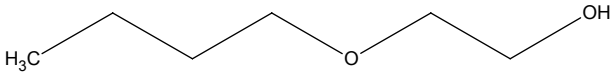
SIDS INITIAL ASSESSMENT PROFILE

CAS Number	111-76-2
Chemical Name	2-butoxyethanol Ethylene Glycol Butyl Ether (EGBE)
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Nearly 100% of orally administered EGBE is absorbed. For dermal absorption studies of liquid EGBE a value of 30 % absorption (after at least 2 hours of exposure) represents a maximum. Depending on the experimental conditions, dermal penetration of vapour EGBE in humans is between 11 and 39 % of the total body burden. In human volunteers' inhalation studies, inhalation absorption of 55 % to 60 % has been measured.
EGBE reaches a maximum blood concentration rapidly after exposure independent of the route of exposure. EGBE is rapidly metabolised (with a plasma half life of about an hour).
Highest concentrations of EGBE were found in the liver, kidneys, thymus and stomach, in particular forestomach in the rat, independent of the route of administration (by oral or inhalation route).
The main metabolic pathway leads to the formation of Butoxy Acetic Acid (BAA) via Alcohol dehydrogenase and Aldehyde dehydrogenase in a saturable mechanism.
Elimination is rapid and mainly via the urinary route (80 to 90 % of the metabolites). The plasma half-life of metabolites is about 4 hours. A small amount is eliminated as CO2 by respiration (10 to 20 %).
According to the available data and the physico-chemical properties of EGBE, excretion into the breast milk and exposure of the developing foetus is possible.

Acute inhalation toxicity studies showed that LC_{50} in rats, mice and guinea pigs were about 500 ppm (2.45 mg/l). The effects seen in acute toxicity studies in animals were mainly acute haemolysis accompanied by non specific signs of toxicity (laboured breathing, lethargy, ataxia). Some hepatic and renal pathology was also seen in these studies. By dermal route, depending on the application (occlusive or not) the LD_{50} varied mainly between 500 mg/kg and > 2000 mg/kg respectively in rabbits. In rats dermal LD_{50} was greater than 2000 mg/kg whereas in guinea pigs LD_{50} values varied between 200 and 6000 mg/kg. For this end point the most reliable studies were those in the rabbit. By the oral route, LD_{50} values were greater than 1000 mg/kg in studies with mice and rats.

In humans following massive oral doses (0.4-4.5 g/kg bw.), the main toxic effect was metabolic acidosis sometimes with haematotoxicity (haematuria). For haematotoxicity, humans are much less sensitive than rodents via any route of administration (rodents are more sensitive than humans). Moreover according to human studies, it appears that there is not a great intraspecies sensitivity (no influence of age or haematological status). This end point was not the most sensitive end point for acute toxicity in human. Indeed, in cases of massive doses, haemotoxicity was not observed in all cases, but metabolic acidosis and CNS depression were invariably observed. The lowest dose leading to metabolic acidosis in human was 400 mg/kg (LOAEL). Mechanistic *in vitro* studies showed that BAA causes haemolysis at very low concentrations. It can be also estimated that BAA is responsible of hematotoxicity *in vivo*.

EGBE liquid is irritating to the skin and eyes. No sign of severe respiratory tract irritation was evidenced in human observations or chronic rodent exposures. Irritation of nose and throat was reported in a study with human volunteers exposed to 200 ppm of EGBE, whereas levels of 25 and 50 ppm were

without symptoms. No sensitisation properties (both skin and respiratory tract) linked directly to EGBE was seen from the available data on humans and animals.

For repeated dose toxicity, target organs identified in the different studies available (including the two-year toxicity studies in rats and mice) were red blood cells, liver, spleen, olfactory epithelium and forestomach. Haemolytic anaemia was observed in several studies. Rodents were more sensitive than human to the haemolytical effects of EGBE. Kupffer cell pigmentation was secondary to the haemolytic effects. Effects on spleen (including spleen fibrosis) were also related to haemolysis. Effects usually occur following administration of substances, which are able to cause iron accumulation in the splenic red pulp. Effects on the forestomach of rodents do not appear to be relevant for humans. The increased incidence of hyaline degeneration of the olfactory epithelium observed in rodents appears to be an adaptive response, the severity of the lesion remained unchanged with increasing exposure concentrations.
In species other than rodents, older studies were available. In dogs and monkeys, haemolysis was also described at relatively low doses. In guinea pigs, a species which is resistant to EGBE-induced haemolysis, mortality was seen at 375 ppm and higher.

The most reliable inhalation LOAEC was 31 ppm derived from a 6 month satellite group in a two-year study in rats. A NOAEC of 25 ppm was obtained in a 90-day rat inhalation study. For the oral route, a LOAEL of 69 mg/kg bw/d in male rats was derived from a 14 week oral study in rats. For dermal exposure, a NOAEL of 150mg/kg/day was established based on a rabbit study which showed no effects at the highest tested dose.

Most of the *in vitro* genotoxicity tests of EGBE in bacteria and in the mammalian cells were negative. Weak aneugenic effects were obtained in the only available study with EGBE and Butoxyaldehyde (BAL), but not with BAA. One of the main metabolites of EGBE, butoxy aldehyde (BAL) was positive in most in vitro genotoxicity tests. All the available in vivo genotoxicity tests were negative.

For reproductive toxicity, no specific effects were seen for fertility. In the continuous breeding study a NOAEL of 720 mg/kg in mice was set based on non specific effects observed at the higher doses tested (weight loss and mortality in dams and decreased number of litters, litter sizes, pup viability, and live pup weights in the presence of severe maternal toxicity. For developmental studies, embryonic and foetal effects seen in animals occurred at doses that also resulted in severe maternal toxicity (haemolysis). Overall based on the available animal data, EGBE was not considered to be a developmental toxicant. There are some epidemiological findings, which indicate that maternal work exposure to solvents or glycol ether and maternal occupations in health care or cleaning may be risk factors for cleft palate and neural tube defects in the studied population. However, it is not possible to distinguish clearly a unique source of glycol ether, Usually studies described co-exposure to various glycol ethers, including known developmental toxins such as EGME (Ethylene Glycol Methyl Ether) and other chemicals as well.

Two inhalation chronic-carcinogenicity studies have been conducted. Results obtained showed that EGBE was carcinogenic in male mice, where it caused a low incidence of haemangiosarcomas, and in female mice, where it caused an increased incidence of forestomach tumours. It was not carcinogenic in rats. In the case of forestomach tumours, these tumours do not appear to be relevant to human because of the specificity of this organ in rodents. In the case of the haemangiosarcomas, mice were more sensitive than rats and the proposed mechanism of action was related to haemolysis observed with EGBE. As humans are less sensitive than rodents to this toxicity, EGBE is not likely to represent a carcinogenic hazard under conditions of normal handling and use.

Environment

EGBE is a neutral, colourless liquid. Its melting point equals –74.8°C and its boiling point is 171°C. EGBE can be considered as volatile based on its vapour pressure of 1.41 hPa. However, due to its high solubility (more than 50 g/L), the volatilisation of EGBE from water will not be important. Indeed a $K_{air\text{-}water}$ of 3.23×10^{-5} indicates that volatilisation of EGBE from surface water and moist soil is expected to be very low. EGBE is not hydrophobic and has a log Kow of 0.8.

No experimental data were available on hydrolysis. However, alcohols and ethers like EGBE are generally resistant to hydrolysis.

EGBE released to the atmosphere is expected to degrade by reaction with hydroxyl radicals. An estimated atmospheric half-life value of ~13 hours has been calculated.

According to standard tests on ready biodegradation and further experimental data which confirmed high biodegradation rates, EGBE can be regarded as readily biodegradable. Therefore, the degradation rates can be estimated for surface water, soil and sediment corresponding to half lives of respectively 15, 30 and 300 days.
In view of the BCFs for fish and worm (0.97 and 1.6) calculated based on the log Kow, EGBE is expected to have a low bioaccumulation potential.

The results from a multimedia fugacity model (MacKay level I) and the physico-chemical properties of EGBE show that the hydrosphere is the preferential target of the substance in the environment (99.2% in water, 0.55% in soil).
For the assessment of the toxicity of EGBE toward aquatic organisms, the data presented in the following table were selected.

Species	**Duration**	**Endpoint**	**Result (mg/L)**	**Lowest short term toxicity result for the same trophic level**
Fish: *Brachydanio rerio*	21 days	NOEC	> 100	*Poecilia reticulata* LC_{50} after 7 days = 983 mg/L
Invertebrates: *Daphnia magna*	21 days	NOEC	100	*Hydra attenuata* EC_{50} after 72 hours =540 mg/L *Daphnia magna* EC_{50} after 48 hours = 835 mg/L
Algae: *Pseudokirchneriella subcapitata*	72 hours	NOEC	286	*Pseudokirchneriella subcapitata* EC_{50} after 72 hours = 911 mg/L

An assessment factor of 10 has been applied to the lowest long-term result and a PNEC of 10 mg/L has been derived for freshwater.
Concerning the toxicity towards wastewater treatment plant micro-organisms, three tests were conducted with protozoa and one with an individual bacteria species. Studies testing ciliated protozoa can be used for the assessment of hazard for the sewage treatment plants. Consequently, the test conducted on *Uronema parduzci* has been chosen (EC5 = 463 mg/L).

Exposure

EGBE belongs to the group of glycol ethers, which are mainly used as solvents. The annual production of EGBE in the European Union has been estimated to be 155,100 tons. The production in the European Union is located at five different sites.

EGBE has a wide range of uses as a solvent. Occupational exposure mainly occur during manufacture, formulation, coating/painting (industrial or decorative), printing (general printing or silk screening) and cleaning (wiping or spraying). Consumer exposures are mainly due to the use of cleaning products and paints. Minor uses have also been identified such as leather treatment operations, cosmetics and fire foams and the formulation of oilfield chemicals.

Emissions of EGBE in the environment principally occur to water and via direct releases in air. Highest exposure concentrations have been identified in water from the use of general industrial paints, automotive OEM coatings, the formulation of inks, use for leather finishing operations and for the formulation of oilfield chemicals. For the atmosphere, the highest calculated exposure concentrations can be attributed to the use of general industrial paints, can coatings and for metal cleaning operations.

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

Human Health: The chemical is currently of low priority for further work. The chemical possesses properties indicating a hazard for human health (irritation and haematotoxicity). The irritation hazard does not warrant further work as it is related to reversible effects which may become evident only at high exposure levels. It should nevertheless be noted by chemical safety professionals and users. Although haematotoxicity is noted in rodents exposed to high oral or dermal concentrations of 2-butoxyethanol, humans are significantly less sensitive to red blood cell toxicity caused by 2-butoxyethanol than rodents."

Environment: The chemical is currently of low priority for further work because of its low hazard profile.
Note : an EU risk assessment is in progress on this substance taking into account all the scenarios available in Europe.