EUROPEAN COMMISSION
DIRECTORATE-GENERAL
Joint Research Centre

Institute for Health and Consumer Protection
European Chemicals Bureau
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TETRASODIUM ETHYLENEDIAMINETETRAACETATE (Na_4EDTA)

CAS No: 64-02-8

EINECS No: 200-573-9

Summary Risk Assessment Report

2004 **Special Publication I.04.220**

TETRASODIUM ETHYLENEDIAMINETETRAACETATE

(NA_4EDTA)

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SUMMARY RISK ASSESSMENT REPORT

Final report, 2004

Germany

The risk assessment of tetrasodium ethylenediaminetetraacetate (Na_4EDTA) has been prepared by Germany on behalf of the European Union.

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Date of Last Literature Search:	**2003**
Review of report by MS Technical Experts finalised:	**2001**
Final report:	**2004**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance tetrasodium ethylenediaminetetraacetate, (Na_4EDTA), that has been prepared by Germany in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

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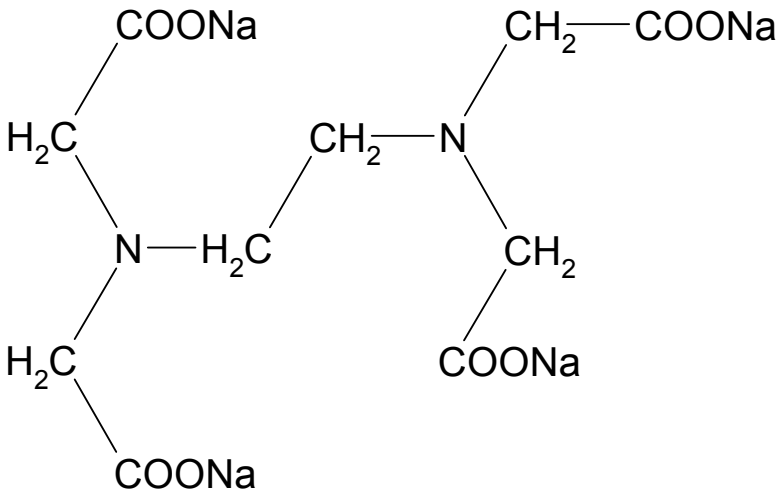
1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No:	64-02-8
EINECS No:	200-573-9
IUPAC Name:	tetrasodium {[2-(bis-carboxymethyl-amino)-ethyl]- carboxymethyl-amino}-acetate
Synonyms:	ethylenediaminetetraacetic acid tetrasodium salt, ethylenedinitrilotetraacetic acid tetrasodium salt, edetic acid tetrasodium salt, Na_4EDTA or EDTA tetrasodium, edetate sodium or Sodium ededate, N,N'-1,2-Ethanediylbis[N-(carboxymethyl)glycine] tetrasodium salt
CA Index name:	Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)-, tetrasodium salt
Empirical formula:	$C_{10}H_{12}N_2Na_4O_8$
Molecular weight:	380.2 g/mol
Structural formula:	



1.2 PURITY/IMPURITIES, ADDITIVES

Purity:		> 76% w/w
Impurities:	disodium ethylenediaminediacetate	≤ 1% w/w
	disodium dihydrogen ethylenediaminetetraacetate	≤ 2% w/w
	trisodium hydrogen ethylenediaminetetraacetate	≤ 7% w/w
	trisodium nitrilotriacetate	≤ 3% w/w
	sodium glycolate	≤ 3% w/w
	sodium hydroxide	≤ 2% w/w
	sodium chloride	≤ 1% w/w
	sodium carbonate	≤ 1% w/w
	sodium formate	≤ 1% w/w
	sodium sulphate	≤ 0.1% w/w
	sodium cyanide	< 10 ppm
	water	≤ 6% w/w
Additives:	none	

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Physico-chemical properties

Parameter	Value
Physical state	at 20 °C, 1013 hPa: white powder
Melting point	> 300 °C
Boiling point	not determined [1)]
Relative density	0.71 [2)]
Vapour pressure	not determined [3)]
Surface tension	not determined [4)]
Water solubility	500 g/l at 20 °C
log P_{ow}	not determined [5)]
Flash point	not determined because substance is solid
Flammability	not flammable [6)]
Ignition temperature	200 °C
Explosive properties	not explosive [7)]
Oxidising properties	no oxidising properties [7)]
Henry's law constant	$1 \cdot 10^{-20}$ Pa·m^3/mol [8)]

1) The tetrasodium salt of edetic acid has a melting point of >300 °C and exhibits thermal decomposition above 150 °C. Therefore a determination of the boiling point is scientifically not meaningful.
2) In the literature only a value for the 'apparent density' was found. While the relative density is no relevant factor for the risk assessment no test was conducted.
3) For ionic substances the vapour pressure is supported to be very low.
4) For structural reasons no surface activity is to be assumed. Therefore no test was conducted.
5) For ionic substances the partition coefficient can not be determinated experimentally. According Hansch and Leo the partition coefficient for the undissociated free acid was calculated to be -5.01.
6) In a preliminary test the ignition level was determined to be 1. Therefore the substance is not flammable.
7) No test was conducted because of structural reasons.

1.4 CLASSIFICATION

Classification according to Annex I

Class of danger: none
R-Phrase: none

The classification of Na_4EDTA is not included in Annex I to Directive 67/548/EEC.

Proposed Classification

At the meeting of 17-19 November 2003 the EU classification and labelling working group (Human Health) agreed upon the following classification for Na_4EDTA:

Xn; R22
Xi; R41

Labelling

Xn
R: 22-41
S: (-2)26-39-46

Xn	Harmful;
R22	Harmful if swallowed
R41	Risk of serious damage to eyes
S2	Keep out of the reach of children
S26	In case of contact with eyes rinse immediately with plenty of water and seek medical advice
S39	Wear eye/face protection
S46	If swallowed, seek medical advice immediately and show this container or label

Concentration limits

C≥ 40%	Xn; R22-41
25%≤C<40%	Xn; R22-36
5%≤C<25%	Xi; R36

2 GENERAL INFORMATION ON EXPOSURE

EDTA is mainly produced and used as acid (H_4EDTA) and as sodium salt (Na_4EDTA). In lower amounts, other salts or metal complexes are produced or used. The environmental exposure from the different uses of all EDTA species is overlapping. Thus, for the environmental risk assessment (Sections 2 and 3) all production and use volumes are given as H_4EDTA equivalents.

Na_4EDTA is synthesised preferably by cyanomethylation of ethylene diamine with sodium cyanide and formaldehyde. Alternatively, a two-step reaction is in practise: first hydrogen cyanide reacts with formaldehyde to ethylene dinitrilo tetraacetonitrile, which is in the second step hydrolysed with sodium hydroxide to Na_4EDTA. From its salt, H_4EDTA is produced by acidification with sulphuric acid and precipitation from aqueous solution.

In the European Union, EDTA is produced or imported at 7 sites. During production, releases occur via wastewater into surface waters. According to the data submitted by the producers, the total yearly releases into the hydrosphere amount to 266 tonnes/annum. The total yearly releases as dust into the atmosphere are 11 tonnes/annum.

EDTA is used as a complexing agent in many industrial branches. The substance is sold either directly from the producers to the consumers or via distributors. The European application volumes (referred as H_4EDTA) were in 1999:

Table 2.1 European use pattern of EDTA

Use	Marketed amount [t/a]
Household detergents	2,619 (7.6%)
Industrial and institutional detergents	10,685 (31%)
Photochemicals	4,191 (12%)
Textiles	639 (1.8%)
Pulp and paper	4,002 (12%)
Metal plating	470 (1.4%)
Agriculture	5,821 (17%)
Cosmetic	756 (2.2%)
Rubber processing	469 (1.4%)
Oil production	358 (1.0%)
Exports	1,143 (3.3%)
Others	3,393 (9.8%)
Total	**34,546**

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

Environmental releases

During the use as complexing agent, the major amount of the applied EDTA is emitted into the wastewater. The emission situation in the individual industry branches is presented in Section 3.1.2.2.

When H_4EDTA and Na_4EDTA are emitted during production, use etc., the same ionic species are formed in the environment, independent to the originally used compound (acid or a salt). Therefore, in the environmental exposure assessment the emissions from both H_4EDTA and Na_4EDTA uses have to be added. In order to obtain comparable values, H_4EDTA equivalents are calculated for emissions of the Na-salt or metal complexes, and the environmental risk assessment is performed on this basis. Also in the literature all figures are generally related to H_4EDTA; when the species is not stated they will be taken as H_4EDTA.

Environmental fate

Degradation

The results of standard biodegradation tests can not be used for the exposure assessment. It was demonstrated by laboratory tests that biodegradation of EDTA is strongly dependent on the complexed metal. Metal-EDTA complexes with a thermodynamic stability constant below 10^{12}, like Ca, Mg and Mn, were degraded under special conditions, while chelates with stability constants above 10^{12}, such as Cu and Fe, are recalcitrant.

In biological treatment plants, EDTA can be removed when a number of specific conditions are present: a relatively high hydraulic and sludge retention time, an alkaline pH value of the wastewater, and when EDTA is not complexed with heavy metal ions. Monitoring data indicate that these conditions are fulfilled in some treatment plants of paper mills and beverage industry, where removal rates up to 95% were determined. In contrast, in municipal treatment plants EDTA is generally not removed. In the exposure scenarios for paper mills and beverage industry, 2 scenarios were calculated. In the first no removal is assumed reflecting a worst-case scenario, and a removal of 90% reflecting the best available techniques. In all other scenarios no removal is assumed.

In sediment and soils, EDTA is aerobically degraded with estimated half-lifes of 300 days.

Fe (III) EDTA was found to be photolytically degraded in aqueous solution. As a relevant part ($^1/_3$ to $^2/_3$ of total EDTA) is released as iron complex, this mechanism is probably predominant in environmental EDTA degradation. For the regional exposure scenario, it is assumed that 50% of the total EDTA releases are photolytically degraded with a half-life of 20 days.

The pathway of both biodegradation and photolysis is identical: carboxymethyl moieties are subsequently cleaved, leading to ethylenediaminetriacetic acid (ED3A) as the first reaction product. ED3A is either further degraded or undergoes intramolecular cyclisation leading to ketopiperazinediacetate (KPDA). The sum of ED3A and KPDA was detected in surface waters in concentrations up to 16 µg/l. KPDA was found to be readily biodegradable failing

the 10-days window. Due to the degradation properties, accumulation of the EDTA metabolites is not expected.

Distribution

EDTA and its metal complexes are highly soluble in water. Because of the ionic properties, volatilisation from aqueous solution will not occur.

The adsorption onto sediments is low: For 3 metal complexes, partitioning coefficients between 3 and 113 l/kg were determined. For the exposure calculation, values for Kp_{soil}, Kp_{sed} and Kp_{susp} of 75 l/kg are used.

Accumulation

Bioaccumulation of EDTA and its metal complexes is low: for the exposure assessment a BCF of 1.8 l/kg was used.

3.1.2 Aquatic compartment (incl. sediment)

3.1.2.1 Production

Exposure scenarios were calculated based on site-specific data of 7 European EDTA producers. The calculated PEClocal values are in the range of 0.095 and maximum 1 mg/l.

3.1.2.2 Use

Releases into household sewage

EDTA is an ingredient of household detergents, cosmetics, pharmaceuticals and food. The main function is the complexation of trace metals. It was assumed that the total application volume (3,669 tonnes/annum) is released via the household sewage without elimination in treatment plants. The resulting PEClocal is 0.195 mg/l.

Industrial detergents

EDTA prevents the precipitation of calcium, magnesium and heavy metals which can cause sedimentation and incrustation in containers, pipes, nozzles and on planes to be cleaned. In alkaline degreasing fleets, phosphates are stabilised and the flocculation of calcium soap is prevented, furthermore the cleaning effect is intensified and tarnishing of metal surfaces is prevented.

The total European market volume was 10,685 tonnes in 1999. There are a large number of use areas within the industrial and institutional detergents (I&I) market. The products formulated to incorporate EDTA described within these functions are distributed to a large number of outlets thus resulting in disparate entry of EDTA to the aquatic environment, mainly via municipal effluent treatment systems. A high level of usage is the dairy and beverage industry, with 50% of the total reported tonnage. The majority of users within the dairy and beverage industry use less than 1 tonne/annum, but three large sites with consumption up to 30 tonnes/annum are known. For the exposure estimation, 3 alternative scenarios are regarded:

- The first scenario should reflect the situation for the majority of the sites. Assuming that the total amount is emitted into the municipal wastewater, a PEClocal of 0.64 mg/l is obtained.
- The second exposure scenario describes the exposure from dairy and beverage sites with a consumption of 10 tonnes/annum. As a worst-case approach, no effective removal in treatment plants is assumed. A PEClocal of 2.6 mg/l is calculated.
- For the third scenario, the same EDTA consumption as for the second (10 tonnes/annum) is regarded, but 90% elimination in a long-termed aerated biological treatment plant (LAS) reflecting the best available techniques is assumed. The resulting PEClocal is 0.35 mg/l.

Photochemicals

In the photoindustry Fe(III)NH_4EDTA is mainly applied in the bleachfix process which is a combination of bleaching (oxidation of the metallic silver) and fixing (removing of silver ions by complexation). The exposure scenario represents a large photofinisher, for which a PEClocal of 0.57 mg/l is calculated.

Wastes from photoindustry are collected by disposal companies. Bath residues are either incinerated or evaporated and deposited, and uses in the cement industry for nitrogen oxide removal from fumes are known. Some monitoring data are available which indicate that at disposal sites EDTA is released into the wastewater. Based on TGD default values, a PEClocal of 2.4 mg/l is calculated.

Textile industry

EDTA is used in textile finishing to support processes like cross linking of cellulose molecules (to produce easy care fabrics) and oxidative bleaching and to prevent catalytical damages of the fibres. The exposure scenario for large textile finishing sites results in a PEClocal of 2.0 mg/l.

Pulp and paper

Bleaching agents are applied by paper mills to remove remaining lignin from the cellulose fibres and to improve the brightness. If hydrogen peroxide is used as bleaching agent, heavy metals like manganese would decompose the peroxide; therefore they have to be chelated. EDTA is not fixed onto the paper; therefore the total use amount is emitted into the sewage.

The exposure estimation is mainly based on site-specific data for 11 Swedish paper mills covering about 75% of the European paper production. 2 scenarios are calculated.

- Monitoring data for mills effluents are reported which demonstrate that EDTA is partially removed in long-termed aerated biological treatment plants. A removal factor of 90% is chosen for those sites reflecting the best available techniques, resulting in a PEClocal of 0.5 mg/l.
- As only a part of the treatment plants are run under favourite EDTA degrading conditions (alkaline pH, long sewage and sludge residence time), at other plants no elimination is assumed as a worst-case approach. This scenario leads to a PEClocal of 4.1 mg/l.

Monitoring data from Swedish and Finnish sites (representing the majority of the European market) reveal that a PEClocal of 4.1 mg/l resulted from the worst-case scenario is not reached for any site. Therefore, this value is not used in the risk characterisation. Instead, the

highest Clocal (2.5 mg/l) derived from monitoring data (leading to a PEClocal of 2.6 mg/l) is considered as the worst case.

Metal Plating

EDTA is used for the production of printed circuit boards. EDTA is mainly used in electroless copper plating, when copper is deposited on the board by catalytic reduction of complexed copper compounds. The exposure scenario, based on the average EDTA consumption of one site and TGD default values for the dilution model, results in a PEClocal of 12 mg/l.

Water treatment

EDTA is used to clean scale deposits from internal boiler surfaces and as additive to incoming boiler feedwater to prevent the formation of calcium and magnesium scales. It is assumed that the 215 tonnes of EDTA yearly used in Europe for this purpose are widespread and will not lead to a high local exposure. Thus for this use a PEC is not calculated.

Polymer and rubber production

EDTA is used in the production of Styrene Butadiene Elastomers (SBR) which is mainly manufactured by emulsion polymerisation. EDTA is a sequestering agent for Fe(II)/Fe(III) ions in the initiator system. Based on the TGD default model, a PEClocal of 1.7 mg/l is calculated.

Oil production

EDTA is used for well cleaning processes at oil platforms. In the cleaning process about 1 tonne of EDTA is used during a 24-hour period, leading to intermittent releases. According to the CHARM (Chemical Hazard and Risk Management) model, a dilution factor of 1,000 is reached at a distance of 500 m from the platform leading to a PEClocal of 0.63 mg/l.

Fuel gas cleaning

EDTA is an ingredient for fume desulfuration at coal power plants and waste incineration plants according to the Wellmann-Lord-process. The EDTA containing solution is run in a circle, and a partial stream is incinerated, thus there are no emissions into the wastewater.

Disposal

From different uses, EDTA containing wastes come up from the industrial processes. From the photoindustry it is known that minilabs are (partially) run waste-water-free, the wastes being collected by waste disposal companies. Furthermore, bath residues from photofinishers and probably from other branches like textile finishing or circuit board production are collected.

There is some monitoring data available indicating that EDTA is released into the wastewater at disposal sites. In the frame of the present risk assessment, it was not possible to gain more information about environmental releases for this life-cycle step. Therefore, the results from photochemicals recovery are used for the risk characterisation (PEClocal = 2.4 mg/l).

Sediments

Because of the low partitioning coefficients, no accumulation in sediments will take place. Thus an assessment of this sub-compartment is not necessary.

Monitoring in municipal treatment plants

During an extended monitoring program in German municipal WWTP effluents, in 1994-1995 the EDTA concentration exceeded 600 µg/l in 5 of 55 sampled plants. In Switzerland, the EDTA concentrations in wastewater are generally in the range between 10 to 500 µg/l, with maximum loads between 1,000 to 5,000 µg/l.

Monitoring in surface waters

During an extended monitoring program, EDTA was measured in German surface waters. From 1993 to 1995, the substance was sampled at 143 locations at 73 rivers and creeks, with 1 to 24 samples per year at each location. The EDTA concentration exceeded 500 µg/l at 2 sampling sites. The highest detected concentration in a creek was 2,000 µg EDTA/l, however this was a singular result.

In 1994, the concentrations were 4.1-17.6 (means 8.69) µg/l in the Rhine at Lobith and 3.5-11.4 (means 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.

3.1.2.3 EDTA metal complexes in the hydrosphere

The most important property of EDTA is the formation of water soluble complexes with multivalent metal ions. Metal ions are ubiquitously present in wastewater and surface waters, thus the agent is always completely complexed in both media. Because of the high complex formation constants, heavy metal ions are bound preferredly. In the thermodynamic equilibrium, the most preferred metal being complexed is Ni, followed by Cu, Zn, or Pb.

EDTA complexes can undergo metal exchange reactions. Due to this property, non-degradable complex species can be transformed into degradable compounds. However, because of the kinetical stability of the complexes (half-lifes up to 20 days are reported), this process is not likely to occur in municipal treatment plants as the retention time is too short.

EDTA is able to solubilise heavy metal ions previously bound onto sediment solids. It is not possible to give a single value for an EDTA concentration at which no effects on metal remobilisation occurs. Because of the complexity of the EDTA-metal interactions (dependent on metal concentrations, pH, nature of the sediment, concentration of organics etc.), it is not possible to come to a general rule for effects which is applicable to each river system. For individual surface waters, model calculations can be performed to receive a rough estimation. In concentrations below the aquatic PNEC (2.2 mg/l), natural surface waters contain a stoichiometric excess of heavy metal ions, leading to a complete complexation of EDTA in the water phase, thus this effect will not lead to an increase of the total heavy metal level. Only metal exchange reactions can occur.

3.1.2.4 Regional exposure

For the regional exposure assessment it is assumed that the total EDTA consumption volume is emitted into the environment. Degradation in treatment plants or waste deposition/ incineration was not considered as the respective amounts are not known. The resulting regional PECs are 95 µg/l for surface waters and 22 µg/kg for agricultural soil.

3.1.3 Atmosphere

At some production sites, EDTA dust is released into the atmosphere. For the strongest point source, a PECair of 6.7 µg/m^3 is calculated.

3.1.4 Terrestrial compartment

3.1.4.1 Production

Dust emission during production will reach the soil in the vicinity of the production sites by wet and/or dry deposition. For the strongest emission source, a PEClocal, soil of 0.31 mg/kg dw and a PECporewater of 4.6 µg/l is calculated.

3.1.4.2 Use

Cu-, Fe-, Mn-, Mg-, Mo- and Zn-EDTA complexes are mixed into fertilisers if there is a lack of trace elements in agricultural soil. As a worst-case approach, the exposure from the use as leaf fertiliser was calculated, leading to a $PEClocal_{soil}$ of 0.51 mg/kg dw and a $PEC_{porewater}$ of 7.6 µg/l.

3.1.5 Secondary poisoning

As there is no bioaccumulation, a biomagnification via the food chain is not expected.

3.2 EFFECTS ASSESSMENT

3.2.1 Aquatic compartment (incl. sediment)

The toxicological profile of EDTA is based on disturbances of metal metabolism. For the interpretation of toxicity tests, the complex formation properties of EDTA have to be taken into account. Beside Ca and Mg, test media contain a certain amount of heavy metal ions being necessary as trace nutrients. The complex formation constants of heavy metal complexes are by several orders of magnitude higher than of Ca/Mg-complexes, thus after addition of the test substance EDTA (as acid or Na-salt) the concentration of uncomplexed trace metals decreases drastically. The degree of Ca/Mg complexation is dependent on the amount of added EDTA. Uncomplexed EDTA is only available when it is present in over-stoichiometric concentrations.

Short-term tests on fish reveal 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 was the concentration of EDTA necessary to cause a toxic effect expressed as mortality. In the test

result obtained with Na_2EDTA and a water hardness of 103 mg/l CaCO3 (96-hour LC50 = 374 mg/l) pH effects of the acid are completely suspended. However, uncomplexed EDTA was applied in a stoichiometric excess which is in contrast to environmental conditions. Using $CaNa_2EDTA$ as test substance, a LC50 of 1,827 mg/l was obtained being in a concentration range where unspecific effects are expected. All tests on acute fish toxicity are of limited relevance for the PNEC derivation.

In an early-life stage test on the zebrafish *Danio rerio*, the NOEC was determined to > 26.8 mg/l H_4EDTA based on analytically determined concentrations. $CaNa_2EDTA$ was used as test substance. This test is considered to be the most relevant fish test for the PNEC derivation.

For daphnids no investigation on the influence of water hardness or possible reduced nutrient conditions are available. The available acute tests are carried out by Bringmann and Kühn in hard water (160 mg/l CaO). It is known that calcium deficiency inhibited the development of fresh water crawfish. 24-hour EC50 values of 480 to 790 mg/l for Daphnia magna were found. In a long-term test a 21-day NOEC of 22 mg/l for reproduction could be obtained. In the latter test a surplus of Ca was present, thus mainly Ca-EDTA was formed in the medium being the active test substance.

The apparent effects of complexing agents to algal growth are related to essential trace metal bioavailability. It was demonstrated that not the absolute EDTA concentration, but rather the ratio of the EDTA concentration to the metal cations is crucial to algae growth. With sufficient trace metal amounts, H_4EDTA concentrations up to 310 mg/l caused no effects. Similar results are obtained when Fe(III)EDTA is used as test substance, due to its slow metal exchange kinetics overchelation of the nutrient metal ions is avoided. Therefore direct effects caused by the intrinsic toxicity of EDTA are not expected in surface waters, where in nearly every case a stoichiometric surplus of metal ions is present.

In addition to the discussed adverse effects, like growth inhibition, mortality and immobilisation of EDTA the growth stimulating effects like eutrophication occurs. For two different river waters a significant increase in phytoplankton production was observed after addition of 30 to 300 µg/l EDTA. The higher availability of trace elements through the complexing agent EDTA depends on the preloading of the water and can significantly stimulate the processes of eutrophication. If trace elements like Fe, Co, Mn, and Zn are sufficiently available in a soluble form, the algae growth will be increased after addition of EDTA only insignificantly. This aspect of effects can not be assessed quantitatively with the methods available.

3.2.1.1 Determination of $PNEC_{aqua}$

The effects assessment of EDTA is based on long-term tests, which are available for fish, daphnids and algae. The most sensitive endpoint could be found for *Daphnia magna* with a NOEC of 22 mg/l H_4EDTA. According to the TGD an assessment factor of 10 has to be used, leading to a $PNEC_{aqua}$ of 2.2 mg/l.

In the frame of the marine risk assessment there is no scenario for intermittent release available. As there are no valid test results with marine organisms available, it is proposed according to the TGD, Chapter “marine risk assessment” to use an AF of 1,000 instead of 100 for $PNECintermittent_{marine}$. Using this factor a $PNECintermittent_{marine}$ of 0.64 mg/l can be calculated.

3.2.1.2 Microorganisms

A respiration test with activated sludge collected from a domestic sewage treatment plant and CaEDTA as the active test substance showed no inhibition of the respiration rate in concentrations up to 500 mg/l. With an assessment factor of 10, a $PNEC_{microorganism.}$ of >50 mg/l is obtained.

3.2.1.3 Influence on the toxicity of heavy metals

In surface waters, EDTA causes an increase of heavy metals in the water phase. The influence of EDTA on the toxicity of heavy metals was demonstrated in a test on Daphnia. The toxicity of most metals was decreased by a factor of 17 to 1,700, except with mercury, for which a different toxicity mechanism is assumed.

3.2.1.4 Ecotoxicity of EDTA metabolites

The toxicity of ketopiperazine diacetate (KPDA) was tested on the zebrafish *Brachidanio rerio,* on *Daphnia magna,* and on the alga *Pseudokirchnerella subcapitata*. For all 3 taxonomic groups tested, the EC50 values for ketopiperazine diacetate (KPDA) are above 100 mg/l. With an assessment factor of 1,000, for KPDA a PNEC of > 100 µg/l is calculated.

3.2.2 Atmosphere

Because there are no fumigation tests available, an effects assessment for this compartment can not be performed.

3.2.3 Terrestrial compartment

There are only test results available which investigate the decrease of heavy metal toxicity caused by EDTA. It is not possible to derive a PNEC with this data. Therefore, the assessment can be based on the pore water concentration only.

3.2.4 Secondary poisoning

As there is no bioaccumulation, a biomagnification via the food chain is not expected.

3.3 RISK CHARACTERISATION

3.3.1 Aquatic Compartment

The risk assessment for aquatic organisms resulted in a $PNEC_{aqua}$ of 2.2 mg/l. The $PNEC_{microorganism}$ was determined to >50 mg/l. For intermittent releases occurring at oil platforms, the $PNECintermittent_{marine}$ was determined to 0.64 mg/l.

Site-specific scenarios

Table 3.1 PEC/PNEC ratios for the aquatic compartment

Scenario	$PEClocal_{aqua}$ [mg/l]	PEC_{aqua} / $PNEC_{aqua}$	Ceffl [mg/l]/ Ceffl	Ceffl. / $PNEC_{microorganism}$
Producer A	only import			
Producer B	0.18	0.08	9.7	<0.19
Producer C	0.095	0.04	0.040	<0.0008
Producer D	max. 1.0	<0.45	no WWTP	-
Producer E *	0.36	0.16	1,500	<30
Producer F	0.10	0.045	no WWTP	-
Producer G	0.22	0.1	no WWTP	-
Producer H	0.098	0.04	0.40	< 0.008
Household sewage	0.195	0.09	1.0	< 0.02
Industrial detergents Scenario 1	0.64	0.29	5.4	< 0.11
Industrial detergents Scenario 2	2.6	1.2	25	< 0.5
Industrial detergents Scenario 3	0.35	0.16	2.5	< 0.05
Photochemicals	0.57	0.26	4.7	< 0.09
Textile industry	2.0	0.9	19	< 0.38
Pulp and paper Scenario 1	0.5	0.23	4.0	< 0.08
Pulp and paper Scenario 2	2.6	1.2	40	< 0.8
Metal plating	12	5.5	116	< 2.3
Polymer and rubber production	1.7	0.77	16	< 0.32
Disposal	2.4	1.1	23	< 0.46

* At site E production was meanwhile stopped

A **conclusion (iii)** was reached for following scenarios:

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

Influence on the distribution of heavy metals

In high concentrations (which can occur when strong point sources are emitting into a small river) EDTA prevents the adsorption of heavy metals onto sediments and can remobilise metals from highly loaded sediments. Both effects lead to increased heavy metal concentrations in the water phase. On the other hand, the aquatic effects assessment resulted that the EDTA complexes of heavy metals are less toxic than the uncomplexed metals. Overall, a risk for the aquatic environment due to the influence of EDTA on the mobility of heavy metals is not expected. **Conclusion (ii)**.

EDTA metabolites

The sum of ketopiperazinediacetate (KPDA) and ethylendiaminetriacetic acid (ED3A) was detected in German rivers and drinking water in concentrations of 0.5 to 16 µg/l. From tests on acute toxicity, a PNEC of > 100 µg/l for KPDA was derived. Assuming that, because of the similar molecular structure, ED3A has a similar toxicity as EDTA (PNEC = 2.2 mg/l), the environmental concentrations are far below both PNECs, thus a risk is not expected.

Further metabolites like ethylenediaminediacetic acid (N,N-EDDA and N,N'EDDA) and ethylenediaminemonoacetic acid (EDMA) are either photolysed or more rapidly biolocical degraded than the mother substance EDTA. Therefore, their environmental concentrations are assumed to be lower than the calculated PECs for EDTA. Because of the similar molecular structure, their ecotoxicity is assumed to be similar (or at least not much higher); therefore a risk from these substances is not expected. **Conclusion (ii)**.

3.3.2 Atmosphere

EDTA is emitted into the atmosphere in dust form during production. The $PEClocal_{air}$ for the strongest emission source was estimated to 6.7 µg/m^3. No appropriate effect tests are available, so a risk characterisation ratio for this compartment can not be calculated. However, because of the relative low toxicity of EDTA, a risk to the environment is not expected. **Conclusion (ii)**.

3.3.3 Terrestrial compartment

Because there are no effect tests on terrestrial organisms available, the risk characterisation is based on the calculated porewater concentrations.

During production, EDTA is emitted into the atmosphere at several sites. Deposition into soil resulted in a porewater concentration of maximum 4.6 µg/l. With a $PNEC_{aqua}$ of 2.2 mg/l, the PEC/PNEC ratio is 0.002.

The use of EDTA as leaf fertiliser was regarded as a worst-case scenario for the exposure estimation, resulting in a $PEC_{porewater}$ of 7.6 µg/l. With a $PNEC_{aqua}$ of 2.2 mg/l, the PEC/PNEC ratio is 0.003.

For both scenarios, a risk to terrestrial organisms is not expected. **Conclusion (ii)**.

3.3.4 Seconday poisoning

As there is no bioaccumulation, a biomagnification via the food chain is not expected. **Conclusion (ii)**.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 Occupational exposure

The exposure assessment for workers is made for both substances, H_4EDTA and Na_4EDTA, summarised as EDTA. The uses of EDTA are determined by its high capacity for complexing metal ions. Diluted substances with EDTA concentrations below 5 % are mainly used, e.g. as detergents (household, industrial), in photochemicals, in agriculture products and in cosmetics.

Detailed information on the production volumes is given in Section 2.

Based on the available information the following relevant occupational exposure scenarios are to be expected:

- production and further processing as a chemical intermediate Scenario 1),
- formulation of preparations (Scenario 2),
- uses of formulations including formulation of preparations on-site Scenario 3).

Occupational exposure limits (OEL) have not been established.

The exposure assessment is based on measured data and literature data, expert judgement and estimations according to the EASE model (Estimation and Assessment of Substance Exposure). The exposure levels should be regarded as reasonable worst-case estimates representing the highly exposed workers.

The results for the different scenarios are summarised in **Table 4.1**. More detailed information on inhalation and dermal exposure is given below.

Inhalation Exposure

For the large-scale chemical industry, it is assumed that the production and further processing of EDTA is mainly performed in closed systems with high levels of protection. Most of the substance is produced in a liquid form. Due to the physico-chemical properties of the substance (low-vapour pressure), inhalation exposure to vapour during the handling of solutions is assessed as negligible.

Higher exposures are expected if EDTA is produced or used as powders. During the production exposure of dusts occurs if the closed systems are breached for certain activities e.g. filling (Scenario 1). If the formulation of products is performed using the powdery substance, possibilities of inhalation exposure occur during weighing and filling (Scenario 2).

Inhalation exposure has to be considered if droplet aerosols are formed during the application of aqueous preparations, e.g. high-pressure cleaning, metal-cutting with cooling lubricants, pre-treatment of metal, electroplating industry, use of herbicides and insecticides. Among the different fields of applications high-pressure cleaning is considered to be the most important exposure scenario (Scenario 3). Inhalation exposure is negligible if aerosols are not formed.

Dermal Exposure

With regard to dermal exposure, measured results are not available. For most occupational exposure scenarios, the regular use of suitable PPE (Personal Protective Equipment) at the workplaces is not probable. Therefore, actual dermal exposure is generally assessed based on the EASE model without considering that PPE might be worn by a part of the exposed collective. In general, dermal exposure is assessed as exposure to part of hands and forearms.

Here on account of the low dermal absorption of the substance (0.001 %), dermal exposure is regarded to be of minor relevance for occupational risks. As a theoretical worst-case estimate might serve an EASE estimation for wide-dispersive use and intermittent contacts leading to a dermal exposure level of 5 mg/cm²/day. Considering an exposed area of 840 cm², dermal exposure is assessed to 4,200 mg/person/day. The calculated internal body burden (4,200 ·0.001% / 70) of 0.6 µg/kg/day is far below the internal NAEL (no adverse effect level) of 21.8 mg/kg/day for H_4EDTA (28.2 mg/kg/day for Na_4EDTA). Taking into account that the resulting MOS (margins of safety) of > 36,000 is clearly beyond concern, and therefore dermal exposure is not assessed quantitatively.

Summary of exposure data

Table 4.1 Summary of exposure data

Exposure scenario	Duration and frequency of activities relevant for exposure	Inhalation exposure Shift average [mg/m³]	Dermal exposure Shift average [mg/p/day]
Production and further processing in the chemical industry			
1) Production and further processing of powdery EDTA	shift length, daily	2 – 5 [1), 2)]	[5)]
Preparation and use of formulations			
2) Preparation of formulations, handling of the powdery substance	1 hour (assumed), daily	a) 0.3 [3)](with LEV) b) 0.6 [3)](without LEV)	[5)]
3) High pressure cleaning (diluted solutions, < 2% EDTA)	4 hours (assumed), daily	0.3 [4)] determined by analogy	[5)]

LEV – local exhaust ventilation

1) Exposure assessment based on model estimates (EASE model), estimate supported by measured results
2) Most of the substance is produced as a liquid formulation. In this case inhalation exposure is assessed as negligible.
3) Due to the low quantities of the substance used, the lower exposure levels of the assessed ranges are taken for risk assessment.
4) Exposure assessment exemplary for all uses of formulations (liquid, powdery) where the formation of aerosols is possible. Exposure is negligible, if aerosols are not formed.
5) On account of the low dermal absorption of the substance (0.001 %), dermal exposure is regarded to be of minor relevance for occupational risk assessment.

4.1.1.2 Consumer exposure

The most important exposure of consumers to Na_4EDTA results from use of household detergents and cosmetics. The use in textiles can not be estimated because of lacking data. Na_4EDTA is used as a component of cosmetics (skin creams and lotions, after care products for hair in concentrations of <0.3%, hair bleaches in concentrations of 1%, washing gels in concentrations of <0.01%), and of cleansing agents, dish washing agents in concentrations of <0.5%, and cleansing agents for orthodontic devices in concentrations of <10%.

Furthermore, it might be assumed that the consumer is exposed to Na_4EDTA by the oral route due to migration of the substance from plastics coming into contact with foods. An estimation of this exposure is not possible due to the lack of data about the amounts used for this purpose and the migration rate.

Dermal exposure to cosmetics

Assuming the use of 16 g of a lotion containing 0.3% of Na_4EDTA per day, the total exposure can be estimated to about 0.8 mg/kg bw/day.

For hair bleaching the use of an amount of 5-6 ml (≈ 5-6 g) of a hair bleaching agent containing 1% of Na_4EDTA is assumed. Taking into account the retention factor of 10, than 6 mg of Na_4EDTA would contact skin, which corresponds to 0.1 mg/kg bw.

Dermal exposure to household cleansers or dish washing agents

To estimate the exposure of consumers to household cleansers the value of weight fraction was set to 10% as a worst-case estimate to cover all of the subcategories of household cleansers. This is the highest concentration reported among 427 products in the BgVV database. The most common concentration of Na_4EDTA in household cleaners, however, is below 1%. The worst-case estimate of the daily dermal exposure was calculated to be 0.12 mg/kg bw/day.

The calculation of the total dermal exposure of consumers results in a value of about 1.02 mg/kg bw/day.

Oral exposure

Oral exposure may result from the use of cleansers of tooth brackets that contain maximum concentrations of 5% of Na_4EDTA. As a worst-case, the residual amount of Na_4EDTA on a bracket would be 3 mg. Because tooth brackets are normally used in childhood, the calculation was related to the bodyweight of a 10 year old child, (30 kg; 5^{th} percentile), and the resulting exposure amounts to be 0.1 mg/kg bw/day.

4.1.1.3 Humans exposed via the environment

The only significant indirect exposure for human occurs to Na_4EDTA via drinking water. A significant intake via fish, plants or meat is not expected because Na_4EDTA does not accumulate in biota. Model calculations have been performed for the local scenario for the different producers resulting in a total daily dose of Na_4EDTA in drinking water in the range from 0.003 to 0.38 mg/kg bw/day. For the regional scenario a total daily dose of 0.0039 mg/kg bw/day was calculated.

4.1.2 Effects assessment

Justification for cross-reading from different EDTA compounds

In general, edetic acid (H_4EDTA) and tetrasodium EDTA show similar properties and exposure pattern. However, with respect to acute toxic and local effects both substances behave differently. Thus, the hazard effects of the two substances are evaluated separately for the endpoints acute toxicity, irritation, corrosivity and sensitisation based on the test substances used in the respective toxicity assays. For systemic effects studies with administration of H_4EDTA or of its salts such as Na_2H_2EDTA, Na_3HEDTA 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 H_4EDTA or Na_4EDTA will be derived from consideration of the overall available data base.

Data from studies with the soluble, but strongly associated complex calcium disodium edetate ($CaNa_2EDTA$) were not considered in the report except the sections on toxicokinetics and reproductive toxicity. Taking into account the stability constant of the calcium EDTA complex (about 10^{10} M^{-1}) the concentrations of free anionic EDTA species in $CaNa_2EDTA$ solutions can be estimated to amount < 0.01% according to the mass action law. Thus, almost all proportion of the $CaNa_2EDTA$ complex is still present as $CaEDTA^{2-}$ species, whereas only a very minor proportion of the $CaNa_2EDTA$ complex exists as free anionic EDTA species in solution which is considered to be too low for detecting generally toxic (systemic) effects of EDTA or sodium salts of EDTA. The $CaNa_2EDTA$ will chelate any other metal that has a higher binding affinity than Ca^{2+} (e.g. lead, iron, zinc, and copper). E.g., zinc chelates with $CaNa_2EDTA$ to form a complex that shows a 10^4 times higher binding affinity than that of the calcium complex. Therefore, application of $CaNa_2EDTA$ will result in complexation of zinc ions thus interfering with the zinc homeostasis and leading finally to developmental toxicity.

Toxicokinetics, metabolism and distribution

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 sodium salts of EDTA and of the free acid 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. In whatever salt EDTA is administered it is likely to chelate metal ions *in vivo*.

Acute toxicity

For three LD50 tests the acute oral toxicity for rats is in the range of 1,700 – 1,913 mg/kg bw. For two LD50 tests values of > 2,000 mg/kg bw are reported. According to these data the substance has a moderate acute oral toxicity. The substance has to be classified as "Xn Harmful" and labelled as "R 22, Harmful if swallowed". In a test system similar to the inhalation hazard test there was no mortality after an 8-hour exposure of an unknown test concentration of the substance that was heated to either 20 or 80°C. This data is considered to be sufficient for the risk assessment of acute inhalation toxicity. There is no need for classification and labelling for acute inhalation toxicity. No data are available on acute dermal toxicity. Taking in account the poor dermal absorption it can be assumed that the result of an acute dermal toxicity test would not reveal toxic properties warranting a classification and labelling for acute dermal toxicity.

Irritation

Treatment of the intact rabbit skin with an 80% aqueous preparation of the substance resulted in mild or no irritation. These data demonstrate that there is no need to classify and label the substance for skin irritating properties according to EU regulations. However, treatment of the abraded skin with an 80% aqueous preparation resulted in superficial necrosis and crust formation after 8 days. From the data obtained with eye tests a risk of serious damage can be deduced when the undiluted substance is instilled into the eye. Therefore, according to EU

regulations, for undiluted Na_4EDTA a classification of "Xi, Irritant" and labelling as "R 41, Risk of serious damage to eyes" is warranted. A 40% aqueous or less of Na_4EDTA solution, however, needs only labelling as “R 36, Irritating to eyes”. The animal data obtained for skin and eye irritation demonstrate a weak effect on the skin and a severe effect on the eye. There is no need to classify the substance as corrosive.

Sensitisation

In a Magnusson Kligman Test with Na_2EDTA according to OECD Guideline 406 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 Na_4EDTA is being used in industry and consumer products for many decades in high quantities the substance is considered as non-sensitising to humans. A labelling with R 43 "May cause sensitisation by skin contact" is not warranted. In dogs with hyperreactive airways bronchoconstriction can be induced. However, this does not warrant a labelling as R 42 "May cause sensitisation by inhalation".

Repeated dose toxicity

From repeated dose toxicity experiments (90-day feed male Holtzmann rats, 2-year bioassay both sexes Fischer 344 rats and B6C3F1 mice) a NOAEL of 500 mg/kg/day for Na_2EDTA and Na_3EDTA could be derived (corresponding to 565 mg/kg bw Na_4EDTA). Although the 90 day study was performed only in male animals and does not provide a full range of today's clinical biochemistry the data provided information on histopathology mainly from the long term study and parameters such as body weight and some hematological parameters do justify this no toxic effect level. The adverse effects seen with higher-dose levels were increase in mortality, reduced body weight, reduced food consumption, diarrhea, emaciation, and sometimes parakeratosis in oesophagus and forestomac as well as decreased hemoglobin and hematocrit levels.

Mutagenicity

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 spermacytogenesis). The effect was bound to the use of an extremely high dose in the LD50 range. 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 Na_4EDTA is not mutagenic for humans.

Carcinogenicity

A bioassay of Na_3EDTA for possible carcinogenicity was conducted by administrating of test material in the diet to Fischer 344 rats and B6C3F1 mice. The studies did not report specific data on kidney toxicity in either species. Although a variety of tumours occurred among test and control animals of both species, no tumours were related to treatment. Thus, there is no concern on a carcinogenic potential of Na_4EDTA.

Toxicity for reproduction

Concerning reproductive toxicity, valid data from human experience are not available. Data from a multigenerational study in rats 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. From a less valid study with Na_2EDTA conducted in rats complete reproductive failure was reported at dietary dose levels of 3,000 mg/kg bw/day.

Developmental toxicity of EDTA, sodium salts and calcium and zinc chelates was investigated in studies in rats, mainly in single dosage studies. After repeated treatment of dams during various periods of gestation and with the use of different routes of substance application (diet, gavage, s.c., i.m.) impaired embryo/fetal development and the induction of a pattern of gross malformations were observed during these investigations with the exception of one study (Schardein et al., 1981)[2]. Gross malformations comprised cleft palate, severe brain deformities, eye defects, micro- or agnathia, syndactyly, clubbed legs and tail anomalies. Almost exclusively these effects were exhibited in studies using maternally toxic dosage levels.

It has been repeatedly reported that the pattern of malformations observed after exposure of pregnant female rats to EDTA, edetic acid salts or calcium EDTA is similar to that observed when dams were held on zinc depleted diets during either short intervals or for the whole period of gestation. Since it has been demonstrated that zinc deficient diets per se lead to developmental and teratogenic effects in offspring the depletion of zinc in the diet and/or the depletion of endogenous zinc tissue concentrations caused by EDTA/Na_4EDTA treatment appear to be of specific significance for embryo/fetal impairment and the induction of malformations. With sufficient zinc supplementation fetotoxic and teratogenic effects could be prevented, respectively minimised.

The teratogenic effect of EDTA/Na_4EDTA has been shown to be attributable to an interference with zinc homeostasis in the dams and fetuses. However, in all but one study with the oral route of administration, the doses leading to teratogenic effects are always paralleled by diarrhea, which in turn will additionally increase zinc deficiency. Therefore, it can be discussed whether the teratogenic effect is primarily attributed to unspecific weight reduction in dams or whether this effect is due to specific interference with zinc homeostasis. Fetotoxicity may be as well related to reduced body weight of the dams. The second point to be discussed is the mechanism of action of zinc depletion and hence teratogenicity. Three mechanisms of zinc depletion can contribute to the teratogenic effects: i) reduction of available zinc by complexation in the upper intestine, ii) enhanced urinary excretion, and iii) enhanced zinc excretion into the gut lumen by diarrhea.

The fetotoxic and teratogenic effects are occurring at exposure levels of approximately 1,000 mg/kg bw/day and above. We do not recommend classifying EDTA/Na_4EDTA as being a reproductive toxicant due to the following reasons: i) the malformations have been demonstrated at relatively high oral dose levels and ii) a steep dose response relationship can be assumed. No oral NOAEL for either developmental toxicity or maternal toxicity could be established.

[2] Please refer to the comprehensive Final RAR for the full reference.

4.1.3 Risk characterisation

4.1.3.1 Workers

4.1.3.1.1 Introductory remarks

H_4EDTA and Na_4EDTA are solid substances with water solubilities of 0.4 g/l and 500 g/l at 20 °C. The vapour pressure is assumed to be very low and evaporation is considered to be not relevant. A widespread use of H_4EDTA and Na_4EDTA is described in section 4.1.1.1 and the central scenarios are listed in **Table 4.1**. Since H_4EDTA and Na_4EDTA are assumed to show similar toxicity in several endpoints an integrated assessment is performed. As far as differences in toxicity have to be regarded they are assessed separately. Toxicological key effects are eye irritation and developmental toxicity at very high doses.

Acute toxicity, repeated dose toxicity and developmental toxicity are assessed on the basis of MOS values and oral studies represent the central database for the quantitative assessment of these endpoints. Performing a risk assessment of dermal contact and inhalation exposure a route to route extrapolation has to be performed and systemic availability via all routes has to be considered. The maximum systemic availability after oral application is 5%, while for the dermal route a maximum value of 0.001% is given. For inhalation a worst-case assumption of 100% systemic availability is applied. Because of the negligible skin absorption systemic effects after dermal contact are not considered to be relevant.

As starting points for MOS calculation the oral toxicity data are converted into values of internal body burden, taking the 5% systemic availability after ingestion into account. The MOS values are calculated as quotient of the converted NAEL/LAEL values and the internal body burden from inhalation exposure at the workplace. The minimal acceptable MOS, as decision mark between conclusion (ii) and (iii), results from the multiplicative combination of different factors, which consider e.g. interspecies differences, intraspecies variability and the nature of effect (see comprehensive risk assessment report). Minimal MOS values may be different for each toxicological endpoint pending on the overall database and the effect under assessment. In a parallel procedure an acceptable exposure concentration is identified indicating concern if occupational exposure concentrations exceed this value.

4.1.3.1.2 Occupational risk assessment

Acute toxicity

Inhalation

There are no valid data on acute inhalation toxicity (H_4EDTA and Na_4EDTA). Thus the assessment is based on oral data, starting with an NOAEL of 2,000 mg/kg for H_4EDTA and 565 mg/kg for Na_4EDTA. As described above an internal NAEL of 100 mg/kg is calculated for H_4EDTA and 28 mg/kg for Na_4EDTA. A minimal acceptable MOS of 20 (4 · 5) is used which results in an acceptable internal body burden of 5 mg/kg/day for H_4EDTA (1.4 mg/kg/day for Na_4EDTA). The minimal MOS of 20 is composed of an interspecies factor of 4 and an uncertainty factor of 5, which covers intraspecies variability, nature of effect and dose response relationship. The corresponding exposure concentration assuming a 100% absorption via inhalation is 35 mg/m^3 for H_4EDTA (9.9 mg/m^3 for Na_4EDTA). All MOS values are higher than 20 and concern is not derived. **Conclusion (ii)**.

Dermal

Acute systemic effects after dermal exposure are not considered to be relevant due to the very low skin absorption. **Conclusion (ii)**.

Irritation/Corrosivity

Weak effects have been observed in skin irritation studies of H_4EDTA and Na_4EDTA. This was not sufficient for classification, concern is not derived.

H_4EDTA is considered to be irritating to the eyes. Na_4EDTA may result in serious damage to the eye. Conclusion (ii) is proposed on the grounds that control measures exist which can minimise exposure and risk of irritation, thereby reducing concern. However, these controls must be implemented and complied with to reduce the risk of damage to eyes. **Conclusion (ii)**.

Sensitisation

Dermal

A very weak response was observed in a skin sensitisation test in guinea pigs and only two reports on skin sensitisation in humans are available. Based on the fact that the substance is being used in industry and consumer products for many decades in high quantities the incidence of positive responses is too low to derive concern as to skin sensitisation. **Conclusion (ii)**.

Inhalation

No acute or chronic respiratory health effects have been observed in workers from exposure to EDTA. There is no valid indication for EDTA as a respiratory sensitiser. **Conclusion (ii)**.

Repeated dose toxicity

Inhalation (local effects)

Valid inhalation studies with single or repeated exposure in animals are not available (H_4EDTA and Na_4EDTA). The eye irritation points to an irritative potential, but there are no reports of effects in humans, that might confirm a potential risk. No concern is derived. **Conclusion (ii)**.

Inhalation (systemic effects)

For the assessment of systemic effects after repeated inhalation the repeated oral studies are taken into account. Subchronic and chronic toxicity studies in rodents resulted in a NOAEL of about 500 mg/kg/day. At higher doses adverse effects like diarrhoea and emaciation were observed. The NOAEL of 435 mg/kg/day for H_4EDTA (565 mg/kg/day for Na_4EDTA) is used for risk assessment.

An internal NAEL of 21.8 mg/kg/day is calculated for H_4EDTA and 28.2 mg/kg/day for Na_4EDTA. A minimal MOS of 20 ($4 \cdot 5$) is used which results in an acceptable internal body burden of 1.1 mg/kg/day for H_4EDTA (1.4 mg/kg/day for Na_4EDTA). The minimal MOS of 20 is composed of an interspecies factor of 4 and an uncertainty factor of 5, which covers intraspecies variability, nature of effect and dose response relationship. The corresponding acceptable exposure concentration assuming a 100% absorption via inhalation is 7.4 mg/m^3

for H_4EDTA (9.9 mg/m^3 for Na_4EDTA). All MOS values are higher than 20 and concern is not derived. **Conclusion (ii)**.

Dermal (local effects)

See under "Irritation/Corrosivity/Dermal", no further information available. **Conclusion (ii)**.

Dermal (systemic effects)

Chronic systemic effects after dermal exposure are not considered to be relevant due to the very low skin absorption. **Conclusion (ii)**.

Mutagenicity and Carcinogenicity

H_4EDTA and Na_4EDTA are not considered to be mutagens in humans. Based on the results of oral long-time studies in rats and mice, H_4EDTA and Na_4EDTA are not considered to be carcinogenic. **Conclusion (ii)**.

Reproductive toxicity (fertility impairment)

No evidence for adverse effects on fertility were observed in a rat multigenerational study conducted with $CaNa_2$EDTA up to the highest tested dose of 250 mg/kg/day. Effects on the reproductive organs are also not reported in subchronic and chronic studies in rodents. Based on these data H_4EDTA and Na_4EDTA are not considered to impair fertility. **Conclusion (ii)**.

Reproductive toxicity (developmental toxicity)

Inhalation

It is assumed that developmental toxicity of EDTA is based on its metal chelating capacity and especially on endogenous zinc depletion. In rats high oral doses of EDTA (as Na_2H_2EDTA) led to fetotoxicity and teratogenicity accompanied by maternal toxicity. The maternal and fetal LOAEL was approx. 1,000 mg/kg/day (application with the diet). An internal LAEL of 50 mg/kg/day is calculated for EDTA. A minimal MOS of 60 is applied which results in an acceptable internal body burden of 0.83 mg/kg/day. The minimal MOS of 60 is composed of an interspecies factor of 4 and an uncertainty factor of 15, which covers intraspecies variability, nature of effect and the dose response relationships of the different studies on developmental toxcity. The corresponding acceptable exposure concentration assuming a 100% absorption via inhalation is 5.8 mg/m^3. Scenario 1 (production and further processing of powdery EDTA, see **Table 4.1**) with the lowest MOS of 70 is considered as a borderline scenario, but having in mind, that worst-case assumptions led to the 100% value of systemic availability after inhalation, concern is not derived. In summary, conclusion (ii) is recommended for all scenarios. **Conclusion (ii)**.

Dermal

Developmental toxicity after dermal exposure is not considered to be relevant due to the very low skin absorption. **Conclusion (ii)**.

4.1.3.1.3 Summary of conclusions for the occupational risk assessment

The occupational risk assessment of dermal and inhalation exposure comes to the conclusion that there is no need for further information and/or testing or for risk reduction measures beyond those which are being applied already (overall conclusion (ii)).

4.1.3.2 Consumers

Exposure

Na_4EDTA is used as a component of cosmetics and of cleansing and dish washing agents**.** Thus, the main route of potential consumer exposure is via dermal contact/absorption through the skin. The calculation of the daily dermal exposure of consumers results in a value of about 1 mg/kg bw/day. Taking the experimental data it is assumed that the amount absorbed after dermal exposure will be 0.001% as given by human studies. Thus, the internal exposure from dermal contact may result in a maximum amount of 0.00001 mg/kg bw/day.

Oral exposure may result from the use of cleansers of tooth brackets if they are not properly cleaned after use. The oral exposure for tooth brackets wearing children amounts to be 0.1 mg/kg bw/day.

Acute Toxicity

Following the exposure assessment, the consumer may be exposed to Na_4EDTA via dermal and oral routes. Consumers are not expected to be exposed to Na_4EDTA in the range of hazardous doses which can be derived from the oral animal LD50 values (> 1,700 mg/kg bw). Taking into account all assumptions being applied in the exposure estimation scenarios, exposure by inhalation should be considered as of no concern for the consumer. Therefore, the substance is of no concern in relation to acute oral or dermal toxicity. **Conclusion (ii)**.

Irritation / Corrosivity

The substance has weak irritant properties on rabbit skin but has irritant properties to the rabbit eye. The risk for consumers, however, related to ocular exposure is low, given the low levels of Na_4EDTA contained in consumer products. According to the dermal exposure scenarios (cosmetics, household cleansers or dish washing agents, reasonable worst case) it can be assumed that irritant concentrations of the substance will not occur. Thus it is concluded that Na_4EDTA is of no concern for consumers in relation to possible irritating effects. **Conclusion (ii)**.

Sensitisation

In a Magnusson Kligman Test with Na_2EDTA 30% of the guinea pigs showed a positive response after the first challenge and 10% after a second challenge. The low result of the second challenge does not support an immunologically mediated mechanism. There are only two reports on single cases in humans demonstrating positive skin results. Based on the fact that the substance is being used in industry and consumer products for many decades in high quantities the incidences of positive responses can be considered as very low. Even taking into account the broad consumer exposure via cosmetics and cleansing and dish washing agents, Na_4EDTA is considered as non-sensitising to humans. **Conclusion (ii)**.

Repeated dose toxicity

Oral application of Na_2EDTA in the diet to rats for 1 month revealed a NOAEL of 1,125 mg/kg/day (2.25%) in diet. From a 90-day investigation in rats a NOAEL of 500 mg/kg/day equivalent to 1% in diet can be deduced for male rats. This dose corresponds to 565 mg/kg bw/day Na_4EDTA. The adverse effects seen were increase in mortality, reduced body weight, reduced food consumption and diarrhea. Investigations with Na_3EDTA over a period of two years in rats and mice revealed a NOAEL of 500 mg/kg/day hence supporting the NOAEL of 565 mg/kg/day seen in the 90-day study.

Dermal exposure

The margin of safety for dermal exposure between the assumed internal exposure level of 0.00001 mg/kg bw/day and the oral NOAEL (Na_4EDTA) of 28.3 mg/kg bw/day is judged to be sufficient, even if special considerations e.g. the nature and severity of the effects are taken into account. The oral NOAEL of 565 mg/kg bw/day has been converted into an internal value of 28.3 mg/kg bw/day considering the maximum oral absorption of 5%. It is concluded therefore that Na_4EDTA is of no concern for consumers in relation to the use cosmetics and household detergents. **Conclusion (ii)**.

Oral exposure

The oral exposure of children (via cleansers for tooth brackets) has been calculated to be 0.1 mg/kg bw/day. The margin of safety between the exposure level of 0.1 mg/kg bw/day and the oral NOAEL (Na_4EDTA) of 565 mg/kg bw/day is judged to be sufficient, even if special considerations e.g. the nature and severity of the effects are taken into account. It is concluded therefore that Na_4EDTA is of no concern for children in relation to use of cleansers for tooth brackets **Conclusion (ii)**.

Mutagenicity

Sodium salts of EDTA show 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 Na_4EDTA is not mutagenic for humans. **Conclusion (ii)**.

Carcinogenicity

There is no evidence on carcinogenic properties of Na_3EDTA from studies in experimental animals. Therefore it can be concluded that Na_4EDTA is of no concern for consumers. **Conclusion (ii)**.

Reproductive toxicity (fertility impairment)

Data from a multigeneration study on rats 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. Hence the NOAEL is 250 mg/kg bw/day corresponding to 255 mg/kg bw/day Na_4EDTA. This oral NOAEL has been converted into an internal value of 12.8 mg/kg bw/day considering the maximum oral absorption of 5%. The margin of safety for dermal exposure between the assumed internal exposure level of 0.00001 mg/kg bw/day and the oral NOAEL of 12.8 mg/kg bw/day is judged to be sufficient. Thus, Na_4EDTA is of no concern for consumers to affect the reproductive performance. **Conclusion (ii)**.

Reproductive toxicity (developmental toxicity)

The studies with Na_2EDTA form the basis for the estimation of LOAEL of 1,000 mg/kg bw/day. This oral LOAEL been converted into an internal value of 50 mg/kg bw/day considering the maximum oral absorption of 5%. The margin of safety for dermal exposure between the assumed internal exposure level of 0.00001 mg/kg bw/day and the oral LOAEL of 50 mg/kg bw/day is judged to be sufficient, even if special considerations on the nature and severity of the effects as well as the lack of an established NOAEL are taken into account. Thus, EDTA is considered without concern for consumers with regard to fetotoxic and teratogenic effects. **Conclusion (ii)**.

4.1.3.3 Humans indirectly exposed via the environment

The only significant indirect exposure for human to Na_4EDTA occurs via drinking water. Model calculations have been performed for the local scenario for the different producers which resulted in a total daily dose in the range from 0.003 to 0.38 mg/kg bw/day. For the regional scenario a total daily dose of 0.0039 mg/kg bw/day was calculated. For the purpose of risk characterisation the highest dose of 0.38 mg/kg bw/day will be used. Thus, the margins of safety expressed by the magnitude between the calculated exposures and the NOAEL/LOAEL are considered to be valid for both the local and the regional scenario.

Repeated dose toxicity

From different repeated dose toxicity studies (2 years; 90-day study's) with mice and rats with sodium salts of EDTA a NOAEL of 500 mg/kg bw/day was derived (respectively 565 mg/kg bw/day Na_4EDTA). The margin of safety between the calculated maximum exposure for the indirect exposure source drinking water (0.38 mg/kg bw/day) and the NOAEL (565 mg/kg bw/day) is judged to be sufficient. Thus, regarding repeated dose effects the substance is of no concern in relation to indirect exposure via the environment **Conclusion (ii)**.

Fertility (same presentation for workers as consumers)

Data from a multigenerational study on rats 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 (respectively 255 mg/kg bw Na_4EDTA). The margin of safety between the calculated exposure for the indirect exposure source drinking water (0.38 mg/kg bw/day) and the NOAEL (255 mg/kg bw/day) is judged to be sufficient. Thus, regarding adverse effects on reproductive performance the substance is of no concern in relation to indirect exposure via the environment. **Conclusion (ii)**.

Developmental toxicity (same presentation for workers as consumers)

Fetotoxic and teratogenic effects occurred in rats at Na_2EDTA exposure levels of approximately 1,000 mg/kg bw/day (LOAEL) and above. The margin of safety between the calculated exposure for the indirect exposure source drinking water (0.38 mg/kg bw/day) and the LOAEL of 1,000 mg/kg bw/day is judged to be sufficient. Thus, regarding fetotoxic and teratogenic effects the substance is of no concern in relation to indirect exposure via the environment. **Conclusion (ii)**.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

Conclusion (ii)

5 RESULTS

5.1 ENVIRONMENT

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

This conclusion is reached because of the high emissions due to the use of EDTA in industrial detergents. The exposure near sites within dairy and beverage industry with no effective EDTA removal in their treatment plants is expected to lead to a risk for aquatic organisms.

The EDTA exposure for paper mills was estimated on the basis of monitoring data. A high exposure is expected in the receiving water of some sites. Several companies are known to plan long-term aerated biological treatment plants which will reduce the releases.

A high exposure is expected by circuit board producers which have no effective wastewater purification leading to a risk for aquatic organisms.

In the frame of the present risk assessment, it was not possible to gain site-specific information about environmental releases for recovery of EDTA containing wastes. Therefore, an exposure model for the recovery of photochemicals based on default values was used for the risk characterisation leading to a risk for aquatic organisms.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

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

Consumers

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

Humans exposed via the environment

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

5.2.2 Human health (risk from physico-chemical properties)

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