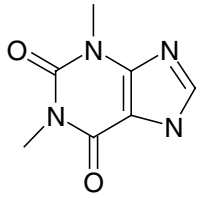
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	58-55-9
Chemical Name	Theophylline
Structural Formula	

RECOMMENDATIONS

The chemical is currently of low priority for further work.

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

Theophylline is moderately toxic after oral uptake and low toxic after dermal and inhalative uptake. LD50, rat (oral): 272 mg/kg bw, LC50, rat (inhalation, aerosol): >6.7 mg/l/4h, LD50, rat (dermal): >2000 mg/kg bw. Main symptoms following exposure are convulsion and accelerated respiration (oral) and irregular and accelerated respiration (inhalation). The undiluted substance was not irritating to the eyes. The substance in a 50% aqueous dilution was not irritating to the skin of rabbits. In repeated dose studies, theophylline was given to rats and mice by feed or by gavage. In rats theophylline caused nephropathy in all fed male rats and a dose-dependent periarteritis in all treated groups. Those effects are discussed to be secondary effects, due to the pharmacological properties (vasodilatation/ -constriction) of methylxanthines. No histo-pathological changes were found in other organs including sex organs of rats and mice. LOAEL: 75 mg/kg bw/d (rat, feed), 37.5 mg/kg bw/d (rat, gavage), LOAEL: 175 mg/kg bw/d (mouse, male, feed), 225 mg/kg bw/d (mouse, female, feed), NOAEL: 75 mg/kg bw/d (mouse, male, gavage), 150 mg/kg bw/d (mouse, female, gavage). Theophylline was not mutagenic or clastogenic in most of the standard *in vitro* tests. Positive results were found only at high, cytotoxic concentrations and without metabolic activations. Theophylline had no mutagenic or clastogenic effects *in vivo*.

In fertility/developmental toxicity studies in mice, the oral administration of theophylline resulted in changes in parental body weight and significant reproductive effects to the offspring (reduced mean number of litters, fewer live pups per litter, decreased live pup weight). No effects were observed in sperm morphology or in the estrous cycle in rats and mice in 14 week studies. LOAEL: 126 mg/kg bw/d. Theophylline was not shown to be teratogenic in CD-1 mice at oral doses up to 396 mg/kg bw/d or in CD-1 rats at oral doses up to 259 mg/kg bw/d. At an oral dose of 218 and 396 mg/kg bw/d, fetotoxicity was observed in rats and mice, respectively, in the presence of maternal toxicity. Intravenous theophylline was fetotoxic and teratogenic in rabbits at maternal toxic doses exceeding the effective therapeutic range (60 mg/kg bw/d i.v.). NOAEL rat maternal/fetotoxicity: 124 mg/kg bw/d, NOAEL rat teratogenicity: 259 mg/kg bw/d. NOAEL mouse maternal/fetotoxicity: 282 mg/kg bw/d, NOAEL mouse teratogenicity: 396 mg/kg bw/d. NOAEL rabbit maternal/fetotoxicity/teratogenicity: 30 mg/kg bw/d. Theophylline showed no carcinogenic activity in rats and mice when tested up to the highest doses (75 mg/kg bw/d rats, female mice and 150 mg/kg bw/d male mice).

In rats theophylline is rapidly and completely absorbed from the digestive tract and distributed to all organs except adipose tissue. It readily crosses the placenta and no blood-brain barrier was observed. Plasma half-life is between

1.2-4 hours in rats and 6-11.5 hours in dogs and strongly dependent on protein binding and dose. Theophylline is metabolized in the liver, mainly by the microsomal system. The metabolites are excreted into the bile and eliminated with the urine. In humans theophylline is readily absorbed after oral intake and distributed in the different body tissues and breast milk. Theophylline is metabolized in the liver and excreted by the kidney. Only 7-12 % is excreted unchanged in the urine. Major metabolites are 1,3-dimethyluric acid (35-55 %), 1-methyluric acid (13-26 %) and 3-methylxanthine (9-18 %). The elimination half-time is 3-11 hours in adults. Signs of intoxication are: headache, gastrointestinal disturbances, hypotension, irritability and insomnia, tachycardia, arrhythmia, cardiac arrest and serious neurological symptoms. Seizures and death have also occurred. Toxicity may be developed at serum levels of 20-30 µg/ml, whereas at levels below 15 µg/ml generally no symptoms were observed. Case-control studies did not show an association between total methylxanthine intake and benign breast disease or breast cancer. No association with congenital abnormalities or stillbirth were seen in studies with females receiving theophylline. In premature infants no effect of theophylline on the development was seen.

Environment

Theophylline has a water solubility in the range of 5.5 to 8.3 g/l, a vapor pressure of $0.7 * 10^{-6}$ Pa and a log Kow of –0.0076. Distribution modelling using Mackay, Level I, indicates that the main target compartment will be water with 99,98%. According to OECD criteria the substance is readily biodegradable. The calculated hydrolysis rate is extremely slow. In the atmosphere theophylline will be indirectly photodegraded by reaction with hydroxyl radicals with a half-life of 20 hours (calculated). Bio- and geoaccumulation is not expected according to the log Kow (-0.0076).

The acute aquatic toxicity has been determined for fish (*Leuciscus idus* LC50(96h) appr. 100 mg/l), for aquatic invertebrates (*Daphnia magna* EC50(48h) 178 mg/l) and for algae (*Scenedesmus subspicatus* EC50(72h) >100 mg/l). Based on these acute toxicity studies theophylline is not considered as hazardous to aquatic organisms. Results from prolonged or chronic studies are not available. Following the EU risk assessment procedure, the PNEC aqua can be calculated to 0.1 mg/l by applying an assessment factor of 1000 on the most sensitive species (*Leuciscus idus* LC50(96h) 100 mg/l).

Exposure

Theophylline is produced with a volume of 1,000 to 5,000 tons per year, world-wide, the same level accounting for Germany and Europe. Theophylline is a substance with wide disperse use. It is predominantly used as an antiastmathic drug in the pharma sector (99%). 1% is used in cosmetic applications. Production sites for the technical product: EU (Germany) 1, NAFTA 1, India 1 and China 5. Furthermore theophylline is a naturally occurring substance in plants e.g. in black tea (200 – 400 mg/kg dry weight), coffee (approx. 5 mg/kg in green coffee beans) and cocoa (trace amounts) and therefore is a component in the respective beverages. The use in pharmaceutical applications and also the use in foods will be the predominant way of human exposure and of exposure of the environment. Exposure of workers to theophylline during production is adequately controlled in the industry of the sponsored country. Workplace measurements Germany: 0.1- ca. 0.5 mg/m^3 (8h). At the German production site, process waters with relevant substance quantities are separated and combusted.

NATURE OF FURTHER WORK RECOMMENDED

The substance is currently of low priority of further work. However there is a recommendation for sharing the information on possible aggregated exposure with regulatory agencies responsible for food, pharmaceuticals and cosmetics.