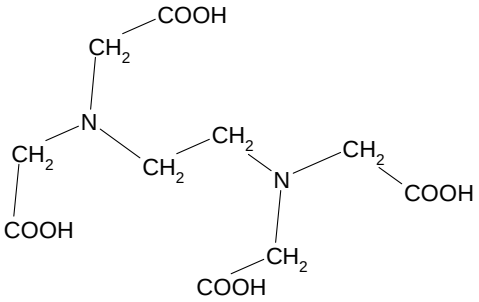
SIDS INITIAL ASSESSMENT PROFILE

CAS No.	60-00-4
Chemical Name	Edetic acid
Structural Formula	

SUMMARY CONCLUSIONS OF THE SIAR

Human Health

EDTA is a strong chelating agent and its toxicological profile is mainly based on this property. There are no oral toxicokinetic studies or skin absorption studies with EDTA itself or its tetrasodium salt available. According to the dissociation equilibrium of edetic acid administration of different sodium salts will result in dependence on the intestinal pH-value to the formation of various anionic species of EDTA. It can be assumed that the oral and dermal absorption of the free acid and of sodium salts of EDTA is comparable to the measured low absorption of $CaNa_2EDTA$. It is poorly absorbed from the gastrointestinal tract (a maximum of 5% was detected in the urine). Only 0.001% of $CaNa_2EDTA$ is absorbed after dermal application. After intake EDTA is not or scarcely metabolized and excreted as a chelated complex via urine following glomerular filtration and tubular secretion. In whatever salt EDTA is administered it is likely to chelate metal ions in vivo.

Animal data show that acute oral toxicity is low. In two tests on rats LD50 values of >2000 mg/kg were reported. No data are available for acute dermal toxicity. The data on acute inhalation toxicity are not valid to be used for hazard assessment. A 50% aqueous preparation of edetic acid resulted in a mild irritation of the skin after a 20 hour exposure time. Instillation of solid edetic acid to the rabbit eye resulted in strong but reversible irritant effects.

In a Magnusson Kligman Test with Na_2EDTA 30% of the guinea pigs showed a positive response after a first challenge and 10% after a second challenge. There are only two reports on single cases in humans demonstrating positive skin results. Based on the fact that EDTA is being used in industry and consumer products for many decades in high quantities the substance is considered as non-sensitising to humans. No adverse acute or chronic respiratory health effects from exposure to EDTA or Na_4EDTA have been observed in workers.

For systemic effects studies with administration of H_4EDTA or of its salts such as Na_2EDTA, Na_3EDTA and Na_4EDTA were considered as relevant information because these compounds are dissociated under physiological conditions (pH 7 - 9) into the sodium cations and the respective anionic species of edetic acid ($HEDTA^{3-}$) depending on the pH-dependent dissociation equilibria of edetic acid. Taken together, any conclusions on EDTA will be derived from consideration of the overall available data base. From repeated dose toxicity experiments (90 day feed male rats, 2 year bioassay both sexes rats and mice) a NOAEL of 500 mg/kg/d for Na_2EDTA and Na_3EDTA could be derived. Range finding studies with higher dose levels revealed diarrhoe, emanciation, loss of body weight and sometimes parakeratosis in oesophagus and forestomac as well as decreased hemoglobin and hematocrit levels.

Bacterial mutation tests are negative, but mutations and DNA damage were found in mouse lymphoma cells after exposure to very high concentrations. For somatic cells in mice (bone marrow cells) negative results with respect to the endpoints micronuclei, aneuploidy and sister chromatid exchanges were described. In germ line cells negative results were obtained for induction of structural chromosomal aberrations in spermatogonia, for induction of aneuploidy in primary and secondary spermatocytes, and also for induction of dominant lethals. A positive result was obtained in a micronucleus test with spermatids, indicating that aneugenic effects may be induced in specific phases of spermatogenesis (late spermacytoge-nesis). The effect was bound to the use of an extremely high dose in the LD_{50} range. Since the induction of aneuploidy is based on a threshold mode-of action, the potential for induction of aneuploidy will not be expressed at low doses. Altogether, EDTA and its sodium salts have a low mutagenic potential at extremely high doses. On the basis of the various negative findings and the assumption of a threshold mode-of action for aneugens, it can be concluded that EDTA and it sodium salts are no mutagens for man.

Epidemiological studies are not available for evaluation of the carcinogenic potential of EDTA. A diet study of Na_3EDTA for possible carcinogenicity was conducted in Fischer 344 rats and B6C3F1 mice. The studies on both species showed no treatment related tumors. Taking into account the negative results of the cell transformation assays and the low mutagenic potential expressed only at extremely high dose levels it can be concludet that there is no concern on carcinogenic properties of EDTA.

Concerning reproductive toxicity, valid data from human experience are not available. Data from animal studies with $CaNa_2EDTA$ did not give evidence for adverse effects on reproductive performance and outcome for doses of up to 250 mg/kg bw/day. Studies on developmental toxicity showed a specific fetotoxic and teratogenic potential of EDTA, Na_2EDTA and $CaNa_2EDTA$; a LOAEL of 1000 mg/kg bw was determined. Increased proportions/litter and significantly lower fetal body weights are indicative for an impaired fetal development. The pattern of malformations comprised cleft palate, severe brain deformities, eye defects, micro- or agnathia, syndactyly, clubbed legs and tail anomalies. These effects were exhibited in studies using maternally toxic dose levels. The mechanism resulting in developmental effects is found to occur via zinc depletion resulting in zinc deficit. These effects are independent of whether the acid or alkali- and/or calcium salts are applied.

Environment

H_4EDTA has a water solubility of 0.4 g/l at 20 °C. As no value for the vapour pressure is known, a Henry's law constant cannot be calculated from vapour pressure and water solubility. Because of the ionic properties of the substance, it has to be assumed that volatilization from aqueous solution will not occur. Mackay level I calculations for EDTA predicts that the hydrosphere is the preferred environmental compartment (99.999 %).

Due to the ionic structure under environmental relevant pH conditions, no adsorption onto the organic fraction of soils or sediments is expected.

EDTA is resistant to hydrolysis, neither strong acids nor alkalis cause any degradation. Investigations reveal that uncomplexed EDTA is not degradable by photolysis under environmental conditions. The half-life for photolytic degradation of Fe(III)EDTA in aqueous solution under environmental conditions was estimated to 20 days. Further abiotic degradation processes as reaction with OH-radicals or singlet oxygen have (compared to the direct photolysis) very low reaction constants and are of no environmental significance.

During photolysis of Fe(III)EDTA in surface waters as well as during biodegradation of other EDTA species in treatment plants and in the environment, reaction products are formed which cause further exposure of the environment. The reaction products ketopiperazinediacetate (KPDA) and ethylenediaminetriacetic acid (ED3A) were detected in German rivers and drinking water.

Different standard OECD tests show, that EDTA is neither readily nor inherently biodegradable. There are data suggesting that under alkaline conditions EDTA complexed with Ca-ions can be biodegraded which could be relevant for certain surface waters. However, in surface waters EDTA is preferably complexed with heavy metal ions and no biological degradation is expected for these complexes. Therefore, EDTA is regarded as not biodegradable in surface waters. Monitoring of EDTA concentration in influent and effluent of several industrial sewage treatment plants results in removal rates in the range of 30 to 95 % dependent on pH, retention time, EDTA concentration and

complexation stage.

Bioaccumulation studies with fish show that EDTA has no bioaccumulation potential.

It could be shown in short-term tests on fish, that EDTA and Na-EDTA are more toxic in an uncomplexed form. This can only occur if they are available in over-stoichiometric amounts to the chelants. Under these conditions the complexing agents can cause nutrient deficiency by reducing the essential concentration of different ions. The higher the water hardness the higher is the concentration of EDTA necessary to cause a toxic effect expressed as mortality. According to the results from different ecotoxicological studies, EDTA mainly influences the pathway of metal ions. The chelating properties of EDTA present a problem to the derivation of the PNEC, because it is difficult to distinguish between intrinsic properties and effects caused by nutrient depletion and other complexation properties under test conditions. In the available tests on acute toxicity, the EDTA concentration was too high to exclude substance-unspecific effects. Generally, tests in such a high concentration range are not considered to be valid, thus it is not likely to determine a PNEC with the available short-term test results. The effect assessment of EDTA is therefore based on long-term tests. For EDTA long-term studies with fish, daphnids and algae are available. The following results were found: Danio rerio: 35 d-NOEC > 26.8 mg/l ($CaNa_2EDTA$); Daphnia magna: 21d-NOEC = 22 mg/l; Scenedesmus subspicatus: 72h-EC10 = > 100 mg/l. With an assessment factor of 10 a PNEC of 2.2 mg/l was derived from the 21 d study with Daphnia magna.

Based on environmental behaviour properties, EDTA seems not to be of concern for sediment, atmosphere and terrestrial compartment and the food chain. No formal PNEC was established for these compartments because of lack of appropriate studies.

Exposure

EDTA is mainly produced and used as acid (H4EDTA) and as sodium salt (Na_4EDTA). In lower amounts, other salts or metal complexes are produced resp. used. The environmental exposure from the different uses of all EDTA species is overlapping. In the European Union, 53,900 t/a EDTA given as H4EDTA equivalents are produced.

EDTA is used as a complexing agent in many industrial branches, e.g. household detergents, industrial & institutional detergents, photochemicals, textiles, pulp and paper, metal plating, agriculture, cosmetics, water treatment and others.

Environmental releases occur during production and use. Because EDTA is a watersoluble compound, it is mainly emitted into the waste water. When H_4EDTA and Na_4EDTA are emitted during production, use etc., the same ionic species are formed in the environment, independent of the originally used compound (acid or a salt). Therefore, the emissions from both H_4EDTA and Na_4EDTA uses have to be added.

A lot of monitoring data are available for EDTA. In German municipal waste water treatment plant effluents EDTA concentrations in the typical range of 60 – 600 µg/l were measured. In 5 out of 55 sampled plants the concentration exceeded 600 µg/l.

During an extended monitoring program, EDTA was measured in German surface waters from 1993 to 1995. EDTA concentrations > 500 µg/l were measured (2/143), while most sampling sites gave values in the range of 6 – 60 µg/l (90/143) and 60 – 500 µg/l (30/143). In 1994, the concentrations were 4.1-17.6 (∅ 8.69) µg/l in the Rhine at Lobith and 3.5-11.4 (∅ 7.7) µg/l in the Ijsselmeer at Andijk. At Lobith, the average concentrations were 7.7 µg/l in 1995, 10.9 µg/l in 1996, and 7.0 µg/l in 1997. In the Lake Constance near Überlingen, the yearly averaged EDTA concentration was 4.8 µg/l in 1989. The value decreased to 2.5 µg/l in 1994. In Swiss rivers, the EDTA concentrations are generally below 20 µg/l. In the river Glatt, maximum concentrations of about 200 µg/l were measured.

In the river Odiel near Huelva (Spain) EDTA was measured at two sites. The first sampling point is near several industrial emission sources, the EDTA concentration was 2.46 mg/l. The second site near the river mouth is influenced by sea water, the EDTA concentration was 0.599 mg/l.

RECOMMENDATION

Environment: The chemical is a candidate for further work.

Human Health: The chemical is of low priority for further work.

RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Environment:

Although EDTA does not posses properties indicating a hazard for the environment, a risk assessment performed in the context of the EU Existing Substances Regulation identified a risk for the following scenarios based on very high releases of the substance:

- for the use of EDTA in industrial detergents by large sites within dairy and beverage industry where no effective waste water treatment is applied,
- for paper pulp mills where no effective waste water treatment is applied,
- for metal plating (circuit board production),
- for releases at waste disposal sites.

Therefore, the substance is a candidate for further work. Countries are invited to perform an exposure assessment to identify possible risks to the aquatic environment caused by the use of EDTA as complexing agent.

In the EU, a risk reduction strategy is currently under discussion.

Human Health:

The chemical possesses properties indicating a hazard for human health (irritation, developmental toxicity). Despite of the wide disperse use of the substance the exposure of workers and consumers is low in regard to the doses producing adverse effects, and therefore the chemical is of low priority for further work.

This substance has been agreed in the European Union Risk Assessment Programme under Regulation EEC/793/93 with the following conclusion:

Consumers: There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

Workers: There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.