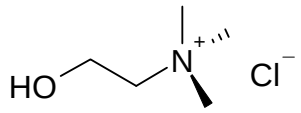
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	67-48-1
Chemical Name	Choline chloride
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Category/Analogue Rationale

In some circumstances, available data for other choline salts (e.g. choline magnesium salicylate) have been evaluated in Human Health to assist the weight of evidence approach for choline chloride. Due consideration was given to potential toxicity exerted by byproducts e.g. in parenteral exposure.

Human Health

Choline is a dietary component and found in foods as free choline and as esterified forms such as phosphocholine, glycerophosphocholine, sphingomyeline, and phosphatidylcholine. It functions as a precursor for acetylcholine, phospholipids, and the methyl donor betaine and is important for the structural integrity of cell membranes, methyl metabolism, cholinergic neurotransmission, transmembrane signaling, and lipid and cholesterol transport and metabolism.

Dietary choline is absorbed from the lumen of the small intestine. Additionally to dietary supply choline can be made available by enzymatic cleavage in the pancreas from other nutritional sources (e.g. phosphatidylcholine). Before choline can be absorbed from the gut, some is metabolised by bacteria to form betaine and methylamines. Fasting plasma choline concentrations vary from 9 to 20 µmol/L.

The critical adverse effect from high intake of choline is hypotension, with corroborative evidence on cholinergic side effects (e.g., sweating and diarrhoea) and fishy body odour. After inadequate dietary intake decreased choline stores and liver damage (as assessed by elevated alanine aminotransferase) may develop.

Animal studies with choline chloride show a low acute toxicity after oral uptake (with a range of LD50s of 3150 – ≥5000 mg/kg bw determined in different studies). . No acute toxicity attributable to choline was observed in humans following oral doses of ≥3000 mg choline magnesium trisalicylate/day.

In rabbits, choline chloride may lead to a slight irritation of the skin and eye. No data on sensitization in animals are available. The skin sensitisation potential of choline chloride is regarded as negligible in humans.

In a limited, specialised, repeated dose study designed to investigate the impact of choline on the liver tumour promoting activity of phenobarbital and DDT in DEN-initiated animals, rats were dosed with approximately 500mg/kg bw/day over 72 weeks via feed, with a post-observation period of 30 weeks. No significant effects were observed relative to controls with respect to survival rates, body weights and relative liver weights. Only limited

pathological investigations were carried out at autopsy (gross examination with histological investigation of only the liver and any tissues showing gross abnormalities). No adverse effects were observed. Therefore the NOAEL for this study was ≥500mg/kg bw/day. The tolerable upper intake level for human adults was set at 3.5 g/day corresponding to approx. 58 mg/kg bw/day (USA's Standing Committee on the Scientific Evaluation of Dietary Reference Intakes).

Choline chloride does not show a mutagenic, clastogenic or DNA damaging potential when tested *in vitro*; furthermore it has no structural alerts. There is therefore no indication of a genotoxic potential *in vivo*.

No developmental toxic effects were observed in mice after oral doses of 1250 mg/kg bw/day on gestation days 1 to 18. Doses above the levels recommended currently (4160 mg/kg bw/day and higher) and associated with maternal toxicity, did produce developmental toxic effects, but these were secondary to the maternal toxicity at the excessive doses used. The compound does not produce any significant developmental toxicity in the mouse.

Thus evidence from animal studies and from human exposure indicates that choline chloride has low toxicity, is not mutagenic and has no developmental toxicity. This is not unexpected in view of its presence in the diet and its production in metabolic processes in the body; it fulfils key roles in nerve transmission, cell membrane integrity, and lipid metabolism. Only limited animal data are available on effects on fertility, but the normal exposure of humans to appreciable amounts of choline chloride both from the diet and formed from normal metabolic processes, would argue against it having any significant adverse effects on fertility. This is supported by the fact that it has been widely used as an animal feed additive for decades with no apparent adverse effects being noted on fertility.

Environment

Choline chloride is a white crystalline solid but is marketed as an aqueous solution (70 – 75 % w/w in water) which is a colorless liquid with an amine-like odor. It has a measured water solubility of ca. 650 g/L (calculated water solubility: 1,000,000 mg/L) and a calculated vapor pressure of $6.57*10^{-10}$ hPa at 25°C. A Henry's Law Constant of $2.06*^{10-}11$ Pa*m³/mole at 25 °C could be calculated. Distribution modeling using Mackay Level I indicates water (100 %) to be the main target compartment. The amount in the other compartments is with < 0.0001 % negligible. Choline chloride is readily biodegradable according to OECD-criteria (MITI-I Test; BOD measurements) reaching 93 % degradation within 14 days. Due to the chemical structure hydrolysis can be excluded. In the atmosphere choline chloride will be rapidly degraded according to a half life time ($t_{½}$) of about 6.9 hours for hydroxyl-radicals based on a 12 hours day. Due to the measured and calculated $\log K_{ow}$ of –3.77 and –5.16 both at 25°C, respectively, and a calculated $\log K_{oc}$ of 0.37 a bio- or geoaccumulation is not to be expected.

The aquatic toxicity has been determined for freshwater and saltwater species according to several GLP and non-GLP test guidelines. For the freshwater fish species *O. latipes* a LC_{50} (96h) of > 100 mg/L and for the saltwater fish species *L. limanda* a LC_{50}(96h) of > 1,000 mg/L could be determined, respectively. The acute toxicity (EC_{50}) for the invertebrate species *D. magna* was found to be 349 mg/L after 48 h of exposure, In a 21d Daphnia reproduction test, a 21d NOEC (reproduction) of 30.2 mg/l was obtained. For the freshwater algae *Pseudokirchneriella subcapitata* an Er(b)C_{50} (72h) of > 1,000 mg/L could be determined.

Exposure

The world production of choline chloride in the year 2002 was in the range of10,000 to 50,000 tons.

At the European production sites choline chloride is produced under pressure and room temperature by reaction of trimethylammonium chloride with ethylene oxide in closed systems. Exposure may occur during manufacture, transportation and industrial use. The likely primary routes of human exposure to choline chloride are skin contact and inhalation at the work place. Worker exposure is limited by enclosed systems, industrial hygiene controls and personal protective measures are adequate.

Choline chloride has a widespread use as a food additive for animal husbandry since the early 1930s. For this

application area almost 100% of the produced choline chloride is either premixed as solid and then directly mixed with animal feed or marketed as a fluid compound to the customers and directly released into special installed mixing apparatus. A very small amount of the choline chloride production is used for formulations in the field of plant growth regulators. In general the following formulations are used for commercial applications: Bulk, in solution (up to 70%), on vegetable carriers, on amorphous silica carriers.

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

The chemical is currently of low priority for further work due to its low hazard profile.