoagulated with heparin and centrifuged at 1000g for 10 min for removal of plasma and buffy coat. The red blood cells were adjusted to a packed cell volume of 10% and incubated in the presence of 0, 0.2, or 2 mM butoxyacetic acid for 1-4 hours at 37 degrees C in a shaking water bath. Samples were taken at the designated times and analyzed for microhematocrit, hemoglobin, red blood cell count, mean cellular volume and percent hemolysis. Erythrocytes were diluted with buffer to 2.5 x 10E8 cells/ml n buffer and infused via a Harvard syringe pump at 2.0 ml/min through a 3.0 micromolar nucleopore filter. Pressure increases were recorded using a pressure transducer. The filtration pressure is a function of deformability and was determined by a software program that analyzed digitized curves. Red blood cells were also fixed in buffer containing 1% glutaraldehyde and observed under light and phase microscopy.

Rat red blood cells had decreased deformability and an increased mean cellular volume after incubation with 0.2 or 2.0 mM BAA for 1-4 hours. Rat red blood cells exposed to BAA became spherocytic and lysed to form erythrocyte membrane ghosts. Hemolysis of rat red blood cells was rapid in 2.0 mM BAA. Changes in deformability appeared to precede hemolysis. Treated rat red blood cells also demonstrated a tendency to agglutinate and release hemoglobin, which formed a visible precipitate. None of these effects were observed in human blood incubated with 2.0 mM BAA.

Reliability : (2) valid with restrictions. The number of rats and humans used as blood donors is unknown.

20.02.2002 (78)

Type : Cytotoxicity
Test substance : other TS (ethylene glycol monobutyl ether)
Remark : Red blood cells from healthy young (N=9, 31-56 years old, five male, 4 female) and older individuals (N= 9, 64-79 years, five male, 4 female) and with red blood cells from patients with hereditary spherocytosis (N=3) and sickle cell disease (N=7) were used in the study. After incubation of red blood cells with or without 2.0 mM BAA for up to 4 hours (conditions that readily hemolyzed rat red blood cells), there were no significant changes between treated or control cells from any of the groups (as determined by t-tests) in any of the parameters measured (microhematocrit, hemoglobin, RBC count, percentage hemolysis, morphology or deformability).

Reliability : (2) valid with restrictions. The number of subjects is limited.
20.02.2002 (79)

Type : Cytotoxicity

Remark : Butoxyacetic acid had markedly higher haemolytic activity than butoxyethanol in vitro. After 1 hour 7.5 mmol butoxyacetic acid completely lysed rat erythrocytes compared to 175-200 mmol for butoxyethanol.

Human erythrocyes incubated for up to 180 minutes showed haemolysis from 150 mmol/l and butoxyacetic acid did not cause haemolysis at up to 15 mmol/l.

The findings show that butoxyacetic acid is more potent than butoxyethanol in causing haemolysis of red blood cells. Human erythrocytes are less susceptible to this effect.

Information came from an IUCLID document for CAS No. 111-76-2 published by the European Chemicals Bureau on 11-FEB-2000.

Source : BP Chemicals Ltd. London
EUROPEAN COMMISSION – European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.

20.02.2002 (4)

Type : Cytotoxicity
Test substance : other TS (ethylene glycol monobutyl ether)
Remark : Blood from different male animals [mouse, rat, hamster, rabbit, guinea pig, dog, cat, pig, baboon and human (N = 3-6 for each species)] was incubated with 0, 1 or 2 mM butoxyacetic acid (the primary metabolite of butoxyethanol) at 37 degrees C in a gently shaking water bath. Complete blood counts and packed cell volume (spun hematocrit) were evaluated 1, 2 and 4 hours after incubation. Complete blood counts were determined using an automated hematology analyzer and included white blood cell count, platelet count, red blood cell (RBC) count, hemoglobin concentration, hematocrit, mean cell volume (MCV), mean corpuscular hemoglobin and men corpuscular hemoglobin concentration. T-tests were used to compare effects at the various doses. The criterion for significance was $p < 0.05$.

Butoxyacetic acid (BAA) caused a time- and concentration-dependent increase in mean cell volume and hematocrit in blood from rats, mice, hamsters, rabbits and baboons. There also was a decreased number of RBCs in blood from mice, baboons or rats after incubation with 2 mM BAA for 4 hours. Hemoglobin was decreased in mouse blood incubated with 1 or 2 mM BAA for 6 hours. There were no significant changes in any parameter in blood from pigs, dogs, cats, guinea pigs and humans.

These findings demonstrate species differences in butoxyacetic acid-dependent hemolysis; human erythrocytes are relatively resistant to this effect.

Reliability : (2) valid with restrictions. Blood from only a few animals was pooled for this test. Whether the effects varied between animals is not known.

20.02.2002 (34)

Type : Toxicokinetics
Test substance : other TS (ethylene glycol monobutyl ether)
Remark : A PBPK model was developed to describe the disposition of EGBE and it major metabolite, BAA, in rats and humans. Physiological constants for rats and humans, blood-air and blood-tissue partition coefficients and biochemical constants describing metabolism of EGBE and excretion of BAA were inputted. The data were obtained from the literature, from experimentation or from additional models. The model was validated by comparing predicted data to data obtained in a pharmacokinetic studies perfomed by Sabourin et al., (Toxicol. Appl. Pharmacol. 114: 232-238,

1992), in which male 344 rats were exposed to [14]CEGBE for 6 hours at concentrations of 4.2, 49 and 438 ppm by nose-only inhalation, and Johanson et al. (Toxicol Lett. 34: 23-31, 1986), who exposed 7 male volunteers to 20 ppm EGBE while exercising on a bicycle ergonometer.

Predictions for respiratory uptake, total metabolism and amount of BAA in urine compared favorably with Sabourin's findings in rats (except for the amount of BAA excreted in the urine at 438 ppm). The model calculated that 39.8 mg would be eliminated (vs. 18.9 mg actually measured). This difference was likely due to toxicity (severe hemolysis was observed in the rats and 2/4 died), which the PBPK model did not compensate for. Simulations of the concentration of EGBE in human blood were similar to those of Johanson et al., assuming that the total uptake of EGBE was by respiration (i.e. no dermal uptake of vapors).

Using the model, the Cmax and AUC for the concentration of blood for rats and humans exposed by inhalation (both nose and whole body) for 6 hrs to various concentrations of EGBE vapor were calculated. BAA was predicted to be formed more rapidly in rats than humans. Conversely, humans were predicted to eliminate BAA slower than rats since the elimination rate constants were scaled from rats to humans by body weight (0.70). However, taken together with known physiological differences, higher Cmax and AUC values were predicted for rats than humans, especially as the vapor concentration was increased.

Assuming a direct correlation occurred between Cmax and blood concentration used in *in vitro* experiments, the model showed that airborne concentrations of EGBE between 200 and 800 ppm would produce peak blood BAA concentrations that are associated with hemolysis in rats (500 to 2000 micromolar). This is consistent with in vitro toxicity data. The model showed that humans would not produce high enough concentrations of BAA to cause hemolysis following 6 hours of inhalation exposure, regardless of the concentration (even up to the saturated vapor concentration of 1160 ppm). In humans inhaling 1160 ppm, the estimated concentration of BAA in blood was 1200- 1500 micromolar (depending whether exposure was nose-only or whole body).

Reliability : (2) valid with restrictions
Data were obtained by modeling

06.06.2005 (22a)

Type : Toxicokinetics and mechanism of action
Test substance : other TS (ethylene glycol monobutyl ether)
Remark : Male F-344 rats (9-12 weeks) were treated with pyrazole (250 mg/kg, i.p) or cyanamide (50 mg/kg, i.p.), one hour before administration of water or butoxyethanol by gavage (> 99% pure). A single dose of butoxyethanol or methyl butoxyacetate (5 ml/kg) was given by gavage. Butoxyacetic acid or the metabolic intermediate of butoxyaldehyde were administered to different groups of rats in a water:emulphor (5:1) mixture by gavage at the molar equivalent of 125 mg/kg of butoxyethanol. After dosing, rats were placed in metabolism cages and urine and feces were collected. Rats were anesthetized with ether and a blood sample was obtained by cardiac puncture. The red blood cell count, hemoglobin concentration, packed cell volume, hematocrit, mean cell volume, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration and platelet count were determined using a hematology analyzer. The concentration of free hemoglobin in plasma also was determined. The hemoglobin concentration in urine was measured with a Coulter hemoglobinometer. Liver, spleen and kidneys of rats treated with butoxyethanol with and without pyrazole were collected, weighed and examined microscopically.

Metabolism experiments also were performed in rats treated with radioactive butoxyethanol (500 mg/kg, 50 – 60 microcuries/kg) with and without pyrazole by gavage. Urine, feces, CO2 and bile were collected and analyzed for butoxyethanol and metabolites as described in reference 123.

Treatment with pyrazole (alcohol dehydrogenase inhibitor) protected rats against butoxyethanol-induced hematotoxicity and inhibited metabolism to butoxyacetic acid. There was increased metabolism to butoxyethanol glucuronide and sulfate. There was approximately a 10-fold decrease in the ratio of butoxyacetic acid to glucuronide plus sulfate in the urine of rats treated with pyrazole plus butoxyethanol compared to butoxyethanol alone. Pretreatment of rats with cyanamide (an aldehyde dehydrogenase inhibitor) also protected rats against hematotoxicity and modified metabolism. Administration of equimolar doses of butoxyethanol, the metabolic intermediate of butoxyaldehyde, or butoxyacetic acid caused similar hematotoxic effects. Cyanamide also protected rats against butoxyacetaldehyde-induced hematotoxicity. Administration of deuterium-labeled butoxyethanol (methyl butoxyacetate) caused a significant delay in hematotoxicity.

Reliability : (1) valid without restriction. Well conducted and documented study.
20.02.2002 (35)
Type : Metabolism
Test substance : other TS (ethylene glycol monobutyl ether)
Remark : Radiolabelled butoxyethanol (125 or 500 mg/kg, 50 microcuries/kg, 99% radiochemical purity) was administered by gavage to male F344 rats (9-13 weeks of age). Animals were placed in metabolism cages and urine was collected at 0-8, 8-24, and 24-48 hours after dosing. Feces were collected 24 and 48 hours after treatment. Carbon dioxide and volatiles were trapped and analyzed for radioactivity using liquid scintillation counting. The common bile duct as cannulated and bile was collected 4, 6, and 8 hours after dosing. Animals were killed 48 hours after treatment and tissues were removed. Urine was analyzed for radioactivity using liquid scintillation counting and for metabolites by HPLC. Solid samples were combusted before analysis by liquid scintillation counting

Butoxyethanol was rapidly absorbed and distributed in all organs. The highest levels were found in the forestomach, liver, kidneys, spleen and glandular stomach. The major route of elimination was in urine followed by exhaled air. The major metabolites in urine were butoxyacetic acid (75% of label) followed by the glucuronide conjugate. Sulphate conjugate and unchanged butoxyethanol were found in the urine of low-dose but not high-dose animals (2.7% and < 2% of urinary radioactivity at 8 hrs, but none at later times). There was evidence of saturation of butoxyethanol metabolizing enzymes. At the high dose, rats eliminated 8% of labelled substance in the bile within 8 hours. The majority of the material in bile early on was the glucuronide conjugate. As time increased, the amount of the glucuronide conjugate decreased, and the amount of butyoxyacetic acid increased, so that by 8 hours, the quantities of these materials in bile were nearly equal.

Reliability : (1) valid without restriction. Well conducted and documented study.
20.02.2002 (36)

Type : Metabolism
Test substance : other TS (ethylene glycol monobutyl ether)
Remark : EGPE and EGHE also were tested in this study.
Result : A single isozyme of rat liver alcohol dehydrogenase (ADH-3) was responsible for oxidizing the test material and other glycol ethers. A Vmax of 5.78 nmol NADH/min/mg protein and a Km value of 0.27 mM were reported for the test material. These values were higher than those of

EGPE and EGHE, suggesting that at equivalent concentrations, metabolism of EGBE will be more rapid than EGPE and EGHE and will be saturated at higher substrate concentrations.

Test condition : Livers from male (247-317 g) Wistar rats were homogenized. The 1000,000 g supernatant was used for the assay after dialysis overnight. The activity of alcohol dehydrogenase following incubation with 0.05 - 10 mM test material was determined. Two isozymes were isolated using gel electrophoresis.

Reliability : (2) valid with restrictions. Basic data given.

(1)

Type : Cytotoxicity

Remark : Im Rahmen der akuten und subakuten Untersuchungen wurde ein Haemolyseversuch in vitro mit Kaninchenblut durchgefuehrt. Dabei trat erst bei Konzentrationen von 0,6 % Haemolyse auf. Da diese Konzentrat. in vivo wohl nicht relevant sind, kann in Verbindung mit den Ergebnissen des osmotischen Resistenztests gefolgert werden, dass das Hauptsymptom "intravitale Haemolyse" - Butylglykol besitzt die gleiche Wirkung - nicht durch eine verminderte Erythrozytenresistenz bedingt ist. [In the area of acute and subacute investigations an *in vitro* hemolysis study was undertaken with rabbit blood. In this study hemolysis occurred only at 0.6% or higher. Since this concentration is not relevant *in vivo*, it follows in combination with the results of osmotic resistance tests, that the main symptom "intravital hemolysis" - butyl glycol possesses the same effect – is not necessitated through a decreased erythrocyte resistance."]

All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(9)

Type : Cytotoxicity

Remark : All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(26)

Type : Cytotoxicity

Remark : All data (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.The study was not available for review
Title: Development of a fixed-dose approach for the fluorescin leakage test

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(22)

Type : Metabolism

Result : The equation for the time course of hydrolysis of the test material was R (peak area ratio) = 1.7341 e-0.717.The half life was 0.96 minutes.

Test condition : The study was not available for review. This study was described in a IUCLID document published by the European Chemicals Bureau as follows: “Butylglykolacetat wird im Rattenserum sehr schnell zu Butylglykol desacetyliert. Die Halbwertszeit betraegt 0,96 Minuten, so dass in sehr

kurzer Zeit Butylglykolacetat, dass in die Blutbahn gelangt, als Butylglykol vorliegen duerfte. " This translates to: Butyl glycol acetate is deacetylated very rapidly to butyl glycol in rat serum. The half-life amounts to about 0.96 minutes, so that in a very short time butylglycol acetate entering the blood is in effect butyl glycol.

Additional information obtained from the study is as follows: Twenty microliters of ethylene glycol monobutylether acetate were mixed with 20 microliters of internal standard (ethylene glycol monomethylether) and 4.96 ml H2O. Fifty microliters of this stock solution were incubated at 37 degrees C with 500 microliters of rat plasma (pooled from Wistar rats). Two minutes later, the first sample was taken and injected into a gas chromatograph equipped with a FID detector at 250 degrees C. The adsorbent was 2.5% Carbowachs 4000 on Chromosorb G at 108 degrees C (HP 80-100 mesh, 3 m glass/2mm). The carrier gas was Helium (24,8 ml/min). An additional sample was taken at 5 minutes and analyzed. Control values were derived from the stock solution and 500 microliters of H2O. The peak area ratio was plotted against time and the half life was calculated.

Test substance : The purity of the ethylene glycol monobutylether acetate was > 99% as indicated by gas/liquid chromatography.

Reliability : (1) valid without restriction. Acceptable, well-documented study that meets basic scientific principles.

(8)

Type : other: Review

Remark : Subakute Inhalationstox.-Studie ueber Loesungsmittel, die u.a. Butyl Cellosolve Acetate enthalten. [Subacute inhalation toxicology. Study of a solvent that contained butyl cellosolve acetate among other components].

All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(75)

Type : other: Review

Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Uebersichtsdarstellung zur akuten und chron. Toxizitaet.[Review paper for acute and chronic toxicity]

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review

(58)

Type : other: Review

Remark : MAK-Liste 1984 mit Hinweis auf Butylglykol als wirksameForm. [MAK list of 1984 with reference to butyglycol as the effective material].

All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(72)

Type : other: Review
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Zfs. Darst. zur akuten/subchronischen und chronischen Wirkung. [Refer to descriptions of acute subchronic and chronic effects].
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.
(30) (71)

Type : other: Review
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Zfs. Darst. zur Reproduktionstoxikologie der Glykolaetherallgemein. [Refer to descriptions of reproduction toxicology of glycol ethers in general].
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.
(43)

Type : other: Eye irritation
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.

Title: Justification of the enucleated eye test with eyes of slaughterhouse animals as an alternative to the Draize eye irritation test with rabbits
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.
(64)

Type : other: Review
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.
(19)

Type : other: Review
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.
(41)

Type : other: Review
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.

(62)

Type : other: Review
Remark : The study was not available for review All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.

(29)

Type : other: Review
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.

(32)

Type : other: Review
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.

(31)

Type : other: Skin irritation
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Title: Use of Human and Rat Keratinocyte Cultures to Assess Skin Irritation Potential
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.

(54)

Type : other: Teratogenicity
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.

(53)

Type : other: in vitro skin toxicology
Remark : All information (except the reliability rating) came from an IUCLID document for CAS No. 112-07-2 published by the European Chemicals Bureau, dated 11-FEB-2000.
Title: Skin 2TM: An in vitro human skin analog
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.

(25)

Type	:	other: elimination
Test substance	:	Ethylene glycol monobutyl ether (EGBE)
Result	:	Mice eliminated both EGBE and butoxyacetic acid (BAA) from blood more rapidly than rats. Half-lives of elimination in mice and rats following 1 day of exposure to 62.5 ppm were 3 min (mice) and 9 min (rats) for EGBE, and 31 min (mice) and 40 min (rats) for BAA. Female rats eliminated BAA more slowly than males, due to a reduced rate of renal elimination. EGBE demonstrated linear kinetics. Elimination of BAA decreased with increasing concentration, indicating non-linear kinetics for this metabolite. After prolonged exposure, elimination rates of EGBE and BAA decreased in both species, resulting in longer blood residence times. The clearance profile of EGBE was similar in aged mice as young mice. However, old mice eliminated BAA from blood > 10 times slower than young mice after 1 day of exposure. The delayed elimination of BAA in old mice was less obvious after 3 weeks of exposure.
Test conditions		Male and female F344 rats and B6C3F1 mice (6-7 weeks old) were exposed by whole-body inhalation to 31.2, 62.5, or 125 ppm (rats) or 62.5, 125 or 250 ppm (mice) EGBE for 6 hours/day, 5 days/week for up to 18 months. Postexposure blood samples were collected after 1 day, 2 weeks or 3, 6, 12, or 18 months of exposure. A separate group of mice that were 19 months old was exposed to EGBE for 3 weeks. Postexposure blood samples were collected after 1 day and 3 weeks of exposure and 16 hour urine samples were collected after 2 weeks of exposure in these aged mice. Blood samples were analyzed for EGBE and butoxyacetic acid (BAA) and urine samples were analyzed for BAA using GC/MS, and their kinetc parameters were estimated by the curve-fitting method of SAS.
Conclusion	:	The elimination kinetics of EGBE and BAA following repeated EGBE exposure are dependent on species, sex, age, time of exposure and exposure concentration.
Test substance	:	Purity of the test material was > 99%, as determined by GC.
Reliability	:	(2) valid with restrictions. Acceptable, well documented publication which meets basic scientific principles.

(27)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

Test substance	:	other TS (ethylene glycol monobutyl ether)
Remark	:	An 18-year old male ingested 360-480 ml of 22% 2-butoxyethanol (2-BE) on two separate occasions. The patient went to the hospital complaining of mild epigastric discomfort approximately 3 hours after ingesting between 360-480 ml of a glass cleaner containing 2% 2-BE. The physical examination was unremarkable at this time. Initial laboratory values including CBC, electrolytes and hepatic function tests were normal. Intravenous isotonic saline was administered at a rate of 200 ml/hour and the patient was admitted to the intensive care unit for observation. Approximately 10 hours after the first ingestion, the patient developed severe CNS depression, metabolic acidosis and mild elevation of hepatic enzymes. The serum 2-butoxy acetic acid (BAA) concentration 16 hours after ingestion was 4.86 mM. The patient was treated initially with sodium bicarbonate (i.v.) but continued to deteriorate and was started on hemodialysis approximately 24 hours after ingestion. During the course of dialysis, the acidosis resolved, as evidenced by the return of bicarbonate to normal. Urinalysis revealed the presence of intact red blood cell counts at a concentration of > 10/HPF, and increased concentrations of protein and ketones. Liver enzymes remained elevated. Oral ethanol therapy was initiated 20 minutes after dialysis was started. This treatment maintained the serum ethanol concentration at 58 mg/dl. Treatment also included i.v. doses of thiamine, folic acid and pyridoxine. The patient was alert, oriented and hemodynamically stable four hours after dialysis. The hepatic and

urinalysis abnormalities resolved 60 hours after ingestion.

Approximately 10 days after discharge, the patient ingested 480 ml of the same product and received ethanol and hemodialysis within 8 hours of hospital readmission. Intravenous ethanol (10%) was administered aft a rate that maintained the serum concentration at 74-88 mg/dl. Treatment also included i.v. administration of thiamine, folic acid and pyridoxine at the same concentrations as the previous episode. During his second admission, the patient did not develop the delayed, severe CNS depression or profound metabolic acidosis. The highest serum BAA concentration (2.07 mM) was measured 22 hours after ingestion and 2 hours after hemodialysis.

Clinically significant hemolytic anemia, oxaluria, ethylene glycol production, and renal failure were not noted in either episode. Complete blood counts and differential showed no evidence of hemolysis throughout each hospital stay.

Reliability : (2) valid with restrictions. Acceptable, well-documented publication which meets basic scientific principles.

(40)

Test substance : other TS (ethylene glycol monobutyl ether)

Remark : Post-shift (Friday afternoon) and pre-shift (Monday morning) urine samples from 6 healthy lacquerers exposed to butoxyethanol-containing detergent at a car manufacturing plant were collected and frozen until analysis. Prior to analysis, 50 micrograms of pentoxyacetic acid (PAA) and 50 micrograms of N-2-ethylhexyloxyacetylglutamine (EHAA-GLN) were added to the urine specimens (500 microliters) as internal standards. The samples were acidified to pH 2-3 and extracted twice with ethyl acetate (2 x 1 ml). The organic phases were combined and dried with MgSO4. The solvent was evaporated under nitrogen. To the dry residue, 20 mg of K2C/O3 and 1 ml of a mixture containing 4-nitrobenzylbromide (1 mg/ml) and 18-crown-6 ether (0.1 mg/ml) in acetonitrile were added. The reaction mixture was heated at 80 degrees C for 30 minutes. Resulting samples (10 microliter) were analyzed for N-butoxyacetylglutamine (BAA-GLN) and N-2-ethylhexyloxyacetylglutamine (EHAA-GLN) by HPLC. For comparison purposes, butoxyacetic acid was determined by GC following extraction and derivitization to the corresponding trimethylsilyl derivatives. Post-shift samples contained butoxyacetic acid (0.13-5.91 mmol/l) and its glutamine conjugate (0.12-2.45 mmol/l). Pre-shift urine samples contained only traces of these metabolites. The ratio of the glutamine conjugate to total butoxyacetic acid ranged from 0.16 to 0.64 (mean value 0.48), indicating that a substantial fraction of butoxyacetic acid was eliminated as the glutamine conjugate.

Reliability : (2) valid with restrictions. Acceptable, well-documented publication which meets basic scientific principles.

20.02.2002 (66)

Test substance : other TS (ethylene glycol monobutyl ether)

Remark : A 50-yr-old woman ingested 250-500 ml of a window cleaning product containing 12% butoxyethanol (i.e. 30-60 ml butoxyethanol ingested). Main effects were coma, absence of response to pain stimulus, breathing difficulties, metabolic acidosis, hypokalemia, rise in serum creatinine and increased urinary excretion of oxalate. Treatment was effective against hydroelectrolytic disturbances but haemoglobinuria inducing progressive erythropenia ensued on days 3-6. Her condition improved gradually and she was discharged on Day 10.
Information came from an IUCLID document for CAS No. 111-76-2 published by the European Chemicals Bureau on 11-FEB-2000.

Source : BP Chemicals Ltd. London

EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.
20.02.2002 (65)

Test substance : other TS (ethylene glycol monobutyl ether)
Remark : A 23-yr-old woman ingested 500 ml of a window cleaning product containing 12.7% butoxyethanol (i.e. equivalent to 63 ml butoxyethanol) and 3.2% ethanol. Main effects were coma, dilated pupils, obstructive respiration, metabolic acidosis, hyperventilation, depression of blood haemoglobin concentration from 11.9 g/dl to 8.9 g/dl over 2 days and haematuria. Urinary oxalate excretion was normal.

She was discharged from hospital on day 8.
Information came from an
IUCLID document for CAS No. 111-76-2 published by the European Chemicals Bureau on 11-FEB-2000.
Source : BP Chemicals Ltd. London
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.
20.02.2002 (37)

Test substance : other TS (ethylene glycol monobutyl ether)
Remark : A 53-yr-old chronic alcoholic male ingested 500 ml of a cleaning fluid containing 9.1% butoxyethanol (equivalent to 45.5 g) and 2.5% ethanol. He was admitted to hospital about 10 hours later in a state of coma with metabolic acidosis, shock and noncardiogenic pulmonary oedema. Heart rate was increased, blood pressure was decreased and there were transient polyuria and hypoxaemia. Hypochromic anemia was evident with haemoglobin concentration of 9.1 g/dl, haematocrit 25% and thrombopenia (85000). The patient was discharged after 15 days.
Information came from an IUCLID document for CAS No. 111-76-2 published by the European Chemicals Bureau on 11-FEB-2000.
Source : BP Chemicals Ltd. London
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.
20.02.2002 (18)

Test substance : other TS (ethylene glycol monobutyl ether)
Remark : 6 men and 3 women exposed for 4-8 hours to butoxyethanol at concentrations including 0.55 and 0.94 mg/l experienced effects such as nasal and ocular irritation, disagreeable metallic taste, increased nasal mucous discharge, headache, vomiting and urinary excretion of butoxyacetic acid. None of these subjects had increased erythrocyte fragility at either exposure concentration.
Information came from an IUCLID document for CAS No. 111-76-2 published by the European Chemicals Bureau on 11-FEB-2000.
Source : BP Chemicals Ltd. London
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The study was not available for review.
20.02.2002 (20)

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SIDS Dossier

and

Robust Study Summaries

for CAS No. 112-25-4

Existing Chemical	:	ID: 112-25-4
CAS No.	:	112-25-4
EINECS Name	:	2-hexyloxyethanol
EINECS No.	:	203-951-1
Molecular Weight	:	146.23
Molecular Formula	:	C8H18O2
Structural Formula	:	O(CCCCCC)CCO

Producer Related Part

Company	:	PCA Services, Inc.
Creation date	:	04.03.2002

Substance Related Part

Company	:	PCA Services, Inc.
Creation date	:	04.03.2002
Memo	:	
Printing date	:	16.06.2005
Revision date	:	16.06.2005
Date of last Update	:	16.06.2005
Number of Pages	:	60
Chapter (profile)	:	Chapter: 1, 2, 3, 4, 5, 7
Reliability (profile)	:	Reliability: without reliability, 1, 2, 3, 4
Flags (profile)	:	Flags: without flag, confidential, non confidential, WGK (DE), TA-Luft (DE), Material Safety Dataset, Risk Assessment, Directive 67/548/EEC, SIDS

1.0.1 OECD AND COMPANY INFORMATION

Type	:	Sponsor Country
Name	:	United States U.S. Environmental Protection Agency Mr. Oscar Hernandez, Director Risk Assessment Division (7403M)
Partner	:	No Partner
Date	:	08.02.2002
Street	:	1200 Pennsylvania Ave., NW
Town	:	Washington, DC 20460
Country	:	USA
Phone	:	202-564-7641
Telefax	:	
Telex	:	
Cedex	:	

Type	:	cooperating company
Name	:	Dow Chemical Company
Partner	:	
Date	:	
Street	:	
Town	:	Midland MI
Country	:	United States
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	

Type	:	
Name	:	BASF AG
Partner	:	
Date	:	
Street	:	Karl-Bosch-Str
Town	:	67056 Ludwigshafen
Country	:	Germany
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type	:	
Name	:	Shell Nederland Chemie B.V.
Partner	:	
Date	:	
Street	:	Vondelingenweg 601
Town	:	3196 KK Rotterdam
Country	:	Netherlands
Phone	:	
Telefax	:	
Telex	:	
Cedex	:	
Source	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Type	:	
Name	:	Union Carbide Benelux
Partner	:	

Date :
Street : Norderlaan 147
Town : 2030 Antwerpen
Country : Belgium
Phone :
Telefax :
Telex :
Cedex :
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.0.2 LOCATION OF PRODUCTION SITE

1.0.3 IDENTITY OF RECIPIENTS

1.1 GENERAL SUBSTANCE INFORMATION

Substance type : organic
Physical status : liquid
Purity : = 98 - 100 % w/w
Source : EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.1.0 DETAILS ON TEMPLATE

1.1.1 SPECTRA

1.2 SYNONYMS

2-(Hexyloxy)ethanol
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

3-Oxa-1-nonanol
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Ethanol, 2-(hexyloxy)-
Source : Union Carbide Benelux Antwerpen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Ethanol, 2-(hexyloxy)- (6CI, 7CI, 8CI, 9CI)
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Ethylene glycol mono hexyl ether
Source : Shell Nederland Chemie B.V. Rotterdam
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Ethylene glycol monohexyl ether
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Ethylene glycol n-hexyl ether

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Glycol monohexyl ether
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Hexyl Ccellosolve
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Hexylcellosolve
Source : Shell Nederland Chemie B.V. Rotterdam
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

n-Hexyl Cellosolve
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

n-Hexylglykol
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

1.3 IMPURITIES

CAS-No : 118-87-5
EINECS-Name : Octanol
Molecular formula : C6H14O
Value : <1 % w/w
Source : The Dow Chemical Company

CAS-No : 111-46-6
EINECS-Name : Diethylene glycol
Molecular formula : C4H10O3
Value : <1 % w/w
Source : The Dow Chemical Company

CAS-No :
EINECS-Name : Peroxides
Value : <1 % w/w
Source : The Dow Chemical Company

1.4 ADDITIVES

Remark : No addititives typically

1.5 QUANTITY

Quantity : 454 – 4,540 metric tons in the U.S.
Source : 2002 US TSCA Inventory Update Report
Remark : (1) valid without restriction. Up to date reference.

1.6.1 LABELLING

1.6.2 CLASSIFICATION

1.7 USE PATTERN

Type	:	Type
Category	:	Wide Dispersive Use
Source	:	Chinn H, Anderson E and Yoneyama M, Glycol Ethers, CEH Marketing Research Report, SRI International. 2000.
Reliability	:	(1) valid without restriction. Up to date reference.
Type	:	Use
Category	:	Coalescing aid for latex paints and in cleaners.
Source	:	Chinn H, Anderson E and Yoneyama M, Glycol Ethers, CEH Marketing Research Report, SRI International. 2000.
Reliability	:	(1) valid without restriction. Up to date reference.

1.7.1 TECHNOLOGY PRODUCTION/USE

1.8 OCCUPATIONAL EXPOSURE LIMIT VALUES

Type of limit	:	MAK (DE)
Limit value	:	
Remark	:	Kein MAK-Wert festgelegt. [No MAK value established] Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. Study was not available for review.

(48)

Type of limit	:	MAK (DE)
Limit value	:	
Remark	:	Kein MAK-Wert festgelegt. [No MAK value established] Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. Study was not available for review.

(47)

1.9 SOURCE OF EXPOSURE

Source of exposure	:	Human exposure during manufacture
Remark	:	Manufactured in closed systems. Some inhalation or dermal exposure may

occur during sampling. Exposure potential during manufacture is less than during intended use.

Source of exposure : Human exposure during intended use.
Remark : Occupational exposure can occur via inhalation and dermal contact during applications of surface coatings and cleaners containing ethylene glycol n-hexyl ether (EGHE) as a solvent or coalescing aid. Exposure is typically minimized by the use of engineering controls and appropriate workplace practices.

Source of exposure : Environmental exposure
Remark : EGHE may be released to the environment into air or water during manufacture. Such releases are minimized through the use of closed systems, engineering controls and biodegradative treatment of aqueous waste streams. EGHE is also released to the environment during use as a component in surface coatings and cleaners through evaporation. Some of these applications may use open processing, but often with engineering controls.

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: Selbsteinstufung [self-classification] BASF AG
Labelled by :
Class of danger : 1 (weakly water polluting)
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Remark : Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Reliability : (4) not assignable. Study was not available for review.

(29)

1.14.2 MAJOR ACCIDENT HAZARDS

Legislation : Stoerfallverordnung [accident regulation] (DE)
Substance listed : no
No. in directive :
Source : BASF AG Ludwigshafen

EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Remark : Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Reliability : (4) not assignable. Document was not available for review.

(44)

1.14.3 AIR POLLUTION

Classified by : other: BASF

Labelled by :

Number : 3.1.7 (organic substances)

Class of danger : III

Remark : begruendete Schaetzung aufgrund unvollstaendiger Daten [protective measures established based on incomplete data]
(1990)
Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. Study was not available for review.

1.15 ADDITIONAL REMARKS

1.16 LAST LITERATURE SEARCH

1.17 REVIEWS

1.18 LISTINGS E.G. CHEMICAL INVENTORIES

2.1 MELTING POINT

Value	:	= -50.1 ° C
Sublimation	:	
Method	:	other : unknown
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Reliability	:	(2) valid with restrictions. Published in a peer-reviewed reference book.
Flag	:	Critical study for SIDS endpoint.

(50)

Value	:	= -45 ° C
Sublimation	:	no
Method	:	other
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 – 1.4
Reliability	:	(2) valid with restrictions. Data were obtained from a MSDS.

(31)

Remark	:	Erstarrungstemperatur [Solidification temperature]: ca. -42 Grad C bei 1013 mbar Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The primary references were not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document.

(23)(24)(26)(44)

2.2 BOILING POINT

Value	:	= 208.1. ° C
Decomposition	:	
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Reliability	:	(2) valid with restrictions. Published in a peer-reviewed reference book.
Flag	:	Critical study for SIDS endpoint

(50)

Value	:	= 207.8 ° C at 1013 hPa
Decomposition	:	
Method	:	
Year	:	
GLP	:	no data
Remark	:	
Test substance	:	as prescribed by 1.1 – 1.4
Reliability	:	(2) valid with restrictions. Data were obtained from a MSDS.

(31)

Value	:	= 208.5 ° C at 1013.3 hPa
Decomposition	:	

Method	:	other: berechnet [calculated]
Year	:	1985
GLP	:	
Test substance	:	
Remark	:	nachvollziehbar und akzeptabel [reproducible and acceptable] Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance	:	Reinheit: 99.93 Fl.%
Reliability	:	(4) not assignable for this submission. The primary reference was not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document.

(10)

2.3 DENSITY

Type	:	density
Value	:	0.89 at 20 degrees C
Method	:	
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Reliability	:	(2) valid with restrictions. Published in a peer-reviewed reference book
Flag	:	Critical study for SIDS endpoint

(50)

Type	:	density
Value	:	= .887 - .89 g/cm3 at 20° C
Method	:	other: DIN 51 757
Year	:	
GLP	:	
Test substance	:	
Remark	:	Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The primary references were not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document.

(24)(25)(27)(46)

2.3.1 GRANULOMETRY

2.4 VAPOUR PRESSURE

Value	:	= .067 hPa at 20° C
Decomposition	:	no
Method	:	other: unknown
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Decomposition	:	no
Remark	:	value listed is 0.05 mm Hg

Reliability : (2) valid with restrictions. Published in a peer-reviewed reference book.
Flag : Critical study for SIDS endpoint

(50)

Value : = .08 hPa at 20° C
Remark : Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The primary references were not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document.

(24)(25)

Value : = .1 hPa at 22.9° C
Decomposition :
Method other (measured): dynamisch unter Argonatmosphäre [Dynamic under an argon atmosphere]
Year : 1985
GLP : no
Test substance :
Remark : nachvollziehbar und akzeptabel [reproducible and acceptable]

1013.25 hPa bei 208.1 Grad C (berechnet aus gemessenen Werten durch Dampfdruckregression)[Calculated from measured values through water vapor pressure regression].

Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Result : Temperatur in Grad C/Dampfdruck in hPa(gemessen) [Temperature in degrees C/vapor pressure in hPa (measured)]:
22.90/0.10; 41.62/0.50; 50.26/1.00; 74.31/5.00; 86.25/10.00; 118.74/50.00; 135.45/100.0; 182.58/500.0; 194.37/700.0; 208.11/1008.0
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance : Reinheit [Purity]: 99.74 %
Reliability : (4) not assignable. The primary reference was not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document.

(11)

Value : = 1013.25 hPa at 208.1° C
Decomposition :
Method other (measured): dynamisch unter Argonatmosphäre [dynamic under an argon atmosphere]
Year :
GLP :
Test substance :
Remark : Reinheit [purity]: 99.74%

Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The primary reference was not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document.

(8) (46)

Value : = 999.77 hPa at 208.2° C
Decomposition :
Method other (measured): dynamisch unter Stickstoffatmosphäre Argonatmosphäre [dynamic under a nitrogen or argon atmosphere]
Year : 1985
GLP : no
Test substance :
Remark : Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Result : nachvollziehbar und akzeptabel [reproducible and acceptable]

Temperatur in Grad C/Druck in hPa (gemessen) [Temperature in degrees C/vapor pressure in hPa (measured)]:
:
49.81/1.000; 66.07/3.000; 86.32/9.997; 107.82/29.999;
135.64/99.970; 194.78/699.850; 208.21/999.770
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance : Reinheit (purity): 99.93 Fl.%
Reliability : (4) not assignable. The primary reference was not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document.

(10)

Value : = 999.77 hPa at 1208.2° C
Decomposition :
Method other (measured): dynamisch unter Stickstoffatmosphäre [dynamic under a nitrogen atmosphere]
Year :
GLP :
Test substance :
Remark : Reinheit [purity]: 99.93 %

Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The primary reference was not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document.

(7)

2.5 PARTITION COEFFICIENT

Log pow : = 1.55 at ° C
Method : other: calculated using the EPIWIN KOWWIN (v1.66) program
Year : 2003
GLP : no
Test substance : as prescribed by 1.1 –1.4
Remark : The input for this model run was CAS No. 112-25-4.
Reliability : (2) valid with restrictions. Data were obtained by modeling.
Flag : Critical study for SIDS endpoint

Log pow : = 1.97 at 25° C
Method : other (measured)
Year : 1989
GLP : no
Test substance :
Remark : nachvollziehbar und akzeptabel [reproducible and acceptable]

Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance : Reinheit [purity] (lt. GC): 99.2 %
Reliability : (4) not assignable. The primary reference was not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document.
Flag : Supporting study for endpoint

(12)

Log pow : = 1.97 at 25° C
Method : other (measured)
Year :
GLP :
Test substance :
Remark : Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The primary reference was not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document.

(9)

2.6.1 WATER SOLUBILITY

Value : = 9.9 g/l
Qualitative :
Pka :
PH :
Method : other: unknown
Year :
GLP : no data
Test substance : as prescribed by 1.1 –1.4
Reliability : (2) valid with restrictions. Published in a peer-reviewed reference book.
Flag : Critical value for SIDS endpoint.

(50)

Value : = 9.46 g/l at 20 ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Method : other
Year :
GLP : no
Test substance : as prescribed by 1.1 –1.4
Reliability : (2) valid with restrictions. Data came from a MSDS.

(31)

Value : = 1.87 other: % at 20 ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Remark : Reinheit: 99 % [purity]

Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The primary reference was not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document.

(35)

Value : = 1.87 other: mass% at 20 ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Method : other: gaschromatographisch gemessen [measured using gas chromatography]
Year : 1993
GLP :
Test substance :
Remark : nachvollziehbar und akzeptabel [reproducible and acceptable]

Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Result : Temperatur in Grad C/Löslichkeit in Massen% (gemessen) [Temperature in degrees C/solubility in mass percent (measured)]:
0/3.24; 10.0/2.53; 30/1.92; 40.0/0.88; 50.0/0.73; 60/0.68;
70/0.71; 80.0/0.68; 90.0/0.65
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance : Reinheit [purity] : 99+ mass%
Reliability : (4) not assignable. The primary reference was not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document.

(43)

Value : at 20 ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Remark : Loeslichkeit in anderen Loesemittelm: Loeslich in vielen organischen Loesemitteln.
Loeslichkeit in Wasser: teilweise mischbar [Solubility in other solvents: Soluble in many organic solvents. Solubility in water: partially miscible]

Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The primary reference was not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document.

(24)

Value : at 20 ° C
Qualitative :
Pka : at 25 ° C
PH : at and ° C
Remark : Loeslichkeit in Wasser: teilweise mischbar [Solubility in water: partially miscible]

Data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Source : BASF AG Ludwigshafen

Reliability	:	EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA) (4) not assignable. The primary reference was not available for review. A reliability rating of 2 (valid with restrictions) was assigned in the original European Chemicals Bureau IUCLID document. (25)

2.6.2 SURFACE TENSION

2.7 FLASH POINT

Value	:	= 94 ° C
Type	:	
Method	:	other: DIN 51 758
Year	:	
GLP	:	
Test substance	:	
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The primary reference was not available for review. (24) (46)

Value	:	= 94 ° C
Type	:	
Method	:	other: DIN 51 758
Year	:	
GLP	:	
Test substance	:	
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The primary reference was not available for review. (25) (27)

2.8 AUTO FLAMMABILITY

Remark	:	Zuendtemperatur: 220 Grad C [Ignition temperature: 220 degrees C] (DIN 51 794) All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The primary reference was not available for review (24) (46)
Remark	:	Zuendtemperatur: 220 Grad C [Ignition temperature: 220 degrees C] (DIN 51 794) All data (except the reliability rating) came from an IUCLID document for

CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.
(4) (25) (27)

2.9 FLAMMABILITY

Remark : Explosionsgrenzen in Luft [Explosion limit in air]:
untere Grenze [lower limit]; 1.2 vol.%
obere Grenze [upper limit]: 8.4 vol.%

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.
(46)

2.10 EXPLOSIVE PROPERTIES

Result : other: Explosionsgrenzen in Luft [Explosion limit in air]: 1.2 - 8.4 Vol.%

Remark : All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.
(24)

Remark : nicht explosionsgefaehrlich aufgrund der chemischen Struktur [not hazardous by explosion based on chemical structure]

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.
(26)

2.11 OXIDIZING PROPERTIES

Remark : nicht brandfoerdernd aufgrund der chemischen Struktur Struktur [does not promote combustion based on chemical structure]

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.

(26)

2.12 ADDITIONAL REMARKS

Remark : Verbrennungswärme [heat of combustion]: 33136 J/g bei 25 Grad C [degrees C]

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.

(46)

Remark : Verdampfungswärme [heat of vaporization] : 475 J/g bei 25 Grad C

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.

(46)

Remark : Azeotrope Zusammensetzung [azeotropic mixture]: 9% n-Hexylglykol, 91% Wasser [water]

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.

(46)

Remark : Angaben über IR- und Massenspektren sind von Grasselli zusammengefaßt [data for IR and mass spectroscopy are summarized from Grasselli]

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.

(33)

Remark : Viskositaet [viscosity]: 5.3 mPa.s bei 20 Grad C

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.

(25) (27)

Remark : Verdampfungswärme am Normalsiedepunkt berechnet nach

Clausius- [Clapeyron Heat of combustion and normal boiling point are calculated according to Clausius-Clapeyron]: 341.5 J/g

All data (except the reliability rating) came from a IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.
(10)

Remark : Kritische Daten [critical data]
Kritische Temperatur [critical temperature]: 359 Grad [degrees] C
Kritischer Druck [critical pressure]: 26.3 bar
Kritische Dichte [critical density]: 0.282 g/cm3
kritische Kompressibilität [critical compressibility]: 0.258

All data (except the reliability rating) came from a IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.
(27)

Remark : Azeotrope Zusammensetzung (Massenanteil) [azeotropic mixture (mass portion)]: 9% n-Hexylglykol,
91% Wasser
Siedepunkt des azeotropen Gemisches [boiling point of the azeotropic mixture]: 99.7 Grad [degrees] C

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.
(27)

Remark : Explosionsgrenzen in Luft [Explosive limits in air]: 1.2 - 8.4 Vol.%

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.
(4) (25) (27)

Remark : Gefährliche Reaktion bei Einwirkung von: Leichtmetallen (Entwicklung von Wasserstoff), starken Oxidationsmitteln [Hazardous reaction under the influence of: light metals (generation of hydrogen), strong oxidizers]

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.

(25)

Remark : Spezifische Wärme (Specific Heat): 1.98 kJ/(kg*K) bei 20 Grad [at 20 degrees] C (berechnet) (Calculated)
All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The primary reference was not available for review.

(27)

Remark : Wärmeleitfähigkeit [caloric conductivity]: 147.1 mW/(m*K) bei 20 Grad [degrees] C

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The primary reference was not available for review.

(27)

3.1.1 PHOTODEGRADATION

Type	:	air
Light source	:	other
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Direct photolysis		
Halflife t1/2	:	4.9 hour(s) (12-hr day)
Degradation	:	% after
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	1.5E6 OH/cm3
Rate constant	:	= .0000000000263395 cm3/(molecule*sec)
Degradation	:	50 % after 4.9 hours
Method	:	other: calculated using the EPIWIN AOP (v1.90) program
Year	:	2003
GLP	:	no
Test substance	:	as prescribed by 1.1 – 1.4
Remark	:	The input to the program was CAS No.112-25-4. No other variables influence this calculation.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint

Type	:	air
Light source	:	
Light spect.	:	nm
Rel. intensity	:	based on Intensity of Sunlight
Indirect photolysis		
Sensitizer	:	OH
Conc. of sens.	:	500000 molecule/cm3
Rate constant	:	= .0000000000258203 cm3/(molecule*sec)
Degradation	:	= 50 % after 14.9 hour(s)
Deg. Product	:	
Method	:	other (calculated): AOP, Version 1.51
Year	:	1994
GLP	:	no
Test substance	:	
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The primary reference was not available for review.

(16)

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
Deg. Product	:	
Method	:	other: calculated using EPIWIN HYDROWIN (v 1.67) program with CAS No. 112-25-4 as the input. No other variables influence this calculation.

Year	:	2001
GLP	:	no
Test substance	:	as prescribed by 1.1 – 1.4
Remark	:	The EPIWIN HYDROWIN (v 1.67) program was used to estimate the rate of hydrolysis in water under neutral abiotic conditions. The input into the program was CAS No. 2807-30-9. No other variables influence this calculation.
Result	:	The EPIWIN HYDROWIN program cannot be used to estimate the hydrolysis rate of ethers in water. In general, ethers are highly resistant to hydrolysis under neutral abiotic aqueous conditions.
Reliability	:	(4) not assignable

3.1.3 STABILITY IN SOIL

3.2 MONITORING DATA

3.3.1 TRANSPORT BETWEEN ENVIRONMENTAL COMPARTMENTS

Type	:	volatility
Media	:	water - air
Air (level III)	:	8.837 %
Water (level III)	:	86.4%
Soil (level III)	:	4.54%
Biota (level II / III)	:	0.195 %
Method	:	other: calculated using EPIWIN Level III Fugacity Model
Year	:	2003
Test substance	:	as prescribed by 1.1 – 1.4
Remark	:	Measured inputs to the EPIWIN program run are melting point (-50 degrees C), boiling point (208 degrees C), vapor pressure (0.09 mm Hg) and water solubility (9.9 g/l). Emission rates inputted to the model were air (1000 kg/hr), water (500 kg/hr) and soil and sediment (0 kg/hr)
Result	:	The EPIWIN HENRY (v3.10) model estimates a Henry's Law Constant of 1.73E-7 atm-m3/mole at 25 degrees C (Bond Estimate). The EPIWIN PCKOC (v1.66) program estimates a Koc (soil-sediment partition constant) of 10. Level III Fugacity model estimates half-lives in: air = 9.746 hours, water = 208 hours, soil = 208 hours and sediment = 832.3 hours.
Reliability	:	(2) valid with restrictions. Data were obtained by modeling.
Flag	:	Critical study for SIDS endpoint

Type	:	adsorption
Media	:	
Air (level I)	:	
Water (level I)	:	
Soil (level I)	:	
Biota (level II / III)	:	
Soil (level II / III)	:	
Method	:	other: berechnet [calculated] (PCKOC, Howard/Meylan, 1993)
Year	:	
Remark	:	Adsorption im Boden: Koc = 2.84 All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen

EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The primary reference was not available for review.
(16)

3.3.2 DISTRIBUTION

Media :
Method : Calculation according Mackay, Level I
Year : 1995
Remark : Bevorzugtes Zielkompartiment [preferred environmental compartment destination]: Wasser [water] (99%)
Zugrundeliegende Daten fuer die Berechnung [resource data for the calculation]:
Wasserloeslichkeit water [solubility] 500000 mg/l (geschaetzt [estimated])
Dampfdruck[vapor pressure] 8 Pa
log Pow 1.86 (aus anderer Quelle [from other sources])

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The primary reference was not available for review.
(28) (38)

3.4 MODE OF DEGRADATION IN ACTUAL USE

3.5 BIODEGRADATION

Type : aerobic
Inoculum : other: non-acclimated sewage microorganisms
Contact time :
Degradation : = 100 % after 20 day
Result :
Deg. Product : not measured
Method : other: as described in "Standard Methods for the Examination of Water and Wastewater", 16th ed., USPHA, Washington, D.C., 1985.
Year : 1987
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Result : The measured and calculated theoretical oxygen demand were 1.89 and 2.52 mg/mg, respectively. After 5, 10 and 20 days of incubation, the percent biooxidation was 72, 93 and 100% (respectively).
Test condition : A modified version of the biochemical oxygen demand (BOD) method published in "Standard Methods for the Examination of Water and Wastewater", 16th edition, Am. Public Health Association, 1985 was used. A discussion of these modifications appears in Price et al., "Brine shrimp bioassay and seawater BOD of petrochemicals", J. Water Poll. Control Fed., Jan. 1974. Nonacclimated domestic sewage organisms were used as seed in the test.

Domestic wastewater was filtered through glass wool and added (3 ml/bottle) as seed material to clean BOD bottles. A buffered, aerated solution containing minerals was then added. Small amounts of test material were added from a 0.1 % stock solution to yield concentrations of

3, 7 and 10 mg/l. A control with no test material also was run. At least two of the concentrations were tested in duplicate. Dissolved oxygen (DO) was monitored five times during the course of the 20-day test. The solution was reaerated when the DO dropped below 4.0 mg/l. Reaeration (if needed) was accomplished by dividing the BOD bottle contents between 2 BOD bottles, sealing, shaking them twenty times, returning contents to the original BOD bottle, recording the oxygen level, resealing, and returning the BOD bottle to the incubator. Samples were analyzed routinely for nitrites and nitrates. Results of the tests were expressed in terms of % biooxidation calculated as the cumulative oxygen uptake for the test material minus a control x 100 / initial concentration of test material x theoretical oxygen demand.

Test substance : Test material was hexyl CELLOSOLVE®.
Reliability : (2) valid with restrictions. Comparable to guideline study with acceptable restrictions. Purity was not stated.
Flag : Critical study for SIDS endpoint

(51)

Type : aerobic
Inoculum : other: Ablauf einer Laborkläranlage, communal [runoff from a clarification plant, communal]
Concentration : 20mg/l related to DOC (Dissolved Organic Carbon)
related to
Contact time :
Degradation : = 86 % after 8 day
Result : other: bezogen auf DOC [obtained from DOC]
Kinetic of test substance : 1 day = 3.3 **%**

5 day = 85.4 **%**
%
%
%

Deg. Product :
Method : OECD Guide-line 301 E "Ready biodegradability: Modified OECD Screening Test"
Year : 1990
GLP : no
Test substance :
Remark : Lag-Phase = 1 Tag
Leicht biologisch abbaubar [easily biodegradable]

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance : n-Hexylglykol: Reinheitsgrad groesser [purity greater than] 98%
Verunreinigungen/Begleitstoffe [impurities and coproducts]: bis zu 0.2% Diethylenglykol-
monobutylether, 0.1% Diethylenglykol, 0.1% Diethylenglykol-monohexylether
Reliability : (4) not assignable. The study was not available for review.

(22)

Type : aerobic
Inoculum : other: BASF-Belebtschlamm [activated sludge process]
Contact time :
Degradation : = 98 % after 5 day
Result :

Kinetic of test substance	:	1 day = 3 **%** 4 day = 86 **%** 7 day = 98 **%** **%** **%**
Deg. Product	:	
Method	:	other: Standversuch [stationary study]
Year	:	1981
GLP	:	no
Test substance	:	other TS: n-Hexylglykol rein pure [n-hexylglycol]
Remark	:	Anfangskonzentration = 400 mg/l bezogen auf TOC [Initial concentration = 400 mg/l based on TOC] Gut eliminierbar, vorwiegend durch biologischen Abbau [Readily eliminated primarily through biologic degradation] All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The study was not available for review.

(15)

3.6 BOD5, COD OR BOD5/COD RATIO

BOD5		
Method	:	other: BSB5-Bestimmung [BSB5 determination]
Year	:	1989
GLP	:	no
Concentration	:	related to
BOD5	:	mgO2/l
COD		
Method	:	other: CSB-Bestimmung [CSB determination]
Year	:	1989
GLP	:	no
COD	:	= 2470 mg/g substance
RATIO BOD5 / COD		
BOD5/COD	:	< .001
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Result	:	BSB5 = 2 mg/g
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance	:	n-Hexylglykol: Reinheitsgrad groesser 98% [purity >98%] Verunreinigungen/Begleitstoffe [Impurities/coproducts]: bis zu 0.2% Diethylenglykol- monobutylether, 0.1% Diethylenglykol, 0.1% Diethylenglykol-monohexylether
Reliability	:	(4) not assignable. The study was not available for review.

(23)

BOD5		
Method	:	other: BSB5-Bestimmung [BSB5 determination]
Year	:	
GLP	:	no
Concentration	:	related to
BOD5	:	mgO2/l

RATIO BOD5 / COD

BOD5/COD : = .07

Remark : All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Result : BSB5 = 154 mg/l
CSB = 2337 mg/l

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The study was not available for review.

(13)

Remark : All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.

Result : CSB = 55-225 mg/l

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. This study was not available for review.

(37)

3.7 BIOACCUMULATION

BCF : 5.398

Elimination :

Method : BCFwin v2.15

Year : 2004

GLP :

Test substance : as prescribed by 1.1- 1.4

Remark : The estimated Log BCF = 0.732. Measured inputs to the EPIWIN program run are melting point (-50 degrees C), boiling point (208 degrees C), vapor pressure (0.09 mm Hg) and water solubility (9.9 g/l).

Reliability : (2) valid with restrictions. Data were obtained by modeling

3.8 ADDITIONAL REMARKS

Remark : Adsorption an Aktivkohle [adsorption in activated carbon]:
Prozentuale Reduktion [per cent reduction] = 87.1%; Anfangskonzentration [initial concentration]: 975
mg/l; Endkonzentration [final concentration]: 126 mg/l.

All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. This study was not available for review.

(32)

4.1 ACUTE/PROLONGED TOXICITY TO FISH

Type	:	static
Species	:	Brachydanio rerio (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	yes
NOEC	:	= 41
LC50	:	> 94 and < 215
Method	:	OECD Guide-line 203 "Fish, Acute Toxicity Test"
Year	:	1984
GLP	:	yes
Test substance	:	as prescribed by 1.1 – 1.4
Result	:	All fish exposed to 46.4 mg/l (nominal) and 100 mg/l (nominal) survived exposure for 96 hours. All fish exposed to concentrations > = 215 mg/l died within 1 hour. Apathy was noted in fish exposed to 100 mg/l (nominal concentration) at all time points. Analytically detected concentrations at 1 and 96 hours were within 85.1-102.6% of nominal. The analytical concentrations corresponding to the No observed effect concentrations (NOEC), LC0 and LC100 (46.4, 100 and 215 mg/l nominal concentrations) at all time points were 41, 94 and 215 mg/l, respectively. The LC50 values were between 94 and 215 mg/l at all time points. The pH and oxygen content ranged from 8.3 – 8.4 and 7.7 – 8.2 mg/l (respectively) throughout the experiment. The temperature remained steady at 23 degrees C.
Test condition	:	Fish: The ranges for body length and weight of the zebra fish were 2.7 – 3.1 cm and 0.17 – 0.3 g, respectively. The approximate age of the fish was 4 months. Fish were fed standard feed for aquarium fish. Food was withdrawn 1 day before exposure. Mortality during the last 2 weeks of housing was 0%. Test water: The fish were housed in a flow-through tank containing unchlorinated, carbon-filtered tap water with a total hardness of 250 mg/l CaCO3, pH of 8.0 – 8.6 and temperature of 20-27 degrees C approximately 1.5 months before being used in the test. The water was aerated with oil-free air to > 60% saturation. The water was regularly tested for the presence of contaminants and microbes. Test conduct: Glass aquaria (30 x 22 x 24 cm3) containing 10 liters of test water were loaded with 10 zebra fish each (0.23 g test fish/ liter of water). Concentrations tested were based on the results of 2 preliminary studies. Zebra fish were exposed over a 96-hour period to a range of concentrations spaced by a factor of about 2.2 (46.4, 100, 215, 464 and 1000 mg/l). An untreated control was included. Fish were placed in the aquaria within 25 minutes of addition of test material. They were not fed during the test. The water was maintained at 23 degrees under slight aeration. Fish were observed 1, 4, 24, 48, 72 and 96 hours after exposure. The pH, temperature and oxygen content were measured 1, 24, 48, 72 and 96 hours after exposure. The LC0, LC50 and LC100 concentrations and the NOEC were to be determined for each time point. The concentrations of test material present at 1 and 96 hours were analytically confirmed. If possible, the LC5 and LC95 were to be calculated using probit analysis.
Test substance	:	Purity was 98.23% by gas chromatography. The stability of the test material over the study period was proved by reanalysis.
Reliability	:	(1) valid with restrictions. OECD Guideline study.
Flag	:	Critical study for SIDS endpoint

(5)

Type	:	static
Species	:	Pimephales promelas (Fish, fresh water)
Exposure period	:	96 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
LC50	:	m = 140
Method	:	other:ASTM
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Test condition	:	Ten organisms were used per test concentration (concentrations were not stated). No other details were given.
Test substance	:	Test material was hexyl CELLOSOLVE®. Purity was not stated.
Reliability	:	(4) not assignable. There was not enough information to assign a reliability rating
Flag	:	Supporting study for SIDS endpoint

(51)

4.2 ACUTE TOXICITY TO AQUATIC INVERTEBRATES

Type	:	
Species	:	Daphnia magna (Crustacea)
Exposure period	:	48 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC0	:	= 58
EC50	:	= 145
EC100	:	= 320
Method	:	other: daphnia study according to DIN 38412/11
Year	:	1989
GLP	:	no
Test substance	:	as prescribed by 1.1 – 1.4
Remark	:	The original record in the IUCLID database has been replaced with a more robust version. Test substance purity data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Result	:	None of the animals exposed to 0, 32 or 58 mg/l died. None of the animals exposed to 100 mg/l died within 24 hours; however, 1/5 and 2/5 animals in 2 vessels containing 100 mg/l died by 48 hours (overall rate of 15%). For Daphnia exposed to 180 mg/l, the mortality rate at 3, 6, 24 and 48 hours was 35%, 45%, 70% and 70%. All animals exposed to 320 or 580 mg/l died within 3 hours. The no effect concentrations at 3, 6, 24 or 48 hours were 100, 100, 100 and 58 mg/l, respectively. The EC100 was 320 mg/l at all time points. The EC50 values at 3, 6, 24 and 48 hours were 194, 183, 158 and 145 mg/l, respectively. The final oxygen concentration and pH of all the vessels ranged from 8.3 to 8.6 mg/l and 7.52 to 7.69, respectively. There was no apparent effect of test material concentration on either of these variables. The temperature remained constant at 21 degrees C.
Test condition	:	Daphnia magna Straus were used in the test. They were fed with Scenedesmus subspicatus once/day. The reproduction rate was 3 animals/day. Animals (age not listed) were placed in 50 ml beakers with 20 ml test water (N = 5 per vessel). Four vessels were prepared per

concentration. The conductivity, Ca/Mg and Na/K ratios of the water were 658 microS/cm, 5:1 and 20:1, respectively. Test water contained 0, 32, 58, 100, 180, 320 or 580 mg/l test material. Water was changed daily (except on weekends). The temperature was to be maintained at 18 to 22 degrees C. Animals were checked for immobilization at 3, 6, 24 and 48 hours. Water was analyzed for pH, temperature and oxygen content at 48 hours. During the test the temperature was to remain constant to within 1 degree, and the oxygen concentration at termination had to be > 2 mg/l for the test to be considered valid. The EC50 values were determined graphically.

Test substance : n-Hexylglykol: Reinheitsgrad groesser 98% [purity >98%] Verunreinigungen/Begleitstoffe [impurities/coproducts]: bis zu [up to] 0.2% Diethylenglykol-monobutylether, 0.1% Diethylenglykol, 0.1% Diethylenglykol-monohexylether

Reliability : (2) valid with restrictions. Acceptable, well-documented study which meets basic scientific principles. A translated version of the study was used to construct this summary.

Flag : Critical study for SIDS endpoint

(18)

Type : static
Species : Daphnia magna (Crustacea)
Exposure period : 48 hour(s)
Unit : mg/l
Analytical monitoring : no data
LC50 : m = 305
Method : other: test procedures followed those recommended by EPA and ASTM
Year : 1987
GLP : no data
Test substance : as prescribed by 1.1 – 1.4
Remark : Lighting conditions, method of calculating the LC50 value, numbers of deaths at each concentration, condition of controls and purity and solubility/insolubility of the test material were not listed.

Data were listed as LC50 values, rather than EC50 values.

Result : The LC50 value was 305 mg/l.

Test condition : Daphnia magna stocks were originally obtained from the EPA laboratory at Duluth, MN. They were maintained at 20-22 degrees C in a series of 600 ml beakers filled with Kanawha River water obtained from the South Side Boat Ramp (Charleston, SC). Daphnia were fed three times a week with a laboratory-prepared food consisting of trout food, yeast and alfalfa powder. Daphnia used in the test were offspring of 20-50 gravid females isolated for 24 hours.

A series of from 5-10 equidistant concentrations based on results of fish toxicity studies (plus control) were tested. Tests were conducted in 250 ml beakers containing 100 ml of test solution (in Kanawha River water) and 5 Daphnia (less than 24 hours old). Tests were run in duplicate. Dissolved oxygen and pH were determined initially and at 48 hours for all test solutions (dissolved oxygen values were not listed). Total hardness, alkalinity, pH and conductivity of the test and holding water were 55 mg/l as CaCO3, 36 mg/l as CaCO3, 6.7, and 250 micromhos/cm. Mortalities were recorded at 24 and 48 hours.

Test substance : The test substance was hexyl CELLOSOLVE®.

Reliability : (2) valid with restrictions. Basic data given.

Flag : Supporting study for SIDS endpoint

(51)

4.3 TOXICITY TO AQUATIC PLANTS E.G. ALGAE

Species	:	Scenedesmus subspicatus (Algae)
Endpoint	:	Other: growth rate and biomass
Exposure period	:	72 hour(s)
Unit	:	mg/l
Analytical monitoring	:	no data
EC10	:	11 (biomass), 23 (growth rate)
EC50	:	98 (biomass), 198 (growth rate)
Method	:	other: Scenedesmus-cell reproduction inhibition test DIN 38412 L 9
Year	:	1989
GLP	:	no data
Test substance	:	as prescribed by 1.1 – 1.4
Remark	:	The original records in the IUCLID database (4) have been replaced with one robust summary. The study was translated into English from German by the reviewer. Test substance purity data came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000. Fluorescence measures chlorophyll content, and chlorophyll content is a measure of biomass. In a study described by Herman et al. (Aquatic Toxicol 18:87-100, 1990), 4 different ways of measuring biomass were checked for sensitivity (cell number, absorbance, chlorophyll content and dry weight). Measuring cell number was the most sensitive means of assessing algal cell growth, followed by absorbance and chlorophyll content, which were of equal utility. Since most test methods use absorbance for calculating biomass, and results of tests measuring chlorophyll content and absorbance are similar, tests employing fluorescence to measure chlorophyll content should be as sensitive as those employing absorbance as a means of assessing algal biomass. Growth medium chemistry (other than pH), source of dilution water, size of exposure vessels and volumes of solution, method of preparation of test solutions and light conditions were not described. The pH limit for a valid test was not listed. However, the range allowed in an OECD 201 study is 7-9. The final pHs of the solutions containing 5 or 10 mg/l were slightly higher than 9 (9.04 and 9.15, respectively). This deviation did not appear to affect the outcome of the study.
Result	:	In algae exposed to 0, 5, 10, 25, 50, 100 or 250 mg/l test material for 72 hours, the reported growth rates were 1.18, 1.14, 1.12, 1.10, 1.04, 0.95 and 0.24, and the biomass inhibition was 6.8, 11.4, 13.8, 22.1, 41.8 and 85.4 percent, respectively. Based on these data EC10 and EC50 values at 72 hours for growth inhibition (GI) and biomass inhibition (BI) were 23 and 198 mg/l (GI) and 11 and 98 mg/l (BI). There was no EC0 value for either inhibition of growth rate or biomass. In algae exposed to 0, 5, 10, 25, 50, 100 or 250 mg/l test material for 96 hours, the reported growth rates were 1.08, 1.09, 1.08, 1.08, 1.06, 0.94 and 0.11, and the biomass inhibition was 6.4, 10.4, 12.0, 23.2, 46.5 and 94.6 percent, respectively. Based on these data EC10 and EC50 values at 96 hours for GI and BI were 89 and 147 mg/l (GI), and 12 and 70 mg/l (BI). The EC0 value for growth rate inhibition was 25 mg/l. There was no EC0 value for biomass inhibition. Values for the 4 replicates at each concentration less than 250 mg/l varied by <= 5.19%. Values were more variable for organisms exposed to 250 mg/l for 72 or 96 hours. pH of the medium increased during the test, with larger increases observed in flasks with lower concentrations. The highest

final pH was 9.15 (at 5 mg/l), and the lowest final pH was 7.55 (at 250 mg/l). Temperature of all media remained constant at 21.6 degrees C. Fluorescence of blank vials was zero for all concentrations of test material at all time points.

Test condition : A SAG 86.81 culture of Scenedesmus subspicatus (10,000 to 16,000 cells/ml) was maintained at 21 to degrees C. Cells in suspension were treated with 0 (control), 10, 25, 50, 100 or 250 mg/l test material in quadruplicate. Test concentrations were chosen based on the results of a preliminary test. The pH of solutions was determined before and at the end of the test. Initial pH values ranged from 7.77 (at 100 mg/l) to 7.84 (in control). The test was conducted at 21 to 25 degrees C. Fluorescence of vials containing treated cells was determined 0, 24, 48, 72 and 96 hours after treatment in a fluorimeter (at wavelengths from 300 to 780 nm). Fluorescence of 2 blank vials containing test material (at each concentration) and medium without cells was subtracted from values obtained for test vials. The values for the four tests were averaged and a standard deviation was calculated. Fluorescence was converted to cell number (N) using the equation fluorescence = N/ml – 4748.47/220.024. The data were analyzed according to the method of Tallarida and Jacob (The Dose-Response Relation in Pharmacology, p. 98- 103, Springer Verlag, 1979).

Test substance : n-Hexylglykol: Reinheitsgrad groesser 98% Verunreinigungen/Begleitstoffe purity >98% impurities/coproducts: bis zu [up to] 0.2% Diethylenglykol-monobutylether, 0.1% Diethylenglykol, 0.1% Diethylenglykol-monohexylether

Reliability : (2) valid with restrictions. Basic data given. The study was translated from German to English by the reviewer.

Flag : Critical study for SIDS endpoint

(17)

4.4 TOXICITY TO MICROORGANISMS E.G. BACTERIA

Type : aquatic
Species : other bacteria
Exposure period : 16 hour(s)
Unit : mg/l
Analytical monitoring : no
IC50 : m = 770
Method : other
Year : 1987
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Test condition : Selected concentrations (not listed) were incubated for 16 hours at 23 degrees C on a shaker table in the presence of nutrients, buffer, growth substrate, and sewer microorganisms. Toxicity was indicated when the resulting turbidity was at (or less than) 50% of the control (IC50).
Details of the test are published in: Alsop et al., "Bacterial Growth Inhibition Tests", J. Water Pollution Control Federation, Vol 52: No. 10, October, 1980.
Test substance : The test substance was hexyl CELLOSOLVE®. The purity was not listed.
Reliability : (2) valid with restrictions. Basic data given.

(51)

Type : aquatic
Species : Pseudomonas putida (Bacteria)
Exposure period : 17 hour(s)
Unit : mg/l

Analytical monitoring	:	
EC10	:	= 1200
EC50	:	= 2100
EC90	:	= 3000
Method	:	other: Bakterienwachstumshemmtest nach [bacteria growth inhibition study according to] DIN 38412/8 Entwurf [design]
Year	:	1990
GLP	:	no
Test substance	:	
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Test substance	:	n-Hexylglykol: Reinheitsgrad groesser 98% Verunreinigungen/Begleitstoffe [purity >98%; impurities/coproducts]: bis zu [up to] 0.2% Diethylenglykol-monobutylether, 0.1% Diethylenglykol, 0.1% Diethylenglykol-monohexylether
Reliability	:	(4) not assignable. This study was not available for review. (17)

Type	:	aquatic
Species	:	other bacteria: BASF-Belebtschlamm [activated sludge process]
Exposure period	:	30 minute(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC50	:	ca. 12
EC80	:	ca. 55 - 360
EC20	:	ca. 3
Method	:	other: Kurzzeitatmungstest [short time respiration test]
Year	:	
GLP	:	no
Test substance	:	other TS: n-Hexylglykol rein (pure)
Remark	:	Atmungsfoerderung [respirable] All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. This study was not available for review. (14)(20)

Type	:	aquatic
Species	:	other bacteria: kommunaler Belebtschlamm aus Laborkläranlage [communal activated sludge from clarification plant]
Exposure period	:	30 minute(s)
Unit	:	mg/l
Analytical monitoring	:	no
EC20	:	= 750
Method	:	OECD Guide-line 209 "Activated Sludge, Respiration Inhibition Test"
Year	:	1990
GLP	:	no
Test substance	:	
Remark	:	All data (except the reliability rating) came from an IUCLID document for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Test substance : n-Hexylglykol: Reinheitsgrad groesser 98% Verunreinigungen/Begleitstoffe [purity >98%; impurities/coproducts]: bis zu [up to] 0.2% Diethylenglykol-monobutylether, 0.1% Diethylenglykol, 0.1% Diethylenglykol-monohexylether

Reliability : (4) not assignable. This study was not available for review. (19)(21)

4.5.1 CHRONIC TOXICITY TO FISH

4.5.2 CHRONIC TOXICITY TO AQUATIC INVERTEBRATES

4.6.1 TOXICITY TO SOIL DWELLING ORGANISMS

4.6.2 TOXICITY TO TERRESTRIAL PLANTS

4.6.3 TOXICITY TO OTHER NON-MAMM. TERRESTRIAL SPECIES

4.7 BIOLOGICAL EFFECTS MONITORING

4.8 BIOTRANSFORMATION AND KINETICS

4.9 ADDITIONAL REMARKS

5.1.1 ACUTE ORAL TOXICITY

Type	:	LD50
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	44
Vehicle	:	
Value	:	= 739 mg/kg bw
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	The acute oral toxicity of diethylene glycol monohexyl ether (DGHE) in Wistar rats also was tested in this study. The LD50 values for ethylene glycol monohexyl ether were lower than the values for DGHE and the slope of the dose-mortality curve was steeper.
Result	:	All animals treated with 2 or 4 ml/kg died within 3 days of exposure. All females treated with 1 ml/kg also died within this time frame. None of the males treated with 1 or 0.5 ml/kg or females treated with 0.71, 0.5 or 0.25 ml/kg died. Signs of toxicity included sluggishness, unsteady gait, and prostrated appearance. Animals that died had red or dark pink lungs. All survivors gained weight over the 14 day period and had normal pathology. The LD50 values (with 95% confidence limits) were 1.67 ml/kg (1.43 - 1.96) for males and 0.83 ml/kg (0.71 - 0.97) for females. The LD50 values in mg/kg for males and females are 1486 and 739, respectively (using a density of .89 g/ml). The slope of the dose-mortality curve was similar for males (13.1) and females (12.8).
Test condition	:	Fasted (18 hr) male and female rats (200 to 260 g) were divided into 10 groups of three to five animals each. Undiluted test material was administered by gavage to males at 0.5 (N = 3), 1 (N = 5), 1.41 (N=5), or 2 ml/kg (N=5) and females at 0.25 (N= 5), 0.5 (N=5), 0.71 (N=5), 1 (N= 5), 2 (N=3), or 4 ml/kg (N=3). Animals were inspected for signs of toxicity twice daily for 14 days. Body weights were taken before dosing, and 7 and 4 days after dosing. Animals that died and all animals surviving the 14 day period were necropsied. LD50 values and their slopes were calculated by the moving average method.
Reliability	:	(2) valid with restrictions. Comparable to guideline study with acceptable restrictions. Purity of the test material was not listed.
Flag	:	Critical study for SIDS endpoint

(3)

Type	:	LD50
Species	:	rat
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Value	:	1480 mg/kg bw
Method	:	other
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	All data (except the reliability rating) were obtained from an IUCLID data set for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.
(42)

5.1.2 ACUTE INHALATION TOXICITY

Type	:	LCLo
Species	:	rat
Strain	:	Wistar
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Exposure time	:	4 hour(s)
Value	:	> 85 ppm
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The mean (+/- SD) chamber concentration was 83 (+/- 15) ppm. There were no mortalities or clinical signs and animals exhibited normal weight gain. There were no gross lesions observed at necropsy.
Test condition	:	Test vapor generation: Vapor was generated by metering the liquid test material into a heated, spiral-grooved evaporator. A countercurrent air stream entered at the bottom of the evaporator, was mixed with the test vapor, and was carried into the chamber. Chamber concentrations of ethylene glycol monohexyl ether were analyzed approximately once per hour by a gas chromatograph (GC) equipped with a flame ionization detector. Vapor standards were prepared in Tedlar bags for calibration of the GC. A second method of standard generation, employing a saturated vapor and the Antoine equation was used to validate the bag mix calibration. Study conduct: Rats (5/sex, 200-300 g) were exposed to test material in 120-liter Plexiglass chambers at the highest obtainable vapor concentration (approximately 85 ppm) for 4 hours. Chamber temperature and relative humidity were generally maintained at 25 degrees C and 43%, respectively. Rats were observed for toxicity during exposure and for 14 days postexposure. Body weights were determined prior to exposure and at 7 and 14 days after exposure. Necropsies were performed on all survivors.
Test substance	:	Compositional analyses indicated the material to be at least 98% pure.
Reliability	:	(1) valid without restriction. The study was comparable to a guideline study.
Flag	:	Critical study for SIDS endpoint

(36)

Type	:	LCLo
Species	:	rat
Strain	:	Sprague-Dawley
Sex	:	male/female
Number of animals	:	10
Vehicle	:	
Exposure time	:	6 hour(s)
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	A saturated vapor of diethylene glycol monohexyl ether also was tested in this study and also was found to produce no adverse effects after a 6-hour exposure.
Result	:	All animals survived the 6 hour exposure. There were no signs of toxicity

or irritancy during or after exposure. Animals gained weight over the fourteen day observation period and had normal pathology.

Test substance : Five rats of each sex (230 to 270 g) were exposed to a statically generated saturated vapor atmosphere of test material. The atmosphere was produced by introducing a sample of material into a sealed 120-liter chamber and allowing the vapor to equilibrate for 18 hours at 26 degrees C. Rats were introduced into separate chambers through gasketted drawers designed to minimize vapor loss. Oxygen content was continuously monitored and maintained at 20%. Animals were removed from the chamber after 6 hours of exposure and were observed for 14 days. Body weights were measured before exposure and 7 and 14 days following exposure. All rats were subjected to necropsy after the 14 day observation period.

Reliability : (2) valid with restrictions. Comparable to guideline study with acceptable restrictions. Purity of the test material was not listed. Concentration of material in the atmosphere was not analyzed.

(3)

Type : other: IRT
Species : rat
Strain :
Sex :
Number of animals :
Vehicle :
Exposure time : 8 hour(s)
Method : other
Year :
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : Keine Mortalitaet nach 8 Stunden Exposition in einer bei Raumtemperatur gesaettigten bzw. angereicherten Atmosphaere. [No mortality after 8 hours exposure in a saturated or enriched atmosphere at room temperature].

All data (except the reliability rating) were obtained from an IUCLID data set for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The reference was not available for review.

(42)

5.1.3 ACUTE DERMAL TOXICITY

Type : LD50
Species : rabbit
Strain : New Zealand white
Sex : male/female
Number of animals : 40
Vehicle :
Value : = 721 mg/kg bw
Method : other
Year : 1987
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : Diethylene glycol monohexyl ether (DGHE) also was tested in this study. The LD50 values for ethylene glycol monohexyl ether were lower than the values for DGHE.
Result : All animals treated with 2.0 or 4.0 ml/kg died within 1 day of exposure.

Four males and three females treated with 1 ml/kg died within 3 days. None of the rabbits treated with 0.5 ml/kg died. Animals that died had dark red or pink lungs. These effects were also noted in some of the animals that survived (doses, sex and number not stated).

Signs of toxicity included salivation, sluggishness, unsteady gait and comatose appearance. These signs occurred during exposure and survivors recovered within 1 day. The surviving male treated with 1 ml/kg and all females treated with 0.5 ml/kg lost weight over the first week of recovery but then recovered.

Erythema, edema, necrosis and ecchymoses were found at the application site up to study termination (number and doses not stated). Ulceration was also noted in a few animals (number and doses not stated).

The LD50 values (with 95% confidence limits) were 0.81 ml/kg (0.59 - 1.12) for males and 0.93 ml/kg (0.63 - 1.38) ml/kg for females. The LD50 values in mg/kg for males and females are 721 and 828, respectively (using a density of 0.89 g/ml). The slope of the dose-mortality curve was similar for males (5.60) and females (4.96).

Test condition : Undiluted test material was applied to the clipped trunk skin of groups of 5 male or female rabbits (2 to 3 kg) at the following concentrations: 0.5, 1, 2 or 4 ml/kg. An occlusive dressing consisting of polyethylene sheeting, adhesive tape and plastic ties was used to keep the material in contact with the skin. Animals were immobilized during the 24 hour contact period. Test material was then removed with moist tissue. Animals were examined twice daily for 14 days for signs of local irritation and systemic toxicity. Body weights were taken before dosing and 7 and 14 days following dosing. Necropsies were performed on animals that died and all animals surviving the 14-day observation period. LD50 values and their slopes were calculated by the moving average method.

Reliability : (2) valid with restrictions. Comparable to guideline study with acceptable restrictions. Purity of the test material was not listed.

Flag : Critical study for SIDS endpoint

(3)

Type : LD50
Species : rabbit
Strain :
Sex :
Number of animals :
Vehicle :
Value : 792 mg/kg bw
Method : other: following Draize, J.H. et al.: J. Pharmacol. Exp. Therap. 82, 377
Year : 1944
GLP : no
Test substance : as prescribed by 1.1 - 1.4
Remark : Originalangabe [original data]: LD50 = 890 ul/kg.

All data (except the reliability rating) were obtained from an IUCLID data set for CAS No. 112-25-4 published by the European Chemicals Bureau, Creation Date 11-FEB-2000.

Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)

Reliability : (4) not assignable. The primary reference was not available for review.

(42)

5.1.4 ACUTE TOXICITY, OTHER ROUTES

Type : LD50

Species	:	mouse
Strain	:	
Sex	:	
Number of animals	:	
Vehicle	:	
Route of admin.	:	i.p.
Exposure time	:	
Value	:	737 mg/kg bw
Method	:	other
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Originalangabe [original data]: LD50 = 5.04 mmol/kg; die Tiere wurden vor der Substanzapplikation mit Olivenoel i.p. vorbehandelt [The animals were prepared with olive oil i.p. before the application of the test substance]. All data (except the reliability rating) were obtained from an IUCLID data set for CAS No. 112-25-4 published by the European Chemicals Bureau, dated 11-FEB-2000, and was translated.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The primary reference was not available for review.

(45)

5.2.1 SKIN IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Exposure	:	occlusive
Exposure time	:	4 hour(s)
Number of animals	:	6
PDII	:	
Result	:	highly irritating
EC classification	:	
Method	:	Directive 84/449/EEC, B.4 "Acute toxicity (skin irritation)"
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Diethylene glycol monohexyl ether (DGHE) also was tested in this study. DGHE was found to be less irritating than ethylene glycol monohexyl ether.
Result	:	Five animals developed a mild to moderate erythema during or within 1 day of exposure, which resolved between 2 to 7 days (average erythema and edema scores were 1.3 and 1.7 at 1 hour, respectively). Three rabbits showed necrosis at the application site between Days 1 and 7, and desquamation was found in 4 animals at Day 7.
Test condition	:	Test material (0.5 ml) was applied to the shaven, dorsal skin of 6 rabbits (2 to 3 kg, sex not noted). The application site was covered for 4 hours with a gauze patch and impervious polyethylene sheeting. After 4 hours, the material was gently removed with a moist tissue. The application site was inspected for local inflammation at 1 hour, and 1, 2, 3, 7 and 14 days after dosing. Erythema and edema were scored according to the method of Draize et al. (J Pharmacol Exp Ther 82:377, 1944).
Reliability	:	(2) valid with restrictions. Comparable to guideline study with acceptable restrictions. Purity of the test material was not stated.

(3)

Species	:	rabbit
Concentration	:	
Exposure	:	

Exposure time	:	
Number of animals	:	
PDII	:	
Result	:	not irritating
EC classification	:	
Method	:	other: Smyth - Carpenter (intakte Haut [intact skin], 24h)
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Grad 1/10. All data (except the reliability rating) were obtained from an IUCLID data set for CAS No. 112-25-4 published by the European Chemicals Bureau, Creation Date 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The primary reference was not available for review.

(42)

5.2.2 EYE IRRITATION

Species	:	rabbit
Concentration	:	undiluted
Dose	:	.01 ml
Exposure Time	:	
Comment	:	not rinsed
Number of animals	:	6
Result	:	highly irritating
EC classification	:	
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Diethylene glycol monohexyl ether (DGHE) also was tested in this study. DGHE was found to be as irritating as ethylene glycol monohexyl ether.
Result	:	A mild hyperemia of the conjuctiva (score of 1), with moderate to severe chemosis (scores of 3-4) and discharge (scores of 2-3) occurred within 4 hours of exposure. This disappeared within 2 to 3 days. There was an accompanying mild iritis (score of 1) of a similar duration. Mild corneal injury that affected up to 3/4 of the cornea developed within 1 hour in all rabbits (average opacity and area scores were 1.0 and 2.5, respectively). No injury was observed in any of the animals after 7 days.
Test condition	:	Rabbits (2 to 3 kg) whose eyes did not stain after exposure to 2% flourescein for 20 seconds were used in the study. Test material (0.005 ml) was applied to the surface of the cornea of one eye of 6 rabbits. Eyes were inspected for signs of local inflammation at 1, 4 and 24 hours and 2, 3, 7, 14 and 21 days after instillation. Particular attention was paid to the development of injection of the conjunctiva and nictitating membrane, chemosis, discharge, irits, and corneal injury (both severity and area of involvement). Corneal opacity and area involved were scored from 0 to 4, injury to the iris from 0 to 2, conjuctival redness and discharge from 0 to 3, and chemosis from 0 to 4.
Reliability	:	(2) valid with restrictions. Comparable to guideline study with acceptable restrictions. Purity of the test material was not stated.

(3)

Species	:	rabbit
Concentration	:	
Dose	:	

Exposure Time	:	
Comment	:	
Number of animals	:	
Result	:	irritating
EC classification	:	irritating
Method	:	OECD Guide-line 405 "Acute Eye Irritation/Corrosion"
Year	:	
GLP	:	no
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	All data (except the reliability rating) were obtained from an IUCLID data set for CAS No. 112-25-4 published by the European Chemicals Bureau, Creation Date 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The reference was not available for review.

(6)

5.3 SENSITIZATION

5.4 REPEATED DOSE TOXICITY

Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	inhalation
Exposure period	:	6 hr/day, 5 days/week for 13 weeks
Frequency of treatment	:	daily (except weekends)
Post obs. period	:	4 weeks
Doses	:	20, 41, and 71 ppm
Control group	:	yes
NOAEL	:	= 41 ppm
LOAEL	:	= 71 ppm
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	Although effects on body liver and kidney weights were observed in rats treated with 41 ppm, the authors concluded that 41 ppm was the concentration “at which no biologically significant toxic effects were observed.” At 41 ppm, kidney weights of females were not increased and were only slightly increased ($p < 0.05$) in males. In all groups of exposed males, the effect on kidney weight was not dose-dependent. Furthermore, although relative liver weight was increased in females exposed to 41 ppm ($p < 0.05$), there were no correlative changes in histopathology or serum chemistry. Therefore, changes occurring at 41 ppm appear to be adaptive. Assignment of a LOAEL of 71 ppm appears to be due to a significant increase in relative liver weight ($p < 0.01$) in both sexes at 71 ppm, which was not reversed after 4 weeks of recovery. The significance of the changes in liver enzymes is unclear, since decreases were observed in ¾ of the enzymes and an increase was observed in only one of the enzymes (alkaline phosphatase).
Result	:	There were no mortalities during the study. An increase in urogenital wetness was observed in all groups of exposed females and in males exposed to 71 ppm. Individual numbers of animals affected were not listed. Significant decreases in body weight gain occurred during the active phase

of the study in both sexes receiving 71 ppm and females receiving 41 ppm. Body weight gains during the recovery period were not affected by treatment. Ophthalmic examinations, hematologies, and urinalyses of treated animals were normal.

Decreases in AST (59 U/l vs. 82 U/l in control), ALT (33 U/l vs. 55 U/l in control) and SDH (12 U/l vs. 23 U/l in control) and increases in ALP (128 U/l vs. 105 U/l in control) were observed in females exposed to 71 ppm. No such changes were observed in males or in females allowed to recover for 4 weeks. Increases in relative weights of kidneys were seen in males exposed to any concentration (0.67, 0.67 and 0.69 in males exposed to 20, 41 or 71 ppm vs. 0.64 in control, $p < 0.05$, 0.05 and 0.01, respectively) and females exposed to 71 ppm (0.76 vs. 0.69 in control, $p < 0.01$). Absolute weights of kidneys were also increased (not significantly) in males exposed to 41 or 71 ppm. Increased absolute or relative kidney weights were not observed in animals allowed to recover. Significant ($p < 0.01$) increases in the absolute and relative weight of the liver were noted in females exposed to 71 ppm after exposure was terminated and the 4-week recovery period. Females exposed to 41 ppm exhibited increased ($p < 0.01$) relative liver weight after 13 weeks of exposure but not after they were allowed to recover. For males, relative liver weights were increased in the 71 ppm group after exposure was terminated ($p < 0.01$) and in the 41 and 71 ppm groups after recovery ($p < 0.05$ and < 0.01, respectively). No histopathologic lesions were found in the liver, kidneys, or any other organ examined in rats exposed to 71 ppm.

Test condition : Animals: Male and female F344 rats were obtained from Charles River, Kingston, NY at an age of 8-10 weeks. Food and water were provided ad libitum except during exposures. Rats were maintained on a 12 hour light/dark cycle throughout the study.

Test vapor generation: Vapor was generated by metering the liquid test material into a heated, spiral-grooved evaporator. A countercurrent air stream entered at the bottom of the evaporator, was mixed with the test vapor, and was carried into the chamber. Chamber concentrations of ethylene glycol monohexyl ether were analyzed approximately once per hour by a gas chromatograph (GC) equipped with a flame ionization detector. Vapor standards were prepared in Tedlar bags for calibration of the GC. A second method of standard generation, employing a saturated vapor and the Antoine equation was used to validate the bag mix calibration.

Study conduct: Twenty rats/sex/group were exposed in 4400-liter stainless-steel and glass chambers to air (control), or 20 (+/- 0.8), 41 (+/- 1.5), or 71 (+/- 5.0) ppm test material for 6 hours/day, 5 days/week for 13 weeks. Airflow was 750-1000 liters/min. Chamber temperature and relative humidity were generally maintained at 25 degrees C and 43%, respectively. Ten rats/sex/group were euthanized during the 14th week and the remaining rats were euthanized at the end of a 4-week recovery period.

Body weights were determined weekly during the active and recovery phases of the study. Ophthalmic examinations were conducted prior to exposure and at termination. Individual urine samples were collected during a 16-hr period prior to termination. Blood samples were obtained at termination by retroorbital bleeding. Animals were examined for gross pathology, organ weights were obtained (kidney, liver, lungs, testes, spleen, brain, thymus), and selected organs from control and high-dose animals (adrenals, brain, epididymis, gastrocnemius muscle, heart, cervical lymph nodes, parathyroids, pituitary, sciatic nerve, thyroid, urinary bladder, lungs, larynx, trachea, nasal turbinates, gonads, liver, thymus, spleen, kidneys, and all gross lesions) were examined histopathologically.

Laboratory analyses: Hematologic parameters measured included leukocyte count, erythrocyte count, hemoglobin, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, platelets, differential leukocyte and reticulocyte counts. Serum chemistries evaluated included glucose, urea nitrogen, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total protein, albumin, globulin, bilirubin (total, direct, indirect), creatinine phosphokinase, lactate dehydrogenase, gamma-glutamyl-transferase, sorbitol dehydrogenase (SDH), alkaline phosphatase (ALP), calcium, phosphorus, sodium, potassium chloride, and carbon dioxide. Parameters measured in urine included pH, protein, bilirubin, urobilinogen, glucose, ketones, occult blood, and osmolality.

Statistics: Results of quantitative continuous variables were analyzed for homogeneity of variance using Bartlett's test. Homogenous data were analyzed using analysis of variance (ANOVA) and means were compared using Duncan's multiple range test. Heterogeneous data were analyzed using ANOVA for unequal variances (Brown and Forsythe, Technometrics 16:129-132, 1974) and means were compared using the Student t-test or the Cochran t-test. Corrected Bonferroni probabilities were used for t-test comparisons. The limit of 0.05 (two-tailed) was used as the critical level of significance for all comparisons. Data also significant at the $p < 0.01$ level were designated as such.

Test substance : Compositional analyses indicated the material to be at least 98% pure.
Reliability : (1) valid without restriction. The study was comparable to a guideline study.
Flag : Critical study for SIDS endpoint

(36)

Species : rat
Sex : male/female
Strain : Fischer 344
Route of admin. : inhalation
Exposure period : 6 hr/day, 5 days/work week for 9 days
Frequency of treatment : daily
Post obs. period : 2 weeks
Doses : 19, 41 or 84 ppm
Control group : yes
NOAEL : = 41 ppm
LOAEL : = 84 ppm
Method : other
Year : 1987
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : This study was performed in conjunction with a 90-day inhalation study (see previous record).
Result : There were no clinical signs or mortalities during the study. Males and females in the 84-ppm group exhibited decreased body weight gains (approximately 20%) during the exposure period. The males continued to have depressed body weight gains (13% lower) during the recovery period, but females did not. There were no abnormalities in any hematological parameter measured. Male and female rats exposed to 84 ppm that were not allowed to recover had higher liver to body weight ratios than controls (increased by 6%). High-dose females allowed to recover for 14 days also exhibited increased liver/body weight ratios (4%). No exposure-related lesions in any organ (including the liver) were noted in high-dose animals.
Test condition : Animals: Male and female F344 rats were obtained from Charles River, Kingston, NY at an age of 8-10 weeks. Food and water were provided ad libitum except during exposures. Rats were maintained on a 12 hour light/dark cycle throughout the study.

Test vapor generation: Vapor was generated by metering the liquid test material into a heated, spiral-grooved evaporator. A countercurrent air stream entered at the bottom of the evaporator, was mixed with the test vapor, and was carried into the chamber. Chamber concentrations of ethylene glycol monohexyl ether were analyzed approximately once per hour by a gas chromatograph (GC) equipped with a flame ionization detector. Vapor standards were prepared in Tedlar bags for calibration of the GC. A second method of standard generation, employing a saturated vapor and the Antoine equation was used to validate the bag mix calibration.

Study conduct: Rats (10-12 weeks old) were exposed in 4400-liter stainless-steel and glass chambers to air (N = 20/sex) or test material at 19 ppm (+/- 0.5)(N = 10/sex), 41 ppm (+/- 1.3)(N =10/sex) or 84 ppm (+/- 3.6) (N = 20/sex) for 6 hours/day, 5 days/week for nine exposures over an 11-day period (weekend days excluded). Airflow was 750-1000 liters/min. Chamber temperature and relative humidity were generally maintained at 25 degrees C and 43%, respectively.

Animals were observed daily for death or clinical signs. Body weights were determined prior to exposure and on days 2, 5, 8, 9 and 12. Ten rats/sex/group were euthanized after the 9th exposure, and the remaining 10/sex were euthanized after a 14 day recovery period. Blood samples were obtained at termination by retroorbital bleeding. Standard hematologic parameters were measured on this blood. Animals were examined for gross pathology, organ weights were obtained (kidney, liver, lungs, testes, spleen, heart, thymus), and selected organs from high-dose and control animals (lungs, larynx, trachea, nasal turbinates, gonads, liver, thymus, spleen, kidneys, and all gross lesions) were examined histopathologically.

Statistics: Results of quantitative continuous variables were analyzed for homogeneity of variance using Bartlett's test. Homogenous data were analyzed using analysis of variance (ANOVA) and means were compared using Duncan's multiple range test. Heterogeneous data were analyzed using ANOVA for unequal variances (Brown and Forsythe, Technometrics 16:129-132, 1974) and means were compared using the Student t-test or the Cochran t-test. Corrected Bonferroni probabilities were used for t-test comparisons. The limit of 0.05 (two-tailed) was used as the critical level of significance for all comparisons.

Test substance : Compositional analyses indicated the material to be at least 98% pure.
Reliability : (2) valid with restrictions. The duration of the test was less than 28 days.

(36)

Species	:	rabbit
Sex	:	male/female
Strain	:	New Zealand white
Route of admin.	:	dermal
Exposure period	:	6 hours/day for 11 days (excluding weekend)
Frequency of treatment	:	daily
Post obs. period	:	
Doses	:	44, 222 and 444 mg/kg
Control group	:	yes
NOAEL	:	222 mg/kg
LOAEL	:	444 mg/kg
Year	:	1987
GLP	:	no data

Test substance : as prescribed by 1.1 - 1.4
Remark : The statistical analysis was not described.
Result : Two females in the high dose group died (one on day 9 and the other on day 12). The cause of death could not be determined. In 9/12 males and 10/12 females exposed to 44 mg/kg bw, mild erythema was noted from Days 3 to 4 to study termination. Mild edema was found in 8 low dose females after Day 5. Moderate erythema and edema were noted by Days 4-5 in 10-11 mid and high dose males and females. A few high dose animals (numbers were not stated) had ecchymoses or ulceration.

Body weights of high dose females were significantly less than control ($p < 0.01$) at Days 8 and 12. Body weight gains and food consumption of high dose males and females were significantly lower than control (at least $p < 0.05$) from Days 1-8. Red blood cell counts ($p < 0.01$), hemoblobin ($p < 0.01$), hematocrit ($p < 0.01$) and mean corpuscular hemoglobin ($p < 0.05$) were lower than control in high dose males. Red blood cell counts and hemoglobin were lower than control in high dose females ($p < 0.01$).

There were no effects of treatment on absolute or relative organ weights. No gross pathology was seen at necropsy. Histological changes were limited to the skin (acanthosis, hyperkeratosis and dermatitis).
Test condition : Groups of male and female specific pathogen free New Zealand white rabbits (20 weeks old) were randomly allocated by weight to groups of 5 animals/sex. Test material (44, 222 and 444 mg/kg bw/day) was applied undiluted to the clipped dorsal skin. A group of control animals received water at 0.5 ml/kg bw/day. Sites were covered with a gauze patch and held in place with a vinylite-lined Lycra-Spandex jacket. The material was kept in contact with the skin for 6 hours/day for five consecutive days, and for an additional four consecutive days after a 2 day rest period (for a total of 9 days over an 11 day period). Animals were observed daily for toxicity. The site of application was inspected before treatment for signs of irritation. Animals were weighed prior to dosing, on day 7, and at termination (on day 12). Food consumption data were collected on days 3, 5, 7, 8, 10 and 12. Before termination, blood for hematological (hemoglobin, hematocrit, red blood cell count, mean corpuscular volume, mean corpuscular hemoglobin concentration, mean corpuscular hemoglobin, total and differential leukocyte count, and platelet count) and chemical analyses (glucose, urea nitrogen, creatinine, total protein, albumin, globulin, bilirubin, P, Na+, K+, Ca2+, Cl-, creatine kinase, lactate and sorbitol dehydrogenases, alkaline phosphatase, gamma glutamyl transferase, and aspartate and alanine aminotransferases) was collected by cardiac puncture. Urinalysis (volume, color, microscopic elements, specific gravity, pH, protein, glucose, ketones, bilirubin, urobilinogen and blood) was performed on urine collected from the bladder at gross necropsy. The liver, kidneys, testes, adrenal glands, brain and heart were weighed. Several organs were fixed and examined histologically (organs were not stated).
Test substance : The purity of the material was 98.16%. Identified impurities were diethylene glycol monohexyl ether (0.12%), n-hexanol (0.49%) and n-octanol (0.74%).
Reliability : (2) valid with restrictions. Acceptable, well-documented study which meets basic scientific principles. The duration of the test was less than 28 days. Types of organs examined histologically and statistical methods were not stated.

(2)

5.5 GENETIC TOXICITY 'IN VITRO'

Type : Ames test
System of testing : S. typhimurium strains TA98, TA100, TA1535, TA1537, TA1538

Concentration	:	300 to 15,000 micrograms/plate
Cytotoxic conc.	:	10,000 micrograms/plate
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1985
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	Test concentrations did not deviate more than 2.5% from stated concentrations. In the tests without metabolic activation, toxicity was observed at 15 and 10 mg/plate in all strains. In the tests without metabolic activation, toxicity was found at 15 mg/plate with all strains, and at 10 mg/plate in strains TA98, TA1537 and TA1538. The number of mutant colonies in negative controls ranged from an average of 6 (TA1537 without activation) to 140 (TA100 without activation). Tests were valid, as positive controls induced anywhere from 83 (TA1535 with activation) to 1847 colonies (TA1535 without activation). The number of colonies observed in cultures treated with nontoxic concentrations of test material ranged from 4 (in TA1537 without metabolic activation) to 139 (TA100 with activation). No concentration of test material induced a 2-fold increase in the number of mutant colonies (with respect to control) in any system.
Test condition	:	The test substance was dissolved in ethanol to a concentration of 300 mg/ml. All subsequent dilutions were made in ethanol on each day of testing. Dilutions were made so that 50 microliters would deliver the required dose. All dilutions were gravimetrically analyzed. A preliminary toxicity test was performed with strain TA100 to determine concentrations to use in the test. Test chemical was added at five doses chosen to span a range that included nontoxic to moderately toxic concentrations (0.3, 1, 3, 10 and 15 mg/plate). All concentrations were tested in triplicate. Since this test showed that 100 microliters of ethanol vehicle was toxic, test material (and vehicle) was added in 50 microliter aliquots. The following positive controls (0.01 mg) were tested: 4-nitro-o-phenylenediamine (TA98 and TA 1538 without activation), sodium azide (TA100 and TA1535 without activation), 9-aminoacridine (TA1537 without activation), and 2-aminoanthracene (all strains with activation). Sterility checks were run concurrently. S-9 liver homogenate was prepared from Aroclor 1254-induced Sprague-Dawley male rats. For tests with metabolic activation, 0.5 ml of S-9 mix containing 50 microliters of S9 was added per plate. For tests without metabolic activation, 50 microliters of phosphate buffered saline were added. Treated cultures were incubated for 48-72 hours (temperature not stated). Colonies were counted using standard methods. The criterion for a positive result was at least a 2-fold, dose-dependent increase in the number of mutant colonies compared to the control.
Test substance	:	Purity of test substance was 98.4% (by weight).
Reliability	:	(1) valid without restriction. The study was comparable to a guideline study.
Flag	:	Critical study for mutagenicity endpoint

(39)

Type	:	Mammalian cell gene mutation assay
System of testing	:	CHO-Zellen [CHO-cells]
Concentration	:	keine Angaben [no data]
Cytotoxic conc.	:	
Metabolic activation	:	with and without

Result	:	negative
Method	:	other: no data
Year	:	
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	All data (except the reliability rating) were obtained from an IUCLID data set for CAS No. 112-25-4 published by the European Chemicals Bureau, Creation Date 11-FEB-2000.
Source	:	BASF AG Ludwigshafen EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability	:	(4) not assignable. The reference was not available for review. (41)

Type	:	Cytogenetic assay
System of testing	:	Chinese Hamster Ovary Cell
Concentration	:	0.1 to 0.4 mg/ml (without activation); 0.08 to 0.4 mg/ml (with activation)
Cytotoxic conc.	:	0.8 mg/ml
Metabolic activation	:	with and without
Result	:	negative
Method	:	other
Year	:	1985
GLP	:	yes
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The percentage of aberrant cells in cultures treated with vehicle, 0.1, 0.2 or 0.4 mg/ml test material for 6 hours in the absence of activation was 4 +/- 0, 2 +/- 0, 4 +/- 2.83, and 5 +/- 1.41, respectively (no significant difference). The values obtained after 10 hours of incubation were 1+/- 1.41, 2 +/- 2.83, 4 +/- 0, and 4 +/- 2.83, respectively (no significant difference). The positive control (TEM) induced 26% of cells to be aberrant after a 6-hour incubation period (tests at 10 hours were not performed). The percentage of aberrant cells in cultures treated with vehicle, 0.08, 0.1 or 0.2 mg/ml test material for 6 hours in the presence of activation was 5 +/- 1.41, 2 +/- 2.83, 4 +/- 2.83, and 3 +/- 4.24 respectively (no significant difference). The values obtained after 10 hours of incubation with vehicle, S-9 homogenate and 0.2, 0.3 or 0.4 mg/ml test material were 4 +/- 0, 2 +/- 2.83, 3 +/- 4.24, and 3 +/- 1.41, respectively (no significant difference). The positive control (cyclophosphamide) induced 26% of cells to be aberrant after a 6 -hour incubation period (tests at 10 hours were not performed). There also was no significant difference in the types of aberrations found between treated and negative control cells. Most aberrations were chromatid breaks or gaps. Test material did not induce an increase in aberrations. The test was valid, as control incidences were within historical limits, and the positive controls induced a significantly greater percentage of aberrants than controls.
Test condition	:	S-9 liver homogenate was prepared from Arochlor 1254-induced, male Sprague-Dawley rats and was screened for metabolic activity by the supplier. Typically, 1.0 of a complete metabolic activation system (including S-9 and cofactors) was added to each 4.0 ml of culture medium. CHO-K1-BH4 (subclone D1) cells were passed once after receipt and were frozen in liquid nitrogen. Stock cultures were prepared from cells thawed at approximately 1- to 2-month intervals. Cells used in tests without S-9 were from passage 7 after thawing, and cells used with S-9 were from passage 3. Dilutions of test chemical were made in ethanol immediately prior to testing

and were verified by gravimetric analyses. Cells (5 x 10E5) were exposed to the highest 3 concentrations of test material that were shown in a preliminary experiment not to produce excessive mitotic inhibition (0.1, 0.2 or 0.4 mg/ml without S-9 or 0.08, 0.1 or 0.2 mg/ml with S-9 in 6 hr experiment or 0.2, 0.3, and 0.4 mg/ml with S-9 in 10-hour experiment) or appropriate positive (15 micrograms/ml cyclophosphamide and triethylenemelamine) and negative (0.5% ethanol) controls for 6 or 10 hours, and harvested. For experiments with metabolic activation, cells were preexposed to test chemical and S-9 for two hours, rinsed, and incubated for an additional 4 or 8 hours. Colchicine was added during the last two hours. Tests were duplicated. The incubation temperature was not listed.

Chromosomes were prepared using standard procedures. A total of 50 cells/culture/harvest interval was examined for chromosome damage. The incidence of chromosome damage was determined for the highest 3 doses that did not produce excessive inhibition of cell division. The number of chromatid and chromosome aberrations, and the total number of aberrations per 50 cells examined (with and without including gaps in the total) were determined.

The Fisher's Exact Test (one-tailed) was used to analyze data. A test was considered positive if a value for at least one test concentration was different from control at the $p < 0.05$ level, and there was evidence of a concentration-dependent effect or reproducibility between duplicate cultures.

A positive effect of treatment was one that caused a statistically significant, dose-related increase in the frequency of structural chromosomal aberrations. A statistically significant effect for at least one dose level that is reproduced in both cultures was considered to be equivocal. A single positive effect in 1 of 2 cultures per dose level was evaluated with respect to the historical control data to help determine possible biological significance.

Test substance : Test sample was 98.4% pure (by weight). Impurities were 0.045% water, 0.62% N-hexanol and 0.68% N-octanol.
Reliability : (1) valid without restriction. The study was comparable to a guideline study.
Flag : Critical study for chromosomal aberration endpoint

(34)

Type : Sister chromatid exchange assay
System of testing : CHO-Zellen [CHO-cells]
Concentration : keine Angaben [no data]
Cytotoxic conc. :
Metabolic activation : with and without
Result : negative
Method : other: no data
Year :
GLP : no data
Test substance : as prescribed by 1.1 – 1.4
Remark : All data (except the reliability rating) were obtained from an IUCLID data set for CAS No. 112-25-4 published by the European Chemicals Bureau, Creation Date 11-FEB-2000.
Source : BASF AG Ludwigshafen
EUROPEAN COMMISSION - European Chemicals Bureau Ispra (VA)
Reliability : (4) not assignable. The reference was not available for review.

(41)

5.6.1 GENETIC TOXICITY 'IN VIVO'

Type	:	micronucleus assay
Species	:	other: mouse and rat
Sex	:	male
Strain	:	other: F344/N (rat) and B6C3F1 (mouse)
Route of admin.	:	i.p.
Exposure period	:	72 hours
Doses	:	Three doses of 7.03, 14.06, 28.12, 56.25, 112.5, 225, 450 mg/kg (rats) and 17.19, 34.38, 68.78, 137.5, 275, 550 and 1100 mg/kg (mice), separated by 24 hours
Result	:	negative
Method	:	other:Shelby et al. 1993. Environ Mol Mutagen 21:160-179.
Year	:	2000
GLP	:	no data
Test substance	:	other TS: ethylene glycol monobutyl ether (CAS No. 111-76-2)
Result	:	Two of five rats given 450 mg/kg and all mice given 1,100 mg/kg died. There were no other deaths. No other information about toxicity was given. There was no effect of treatment on the number of micronucleated cells in either rats or mice. The number of micronucleated polychromatic erythrocytes (PCEs)/1000 polychromatic erythrocytes ranged from 1.2-2.2 +/- 0.8 in treated rats (compared to 1.9 +/- 0.2 in controls) and from 2.3-3.8 +/- 0.8 in treated mice (compared to 2.5 +/- 0.2 in controls). The positive control induced 21.0 +/- 0.4 and 12.9 +/- 1.3 micronucleated PCEs/1000 PCEs in rats and mice, respectively.
Test condition	:	Published toxicity data were used to select doses. Factors affecting dose selection included solubility, toxicity and the extent of cell cycle delay caused by the material. Male rats and mice (5 animals/group) were injected i.p. 3 times at 24 hours with test material dissolved in phosphate-buffered saline (PBS). Rats were given 7.03, 14.06, 28.12, 56.25, 112.5, 225 or 450 mg/kg and mice were given 17.19, 34.38, 68.78, 137.5, 275, 550 or 1100 mg/kg at each injection). The total dosing volume was 0.4 ml. Negative and positive control animals were injected with the same volume of PBS or cyclophosphamide (7.50 and 10 mg/kg in rats and mice, respectively). The animals were killed 24 hours after the final injection, and blood smears were prepared from bone marrow cells obtained from femurs. Air-dried smears were fixed and stained; 2,000 polychromatic erythrocytes (PCEs) were scored for the frequency of micronucleated cells. The results were tabulated as the mean of the pooled results from all animals. The frequency of micronucleated cells among PCEs was analyzed by a program that tested for increasing trend over dose groups with a one-tailed Cochran-Armitage trend test, followed by pairwise comparisons between each dosed group and the solvent control group. In the presence of excess binomial variation (as detected by a binomial dispersion test), the binomial variance of the Cochran-Armitage test was adjusted upward in proportion to the excess variation. An individual trial was considered positive if the trend test P value was less than or equal to 0.025 or if the P value for any single dose group was less than or equal to 0.025 divided by the number of dose groups. The magnitude and reproducibility of the effects was taken into consideration when making conclusions about the results.
Reliability	:	(2) valid with restrictions. Comparable to guideline study with acceptable restrictions. Purity of the test material was not listed.
Flag	:	Supporting study for chromosomal aberration endpoint

19.02.2002 (40)

5.7 CARCINOGENICITY

5.8 TOXICITY TO REPRODUCTION

Type	:	other: examination of reproductive organs from 91-day study
Species	:	rat
Sex	:	male/female
Strain	:	Fischer 344
Route of admin.	:	inhalation
Exposure period	:	6 hr/day, 5 days/week for 13 weeks
Frequency of treatment	:	daily (except weekends)
Premating exposure period		
Male	:	
Female	:	
Duration of test	:	17 weeks
Doses	:	20, 41 and 71 ppm
Control group	:	yes
NOAEL Parental	:	= 41 ppm
Method	:	other
Year	:	1987
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Result	:	The NOAEL for reproductive effects was > = 71 ppm. There was no effect of treatment on weights or histology of reproductive organs. The NOAEL for systemic effects was 41 ppm. Rats exposed to 71 ppm exhibited changes in weights of the liver and kidney and alterations in some clinical chemistry values. Refer to section 5.4 for additional information.
Test condition	:	Test vapor generation: Vapor was generated by metering the liquid test material into a heated, spiral-grooved evaporator. A countercurrent air stream entered at the bottom of the evaporator, was mixed with the test vapor, and was carried into the chamber. Chamber concentrations of ethylene glycol monohexyl ether were analyzed approximately once per hour by a gas chromatograph (GC) equipped with a flame ionization detector. Vapor standards were prepared in Tedlar bags for calibration of the GC. A second method of standard generation, employing a saturated vapor and the Antoine equation was used to validate the bag mix calibration. Study conduct: Twenty rats/sex/group (8-10 weeks old) were exposed in 4400-liter stainless-steel and glass chambers to air (control), or 20 (+/- 0.8), 41 (+/- 1.5), or 71 (+/- 5.0) ppm test material for 6 hours/day, 5 days/week for 13 weeks. Airflow was 750-1000 liters/min. Chamber temperature and relative humidity were generally maintained at 25 degrees C and 43%, respectively. Ten rats/sex/group were euthanized during the 14th week and the remaining rats were euthanized at the end of a 4-week recovery period. Body weights were determined weekly during the active and recovery phases of the study. Ophthalmic examinations were conducted prior to exposure and at termination. Individual urine samples were collected during a 16-hr period prior to termination. Blood samples were obtained at necropsy by retroorbital bleeding. Standard hematological and clinical chemistry endpoints were measured (consult Section 5.4 for further information). Animals were examined for gross pathology, organ weights

were obtained (kidney, liver, lungs, testes, spleen, brain, thymus), and selected organs from control and high-dose animals (adrenals, brain, epididymis, gastrocnemius muscle, heart, cervical lymph nodes, parathyroids, pituitary, sciatic nerve, thyroid, urinary bladder, lungs, larynx, trachea, nasal turbinates, gonads (types not stated), liver, thymus, spleen, kidneys, and all gross lesions) were examined histologically.

Statistics: Results of quantitative continuous variables were analyzed for homogeneity of variance using Bartlett's test. Homogenous data were analyzed using analysis of variance (ANOVA) and means were compared using Duncan's multiple range test. Heterogeneous data were analyzed using ANOVA for unequal variances (Brown and Forsythe, Technometrics 16:129-132, 1974) and means were compared using the Student t-test or the Cochran t-test. Corrected Bonferroni probabilities were used for t-test comparisons. The limit of 0.05 (two-tailed) was used as the critical level of significance for all comparisons.

Reliability : (1) valid without restriction. The study was comparable to a guideline study.

Flag : Critical study for SIDS endpoint

(36)

5.9 DEVELOPMENTAL TOXICITY/TERATOGENICITY

Species	:	rat
Sex	:	female
Strain	:	Fischer 344
Route of admin.	:	inhalation
Exposure period	:	6 hours/day on gestational days 6-15
Frequency of treatment	:	daily
Duration of test	:	16 days
Doses	:	20.8, 41.4, 79.2 ppm
Control group	:	yes
NOAEL Maternalt.	:	= 20.8 ppm
NOAEL Teratogen	:	>= 79.2 ppm
Method	:	other
Year	:	1989
GLP	:	no data
Test substance	:	as prescribed by 1.1 - 1.4
Remark	:	In this study (as opposed to the 13-week study by the same authors) the effect on weight gain caused by inhalation of 41 ppm was considered to be adverse. Rabbits (22/chamber) were exposed concurrently with rats. Results of the rabbit study appear in next record.
Result	:	Exposure concentrations: Test concentrations were analytically determined to be 20.8 (+/- 0.9), 41.1 (+/- 1.77) and 79.2 (+/- 10.8) ppm. The values in mg/l are 0.13, 0.25 and 0.48, respectively. Maternal: No dams died or aborted, but one dam in the 20.8 ppm group and another in the 41.1 ppm group delivered early. The number of pregnant dams was comparable across all groups. Excess lacrimation was observed throughout the exposure period in rats exposed to 79.2 ppm. There was a slight, but significant decrease in body weight in the 79.2 ppm group on gestation days 12 and 15. Weight gain for rats exposed to 79.2 or 41.1 ppm was significantly less than control on days 6-9 and 6-15. For rats exposed to 79.2 ppm, food consumption was lower than control during these intervals, and higher than control during days 18-21. Water consumption in rats exposed to 71.1 ppm increased over gestation days 12-15 and 15-18.

There were no treatment-related effects on blood, gross pathology, gravid uterine weight, body weight at termination, gestational body weight change, or absolute or relative liver weight. There also was no effect of treatment on the number of corpora lutea or implantations or losses.

Fetal: There was no effect of treatment on sex ratio or fetal body weight. There were no increases in the incidences of individual malformations, malformations or variations by category (external, visceral or skeletal), or total malformations or variations with respect to control. The incidence of fetal atelectasis (a variation) was increased in the 20.8 ppm group (6 abnormalities in 5 litters versus 0 in controls) but not in the 41.1 or 79.2 ppm groups.

Test condition : Animals: Virgin male (69 days old) and female (62 days old) COBS CDF (F-344)/CrlBR rats were obtained from Charles River, Kingston, NY. They wre quarantined for two weeks, during which quality control data indicated that they were in good health. They were allowed free access to food and water (except during exposure) and were housed under a 12 hr light/dark cycle.

Test vapor generation: Vapor was generated by metering the liquid test material into a heated, spiral-grooved evaporator. A countercurrent air stream entered at the bottom of the evaporator, was mixed with the test vapor, and was carried into the chamber (4320-liter volume). Airflow in each chamber (total of 4) was approximately 1000 liters/min (14 air changes per hour). Chamber concentrations of ethylene glycol monohexyl ether were analyzed approximately once every 30 minutes by a gas chromatograph (GC) equipped with a flame ionization detector. Chamber temperature, relative humidity and airflow rate were monitored throughout each exposure period. Animal cages were rotated daily to compensate for any possible variation in chamber exposure concentrations.

Study conduct: Virgin male and female rats were mated one male:one female in mesh cages, and the paperboard underneath the cages was checked twice daily for copulation plugs. The day a copulation plug was found was designated as gestation day 0. Twenty-five plug-positive females were assigned to each exposure group:
0 (air control), 20, 40, and 85 ppm. Rats were exposed 6 hr/day from gestation days 6 through 15. Rats were euthanized on gestation day 21.

Animals were observed daily for clinical signs of toxicity. Maternal body weights were measured on gestation days 0, 6, 12, 15, and 21. Food and water consumption were measured over the following intervals: gestation days 0-3, 3-6, 6-9, 9-12, 12-15, 15-18, and 18-21. Blood was collected from the retroorbital venous plexus and rats were euthanized on gestation day 21. Hematologic parameters measured included erythrocyte count, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and total leukocyte counts. Blood smears were also analyzed for differential leukocyte count. Pelvic, abdominal, and thoracic viscera were examined macroscopically, and ovarian copora lutea were counted. Maternal liver and gravid uterine weights were measured. The number of live/dead fetuses and the number of resorption sites (early and late) were recorded, and uteri of apparently nongravid females were placed in 10% ammonium sulfide solution for detection of early resorptions. All fetuses were sexed, weighed and examined for external malformations and variations. One-half of the rat fetuses were examined for thoracic and abdominal visceral abnormalities and decapitated. Heads were fixed and decalcified in Bouin's fluid for examination of craniofacial structures. Fetuses that were not decapitated were eviscerated and examined for skeletal malformations and variations.

Statistics: The unit of comparison was the pregnant female or the litter. Results of quantitative continuous variables were analyzed for homogeneity of variance using Levene's test. Homogenous data were analyzed using analysis of variance (ANOVA) and means were compared using a pooled t-test. Heterogeneous data were analyzed using ANOVA for unequal variances (Brown and Forsythe, Technometrics 16:129-132, 1974) and means were compared using the separate variance t-test. Corrected Bonferroni probabilities were used for t-test comparisons. Nonparametric data were statistically analyzed using the Kruskal-Wallis test. Incidence data were compared using Fisher's exact test. The limit of 0.05 (two-tailed) was used as the critical level of significance for all comparisons.

Test substance : Compositional analyses indicated the material to be at least 99% pure.
Reliability : (1) valid without restriction. The study was comparable to a guideline study.
Flag : Critical study for SIDS endpoint

(49)

Species : rabbit
Sex : female
Strain : New Zealand white
Route of admin. : inhalation
Exposure period : 6 hours/day on gestation days 6-18
Frequency of treatment : daily
Duration of test : 24 days
Doses : 20.8, 41.1 and 79.2 ppm
Control group : yes
NOAEL Maternalt. : = 41.1 ppm
NOAEL Teratogen : >= 79.2 ppm
Method : other
Year : 1989
GLP : no data
Test substance : as prescribed by 1.1 - 1.4
Remark : Rats (25/chamber) were exposed concurrently with rabbits. Results of the rat study appear in the previous record.
Result : Exposure concentrations: Test concentrations were analytically determined to be 20.8 (+/- 0.9), 41.1 (+/- 1.77) and 79.2 (+/- 10.8) ppm. The values in mg/l are 0.13, 0.25 and 0.48, respectively.

Maternal: No does died or delivered early. One doe in the 20.8 ppm group aborted and was removed from the study. The number of pregnant does did not differ between groups. There were no significant differences in body weights over the course of the study. A significant reduction in weight gains occurred in does exposed to 79.2 ppm during gestation days 6-12 and 6-18. No clinical, hematological or gross pathological signs of toxicity were noted. There were no effects of treatment on implantations. One litter in the 0 ppm group, 2 in the 20.8 ppm group and one in the 79.2 ppm group were found completely resorbed.

Fetuses: There were no effects of treatment on the number of live fetuses, sex ratio, fetal body weight, incidence of individual malformations or variations, malformations or variations by category (external, visceral, or skeletal), or the total number of malformations or variations.

Test condition : Animals: Virgin female New Zealand White rabbits of at least 2.5 kg (5-5.5 months of age) were obtained from Hazelton Dutchland Laboratories Inc., Denver, PA. They were quarantined for two weeks, during which quality control data indicated that they were in good health. They were allowed free access to food and water (except during exposure) and were housed

under a 12 hr light/dark cycle.

Test vapor generation: Vapor was generated by metering the liquid test material into a heated, spiral-grooved evaporator. A countercurrent air stream entered at the bottom of the evaporator, was mixed with the test vapor, and was carried into the chamber (4320-liter volume). Airflow in each chamber (total of 4) was approximately 1000 liters/min (14 air changes per hour). Chamber concentrations of ethylene glycol monohexyl ether were analyzed approximately once every 30 minutes by a gas chromatograph (GC) equipped with a flame ionization detector. Chamber temperature, relative humidity and airflow rate were monitored throughout each exposure period. Animal cages were rotated daily to compensate for any possible variation in chamber exposure concentrations.

Study conduct: Female rabbits) were bred with in-house breeding colony males. The date of copulation was designated as gestation day 0. Twenty-two mated females were assigned to each exposure group: 0 (air control), 20, 40, and 85 ppm. Rabbits were exposed 6 hr/day from gestation days 6 through 18.

Animals were observed daily for clinical signs of toxicity. Maternal body weights were measured on gestation days 0, 6, 12, 18, and 29. Blood was collected by cardiac puncture and rabbits were euthanized on gestation day 29. Hematologic parameters measured included erythrocyte count, hemoglobin concentration, hematocrit, mean corpuscular volume, mean corpuscular hemoglobin, and total leukocyte counts. Blood smears were also analyzed for differential leukocyte count. Pelvic, abdominal, and thoracic viscera were examined macroscopically, and ovarian copora lutea were counted. Maternal liver and gravid uterine weights were measured. The number of live/dead fetuses and resorption sites (early and late) were recorded, and uteri of apparently nongravid females were placed in 10% ammonium sulfide solution for detection of early resorptions. All fetuses were sexed, weighed and examined for external malformations and variations. All live fetuses were examined for thoracic and abdominal visceral abnormalities and one-half were decapitated. Heads were fixed and decalcified in Bouin's fluid for examination of craniofacial structures. Fetuses that were not decapitated were eviscerated and examined for skeletal malformations and variations.

Statistics: The unit of comparison was the pregnant female or the litter. Results of quantitative continuous variables were analyzed for homogeneity of variance using Levene's test. Homogenous data were analyzed using analysis of variance (ANOVA) and means were compared using a pooled t-test. Heterogeneous data were analyzed using ANOVA for unequal variances (Brown and Forsythe, Technometrics 16:129-132, 1974) and means were compared using the separate variance t-test. Corrected Bonferroni probabilities were used for t-test comparisons. Nonparametric data were statistically analyzed using the Kruskal-Wallis test. Incidence data were compared using Fisher's exact test. The limit of 0.05 (two-tailed) was used as the critical level of significance for all comparisons.

Test substance : Compositional analyses indicated the material to be at least 99% pure.

Reliability : (1) valid without restriction. The study was comparable to a guideline study.

Flag : Critical study for SIDS endpoint

(49)

5.10 OTHER RELEVANT INFORMATION

Type : absorption
Remark : The toxicokinetics of ethylene glycol monohexyl ether (EGHE) were investigated in Fisher 344 rats and New Zealand white rabbits by i.v. And 48-hour occluded epicutaneous dosing. Given i.v. to 4 male rats (2.5 – 25 mg/kg bw), [14C]EGHE demonstrated first order kinetics. Carbon-14 was eliminated mainly in urine (68-74%) as metabolites, with no free EGHE. The plasma free EGHE concentration declined rapidly after dosing and was not detectable by 8 hours. Similar results were obtained for [14C] EGHE given i.v. to 4 male rabbits at 1-10 mg/kg bw, except that the metabolism of EGHE was more rapid, with no free EGHE being detected in plasma 1 hour after dosing.

After cutaneous dosing of four male and four female rats with 25 mg/kg bw, there was rapid percutaneous absorption, with > 95% of the radiolabel being recovered. Percutaneous bioavailability was > 75%. Carbon-14 was excreted in urine (21-33%) to a lesser extent than by the i.v. route, and 14CO2 and volatiles accounted for 15-18%. Carbon-14 recovery was low from tissues and organs (0.39-0.46%), with no preferential accumulation. Extensive metabolism was indicated by the rapid decline in plasma free EGHE, with none being detected at 48 hours. Free EGHE was not present in urine. Urinary radioactivity was associated with up to seven unidentified metabolites. After cutaneous dosing of four male and four female rabbits (10 mg/kg bw), approximately 75% of the dose was recovered, with most 14C in urine (58-60%). Urine radioactivity was associated with up to 9 unidentified metabolites, but no free EGHE.
Test material : The purity of the material was 98.16%. Identified impurities were diethylene glycol monohexyl ether (0.12%), n-hexanol (0.49%) and n-octanol (0.74%).
Reliability : (1) valid without restriction. Comparable to a guideline study

(2)

Type : Metabolism
Remark : EGPE and EGBE also were tested in this study.
Result : A single isozyme of rat liver alcohol dehydrogenase (ADH-3) was responsible for oxidizing the test material and other glycol ethers. A Vmax of 1.66 nmol NADH/min/mg protein and a Km value of 0.15 mM were reported for the test material. These values were lower than those of shorter chain glycol ethers (EGPE and EGBE), suggesting that at equivalent concentrations, metabolism of ethylene glycol hexyl ether will be less rapid than EGPE and EGBE and will be saturated at lower substrate concentrations.
Test condition : Livers from male (247-317 g) Wistar rats were homogenized. The 1000,000 g supernatant was used for the assay after dialysis overnight. The activity of alcohol dehydrogenase following incubation with 0.05 - 10 mM test material was determined. Two isozymes were isolated using gel electrophoresis.
Reliability : (2) valid with restrictions. Basic data given.

(1)

5.11 EXPERIENCE WITH HUMAN EXPOSURE

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