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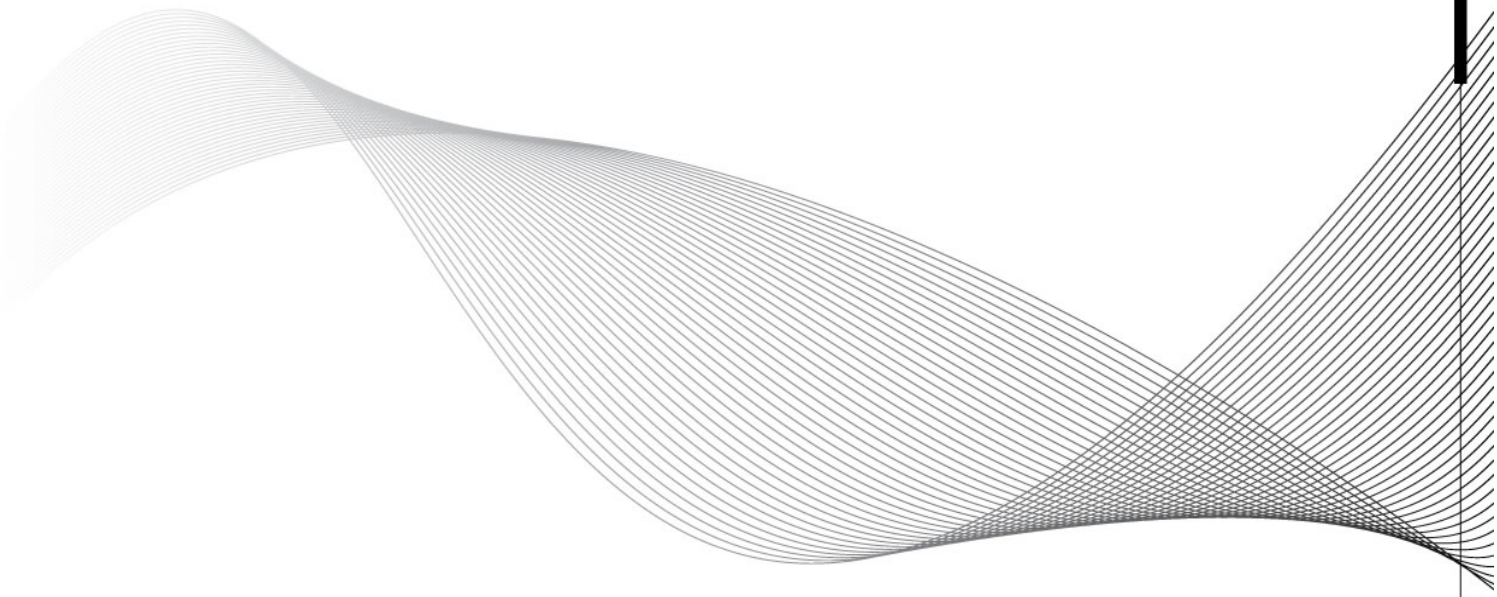

Recommendation from the Scientific Committee on Occupational Exposure Limits for edetic acid

SCOEL/SUM/135
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European Commission

Table of Contents

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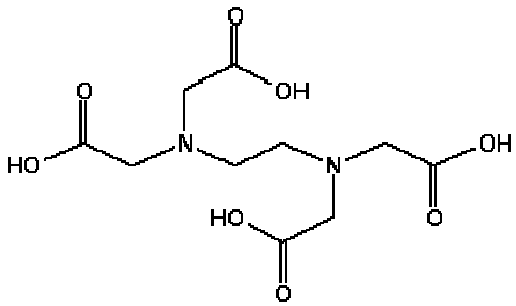
8 hour TWA:	Not assigned (see *recommendation*)
STEL (15 mins):	Not assigned
Notation:	Not assigned
BLV:	Not assigned

Substance identification

Molecular formula $C_{10}H_{16}N_2O_8$

Structural formula



Synonyms: {[2-(Bis-carboxymethyl-amino)-ethyl]-carboxymethyl-amino}acetic acid; Ethylenediaminetetraacetic acid; Ethylenedinitrilotetraacetic acid; N,N'-1,2-ethanediylbis[N-(carboxymethyl)glycine]; H_4EDTA; EDTA.

EINECS No.: 200-449-4
EU Classification: Not classified in Annex I of Directive 67/548/EEC.
CAS No.: 60-00-4
MWt: 292.3 $gmol^{-1}$
Physical properties:
Density: 0.86 g/cm^3 , Solubility in water: 0.5 g/l at 25 °C

Conversion factor (25 °C, 101 kPa): 1 ppm = 11.96 mg/m^3; 1 mg/m^3 = 0.0836 ppm

This evaluation is based on EU-RAR. (2004). Edetic Acid (EDTA). European Risk Assessment Report, 1st Priority List. Volume 49. European Chemicals Bureau.

1. Occurrence/use and occupational exposure

EDTA is mainly produced and used as EDTA acid (H_4EDTA) and as the tetrasodium salt (Na_4EDTA). About 53,900 tonnes per annum were produced in the EU in the late 1990s.

H_4EDTA is produced from Na_4EDTA by acidification with sulphuric acid and precipitation from aqueous solution. Na_4EDTA is synthesised by cyanomethylation of ethylene diamine with sodium cyanide and formaldehyde to ethylene dinitrilo tetraacetonitrile which is hydrolysed with sodium hydroxide to Na_4EDTA.

H_4EDTA and its salts are used as complexing agents in a range of industries. They are mainly used in detergents for industrial, institutional and domestic use and also in the photochemical, textile, pulp and paper, metal plating, and cosmetic industries, agriculture and water treatment. Smaller quantities are used for disinfection, in printing inks and dyes, food/feed ingredients, fuel gas cleaning, pharmaceuticals, polymer and tuber processing, leather tanning, oil production, concrete, lubricants and other chemical processes.

Methods of exposure monitoring and analysis

An appropriate measurement method specific to H4EDTA in air was not identified.

2. Health significance

2.1. Toxicokinetics

There are no studies available on inhalation, oral toxicokinetics or skin absorption with H_4EDTA or its sodium salts.

According to EU RAR, it can be assumed that oral and dermal absorption of H_4EDTA is comparable to the measured low oral and dermal absorption of $CaNa_2$EDTA.

Particle size may play an important role in the uptake of inhaled EDTA. Larger particles deposited within the upper airways may be largely cleared via the digestive system whereas particles deposited in the lung may be more likely to dissolve and may be absorbed through the lung.

Biological monitoring

Biological monitoring is not in use for H4EDTA exposure at present and Biological Exposure Index has not been identified.

2.2. Acute toxicity

2.2.1. Human data

No human data are available regarding the acute toxicity of H_4EDTA

2.2.2. Animal data

For H_4EDTA EU-RAR and BUA Report indicate the following oral LD50 values in rats: >2000, 2580 or 4500 mg/kg body weight, indicating a low level of acute toxicity.

An 8-hour inhalation test with rats, exposed to unmeasured concentration of edetic acid dust, revealed only a mild irritation of the mucous membranes (BASF AG, 1973; cit. EU RAR 2004).

No data are available on dermal toxicity.

2.3. Irritation and corrosivity

2.3.1. Human data

No studies are available in the peer-reviewed literature on skin, eye or respiratory irritation caused by H4EDTA in human, despite of its wide-spread use in large quantities.

2.3.2. Animal data (BASF AG, 1973; cit. EU RAR 2004)

Skin

Industry study in a rabbit has shown that a 50% aqueous preparation of H_4EDTA of unknown purity resulted in a mild irritation on the skin of the ear, but not on the skin of the back of the animal after a 20-hour exposure time.

Eyes
Instillation of 50 mg of solid H_4EDTA to the rabbit eye resulted in strong, irritant effects, reversible within 8 days. Irritation scores are not mentioned.

Respiratory tract
An 8-hour inhalation test with rats, exposed to unmeasured concentration of H_4EDTA dust revealed only a mild irritation of the mucous membranes.

The EU-RAR concluded that the data did not warrant classification of H_4EDTA as a skin irritant but did warrant classification as an eye irritant

2.4. Sensitisation

2.4.1. Human data

Only two case reports of possible human skin sensitisation are available. Raymond and Gross (1969) reported positive responses in 3 out of 50 subjects patch tested with 1% EDTA. The North American Contact Dermatitis Group reported an incidence of 0.9 % of positive responses in 215 subjects patch tested with EDTA of 1 % concentration (Runder, 1977). In another study no positive response was observed in several hundreds of patients tested with EDTA (Fisher, 1986. cit. EU-RAR 2004).

The human data available on the bronchoconstriction inducing effect of EDTA inhalation in asthmatic patients are of limited use in the assessment of respiratory sensitisation (Beasley et al. 1987).

2.4.2. Animal data

No data are available on sensitization caused by H_4EDTA .

The EU RAR concluded - taking into account the fact that H_4EDTA (and its sodium salts) is being used in industry and consumer product for many decades in high quantities - that the law incidences of positive responses were insufficient evidence to justify classification as a sensitizer following skin contact or inhalation.

2.5. Repeated dose toxicity

2.5.1. Human data

There are no published studies on the effects of occupational exposure to H4EDTA.

2.5.2. Animal data

Inhalation
There are no repeated dose inhalation studies for H_4EDTA or its sodium salts available.

Oral
There is only one repeated dose oral study with H_4EDTA available.
Krari and Allain (1991) reported that oral exposure to H_4EDTA at 293 mg/kg/day for 35 days induced moderate changes of the concentrations of some elements (Ca, Mg, Fe, P) in rat tissues, but without signs of toxicity.

Dermal
There are no repeated dose dermal studies for H_4EDTA or its sodium salts available.

2.6. Genotoxicity

2.6.1. In vitro

Bacterial mutation tests
No bacterial mutation tests are available for H4EDTA.

Mammalian cell culture tests
In a mouse lymphoma cell assay, without metabolic activation, 2-6 fold increases of mutant frequencies were induced by H_4EDTA at very high concentrations of 25-30 mmol/l for 4 hours (Wagenheim and Bolcsfoldi, 1988). In an alkaline elution assay with mouse lymphoma cells, without metabolic activation, DNA single strand breaks were induced at extremely high concentrations from 40 mmol/l upwards (Garberg et al, 1988). In an alkaline elution assay with V79 cells at concentrations of EDTA up to 30 mmol/l, no effects were seen with and without S-9 mix (Swenberg et al. 1976; Swenberg, 1981).

2.6.2. In vivo – Human data

There are no human data on mutagenicity available.

2.6.3. In vivo – Animal data

In an assay with Drosophila melanogaster for non-disjunction and loss of the sex chromosomes H_4EDTA (700 ppm, oral feed, undefined exposure period) proved to be positive for chromosomal loss (Ramel and Magnusson, 1979). The EU-RAR concluded that

EDTA and its sodium salts are not mutagenic to humans, having a low mutagenic potential at extremely high doses.

2.7. Carcinogenicity

2.7.1. Human data

There are no human data on the carcinogenicity of H4EDTA.

2.7.2. Animal data

There are no animal data for H_4EDTA, available

The EU-RAR concluded that the carcinogenic potential of EDTA was of no concern on the basis of the negative results of the carcinogenicity study with Na_3EDTA in rats and mice (NTIS 1977) and of cell transformation assays and also its low mutagenic potential that is only expressed at (extremely) high dose levels.

2.8. Reproductive toxicity

2.8.1. Human data

There are no human data on reproductive toxicity of H_4EDTA acid.

2.8.2. Animal data

Fertility
Fertility studies with H_4EDTA are not available.

Developmental toxicity
In a study 1000 mg/kg of H_4EDTA administered by gavage on gestation days 7 to 14 failed to induce foetoxic effects, although maternal toxic effects were manifested (Schardein *et al*, 1981).

Recommendations

H_4EDTA is a crystalline solid with low vapour pressure and it is not absorbed by the skin. Occupational exposure occurs most likely by inhalation of the dust, when handling the powdery substance or by inhalation of the aerosol during spray application of the aqueous preparations.

The results of the available animal experiments indicate a low acute oral toxicity of H_4EDTA.

In repeated dose oral experiments, Krari and Allain (1991) found evidence of effects on trace element content in tissues at level of exposure to 293 mg/kg/day H_4EDTA, p. o., for 35 days, but no evidence of adverse effects.

H_4EDTA does not appear to be a sensitiser and it is not associated with skin irritation, but it proved to be irritating to the eyes in rabbits.

There is no evidence that EDTA is mutagenic or carcinogenic.

H_4EDTA failed to induce foetotoxic effects even at high oral doses with definite maternal toxicity (1000 mg/kg/day - Schardein et al, 1981).

Having considered that:

- no reports of adverse health effects (local or systemic) occurring in humans were found in the literature, due to acute or repeated, oral, dermal or inhalation exposure to H_4EDTA, despite that it is a widely used industrial chemical;
- there is no information about the absorption of inhaled H_4EDTA in humans or in animals;
- repeated dose inhalation animal experiments were not identified in the available literature,

SCOEL concluded that no OEL values can be established so far.

Furthermore, no adequate method of measurement for H_4EDTA has been identified.

References

Beasley CR, Rafferty P, Holgate St. (1987). Bronchoconstrictor properties of preservatives in ipratropium bromide (Atrovent) nebuliser solution. Brit. Med J. 294: 1197-1198.

BUA Report 168 (1995). Ethylenediaminetetraacetic acid/Tetrasodium ethylenediaminetetraacetate. S Hirzel. WV Stuttgart.

EU-RAR. (2004). Edetic Acid (EDTA). European Risk Assessment Report, 1st Priority List. Volume 49. European Chemicals Bureau.

Garberg P, Akerblom EL, Bolcsfoldi G. (1988). Evaluation of a genotoxicity test measuring DNA-strand breaks in mouse lymphoma cells by alkaline unwinding and hydroxyapatite elution. Mutat. Res. 203: 155-176.

Krari N, Allain P.(1991). Effects of three chelating agents, EDTA, NTA and TPP on the concentration of elements in rat tissues. Biological Trace Element Research; 31:199125-207131.

NTIS. (1977). Bioassay of trisodium ethylenediamintetraacetate trihydrate (EDTA) for possible carcinogenicity. PB-270-938

Ramel C, Magnusson J. (1979). Chemical induction of nondisjunction in Drosophila. Environ. Health Persp. 31: 59-66.

Raymond JZ, Gross PR. (1969). EDTA: Preservative dermatitis. Arch. Derm. 100: 436-440.

Runder, EJ. (1977). North American Group Results. Contact Dermatitis 3: 208-209.

Schardein JL, Sakowski R, Petrere J, Humphrey RR. (1981). Teratogenesis studies with EDTA and its salts in rats. Toxicology and Applied Pharmacology; 61: 423-428.

Swenberg J. A. (1981). Utilization of the alkaline elution assay as a short term test for chemical carcinogens, pp. 48–58. Springer, New York.

Swenberg JA, Petzold GL, Harbach PR. (1976). In viro DNA damage/alkaline elition assay for predicting carcinogenic potential. Biochem. Biophys. Comm. 72: 732-738.

Wagenheim J, Bolcsfoldi G. (1988). Mouse lymphoma L5178Y thymidine kinase locus assay of 50 compounds. Mutagen 3: 193-205.