European Chemicals Bureau

Institute for Health and Consumer Protection

European Chemicals Bureau

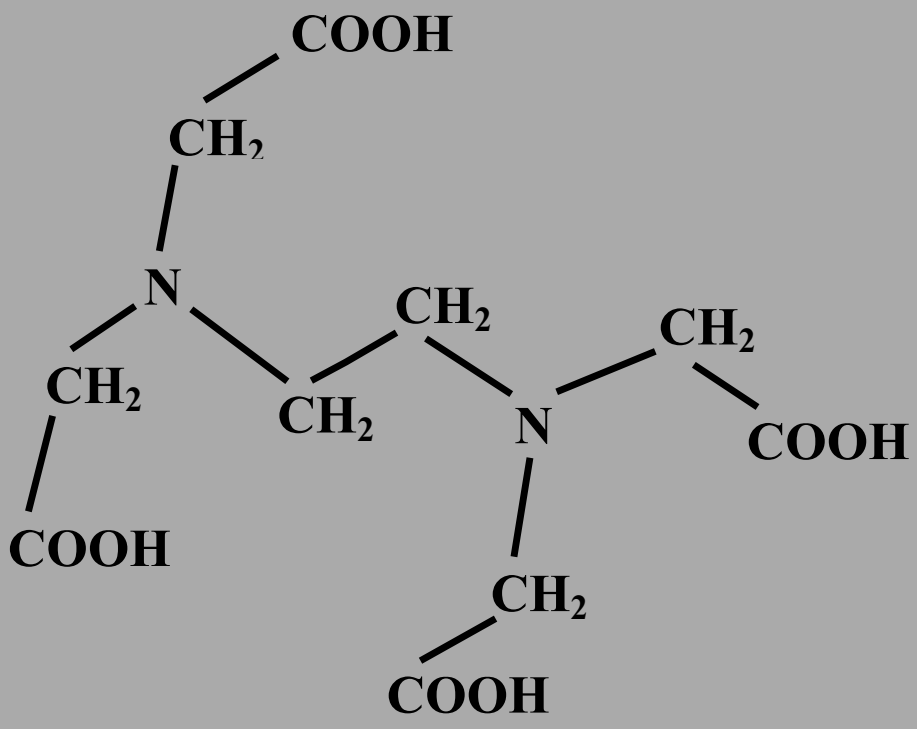
Existing Substances

European Union Risk Assessment Report

CAS No: 60-00-4

EINECS No: 200-449-4

edetic acid (EDTA)



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European Union Risk Assessment Report
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49

European Union Risk Assessment Report

EDETIC ACID (EDTA)

CAS No: 60-00-4

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RISK ASSESSMENT

Cataloguing data can be found at the end of this publication
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EDETIC ACID (EDTA)

CAS No: 60-00-4

EINECS No: 200-449-4

RISK ASSESSMENT

Final Report, 2004

Germany

The risk assessment of edetic acid 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**

Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.

The Risk Assessment was carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

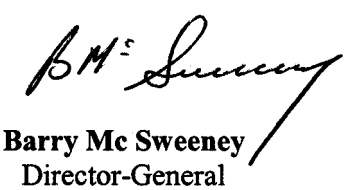
There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Toxicity, Ecotoxicity and the Environment (CSTEE) which gives its opinion to the European Commission on the quality of the risk assessment.

If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.

The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992.

This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.



Barry Mc Sweeney
Director-General
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Catherine Day
Director-General
DG Environment

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1 O.J. No L 084, 05/04/199 p.0001 – 0075

2 O.J. No L 161, 29/06/1994 p. 0003 – 0011

3 Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT

CAS No:	60-00-4
EINECS No:	200-449-4
IUPAC Name:	{[2-(Bis-carboxymethyl-amino)-ethyl]-carboxymethyl-amino} acetic acid
Synonyms:	Ethylenediaminetetraacetic acid, EDTA

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 releases

- due to the use of EDTA in industrial detergents,
- due to the use by paper mills,
- due to the use by circuit board producers,
- during recovery of EDTA containing wastes.

The risk characterisation for these scenarios led to a risk for aquatic organisms.

Human Health

Human Health (toxicity)

Workers

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

Human Health (risks from physico-chemical properties)

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

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Euses Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

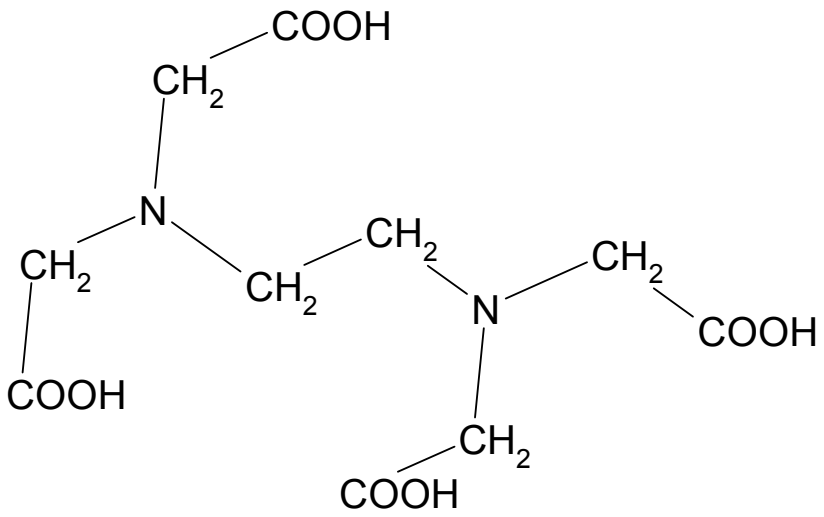
TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS No:	60-00-4
EINECS No:	200-449-4
IUPAC Name:	{[2-(Bis-carboxymethyl-amino)-ethyl]-carboxymethyl-amino}acetic acid
Synonyms:	Ethylenediaminetetraacetic acid; Ethylenedinitrilotetraacetic acid; N,N'-1,2-ethanediylbis[N-(carboxymethyl)glycine]; Edetic acid; H_4EDTA; EDTA
CA Index name:	Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)-
Empirical formula:	$C_{10}H_{16}N_2O_8$
Molecular formula:	292.3 g/mol
Molecular weight:	292.3 g/mol

Structural formula:



1.2 PURITY/IMPURITIES, ADDITIVES

Purity:	98-100% w/w
Impurity:	< 0.3 trisodium nitrilotriacetate < 0.3 ethylenediaminetriacetate < 0.3% w/w nitrilotriacetic acid < 1% water
Additives:	none

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Physico-chemical properties

Parameter	Value	Reference
Physical state	at 20°C, 1,013 hPa: colourless crystals	
Melting point	n.a. (decomposition above 150°C)	Römpp (1990)
Boiling point	not applicable [1)]	BASF AG (1973a)
Relative density	0.86 at 20°C	Sorbe (1996)
Vapour pressure	not determined [2)]	BASF AG (1973a)
Surface tension	not determined [3)]	BASF AG (1973a)
Water solubility	0.4 g/l at 20°C	Ullmann (1974)
log Pow	-5.01 (calculated according Hansch and Leo) [4)] -3.34 (calculated according Rekker)	BASF AG (1994)
Flash point	not determined because substance is a solid	BASF AG (1973a)
Flammability	not flammable [5)]	BASF AG (1973a)
Ignition temperature	no self ignition up to the decomposition at 150°C (VDI 2263)	BASF AG (1973a)
Explosive properties	not explosive [6)]	BASF AG (1973a)
Oxidising properties	no oxidising properties [6)]	BASF AG (1973a)
Henry's law constant	1.10^{-20} Pa.m^3/mol [7)]	

1) A determination of the boiling point is scientifically not meaningful because the substance decomposes above 150°C.
2) The vapour pressure is estimated to be very low for partically ionic substances. Therefore a determination was not conducted.
3) The surface tension was not determined because of structural reasons.
4) This value is used in the following risk assessment.
5) In a preliminary test the ignition level was determined to be 1. Therefore the substance is not flammable.
6) No test was conducted because of structural reasons.
7) As no value for the vapour pressure is known, a Henry's law constant can not be calculated from vapour pressure and water solubility. So a fictitious low value is used for the risk assessment.

1.4 CLASSIFICATION

Classification according to Annex I

Class of danger: none
R-Phrase: none

The classification of H_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 EDTA:

Xi; R36

Labelling

Xi
R: 36
S: (2-)26

Xi	Irritant
R36	Irritating 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

Environment

Most of the acute tests performed with fish and daphnids revealed LC/EC50-values well above 100 mg/l, indicating for complexed and non complexed EDTA no need for classification as dangerous for the environment. Exceptions are two fish tests using H_4EDTA, where the tests were performed in very soft (LC50=41 mg/l) or soft water (LC50=59.8 mg/l). In the test media a surplus of uncomplexed EDTA was present which is not expected in the environment, therefore this tests are not relevant for the assessment.

Tests on acute toxicity with Daphnia magna resulted in 24-hour EC50 values of 480 and 790 mg/l.

Algae tests performed in standard media resulted in effect values below 1 mg/l, the effect is probably caused by nutrient deficiency. This indirect effect is an artefact and not used in the effects assessment. Further experiments with increased nutrient metal concentrations reveal that the direct toxicity on algae is above 310 mg/l. Indirect effects like nutrient deficiency and eutrophication could only qualitatively be assessed; they are unlikely to occur in the environment although it cannot absolutely be excluded.

Therefore, on the basis of the data it was concluded that there is no need for classification with R 52/53.

Annotation

The German manufacturer gives a purity of 74% (wt.%) Na_4EDTA for the technical grade product.

The content of Nitrilotriacetic acid (NTA) in the technical grade product is 3%. NTA. There might be consequences for classification and labelling of the technical grade product Na_4EDTA. The risk assessment on trisodiumnitrilotriacetate is performed evaluating the substances of the third priority list.

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.

2.1 PRODUCTION AND IMPORT

Table 2.1 Producers and/or importers of EDTA

Company	Substance
Akzo Nobel Chemicals B.V. (NL)	Na4EDTA, H4EDTA
Akzo Nobel Chemicals B.V. (SWE)	Na4EDTA, H4EDTA
BASF AG (GER)	Na4EDTA, H4EDTA
Contract Chemicals (UK)*	Na4EDTA, H4EDTA
Dow Europe S.A., (NL)	Na4EDTA
Dow Europe S.A. (UK)	Na4EDTA
S.A. Dabeer (ES)	Na4EDTA, H4EDTA
Synthron (F)	Na4EDTA

* Production was stopped in January 2001

According to the data supplied by industry for this report, 53,900 tonnes/annum (calculated as H_4EDTA) are produced in the EU. With a European consumption of 34,546 tonnes in 1999, about 19,000 tonnes are yearly exported by the producers. Further exports of 1,143 tonnes by distributors and 805 tonnes by companies of photoindustry are known. There might be further exports and imports of EDTA in formulations and consumer products, although no data are available.

2.2 USE PATTERN

The EDTA amounts (calculated as H_4EDTA) marketed in the Western European countries are given in **Table 2.2**. The figures are derived from sales information of the producers. A direct correlation to the consumption volume is therefore not precise; however the figures may be regarded as an approximation for the European consumption. Imports and exports of EDTA containing formulations are not considered. In order to describe the development of the use volumes, the change in the previous year comparing to the last 8 years is presented in **Table 2.2** (CEFIC, 1998; 2000).

Table 2.2 Development of use volumes

Country	Sales [tonnes] 1999	Change [%] 1997 to 1999	Change [%] 1991 to 1999
Great-Britain	6,919	+ 9.8	+ 70 *
Eire	247	- 8.9	+ 22 *
Germany	3,894	+ 1.9	- 23
France	4,689	+ 2.6	+ 21
Italy	5,416	+ 11	+ 57
Sweden 1)	2,760	- 2.5	+ 205
Belgium / Luxembourg	2,864	- 3.0	+ 23
Netherlands	1,594	- 2.6	+ 36
Finland	1,192	- 7.0	+ 42
Spain	2,478	+ 33	+ 90
Denmark 2)	1,070	+ 5.7	+ 1.7
Norway 3)	442	+ 55	+ 30
Greece	435	+ 23	+ 84
Switzerland	147	- 18	- 15
Portugal	159	- 1.2	0
Austria	240	+ 46	+ 33
Total Western Europe	34,546	+ 6.1	+ 35

* Change for Great-Britain and Eire related to 1992
1) Swedish Product Registry: 3,240 tonnes in 1997 (as H_4EDTA)
2) Danish Product Register: 1,714 tonnes (January 1995) (as H_4EDTA)
3) Norwegian Product Register: 651 tonnes (1993) (as H_4EDTA)

The consumption of EDTA in Germany has a decreasing tendency compared to Western Europe as a whole for which consumption tends to increase. The development of EDTA sales (calculated as H_4EDTA) in the last years is in presented in **Table 2.3** (CEFIC, 1995; 1998; 2000; VCI 1996).

Table 2.3 Development of EDTA sales (calculated as H4EDTA) in the last years (CEFIC, 1995, 1998, 2000; VCI, 1996)

Year	Germany		Western Europe	
	Volume [tonnes/annum]	Change [%] to previous year	Volume [tonnes/annum]	Change [%] to previous year
1989	5,675	+ 13.7	26,763	+ 4.8
1990	5,298	- 6.6	27,057	+ 1.1
1991	5,089	- 3.9	25,637	- 5.2
1992	4,467	- 12.2	25,911	+ 1.1
1993	4,271	- 4.4	27,189	+ 4.9
1994	4,350	+ 1.8	30,006	+ 10.4
1995	4,030	- 7.4	29,560	- 1.5
1996	3,686	- 8.5	29,422	0
1997	3,822	+ 3.7	32,547	+ 10.6
1999	3,894	+ 1.9 *	34,546	+ 6.1 *

* Changes related to 1997

The decrease of the EDTA consumption in Germany is caused by a joint declaration on the reduction of the EDTA pollution in surface waters which aimed at reducing the EDTA concentrations of 1991 by 50% within 5 years. However, this goal was not reached.

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. For Western Europe, a CEFIC search on the breakdown in application areas for the distributors is available. In **Table 2.4**, these amounts are added to the direct sales. For the German use pattern, such a search is not available; therefore the application figures cannot be compared directly. The application volumes (calculated as H_4EDTA) were (CEFIC, 2000; Swedish Product Register):

Table 2.4 Breakdown of EDTA sales in application areas

	IC/UC *	Germany (1999)	Sweden (1997)	Western Europe (1999)
Marketed amount		3,894 t	3,240	34,546 t
Household detergents	5/9	458 (12%)		2,619 (7.6%)
Industrial and institutional detergents	6/9	577 (15%)	180 (5.6%)	10,685 (31%)
Photochemicals	10/11	1,135 (29%)	16-17 (0.5%)	4,191 (12%)
Textiles	13/11	56 (1.4%)		639 (1.8%)
Pulp and paper	12/11	-**	~3,000(93%)	4,002 (12%)
Metal plating	4/11	0	13-14 (0.4%)	470 (1.4%)
Agriculture	1/19	146 (3.7%)	9 (0.3%)	5,821 (17%)
Cosmetic	5/49	176 (4.5%)		756 (2.2%)
Water treatment	6/11	- **		215 (0.6%)
Others Disinfection Printing inks/ dye additives Food / Feed ingredients Fuel gas cleaning Pharmaceutical Polymer and rubber processing Leather tanning Oil production Concrete admixtures Lubricants Sales to chemical industry Exports others		Σ 734 (19%)	Σ 30 (0.9%)	 68 166 110 595 184 469 113 358 12 42 244 1,143 1,137
Distributors		574 (15 %)		45

* Industrial category / use category

** Not published. With the difference of the annual marketed amount (3,894 t) and the total sum for the uses in German industrial branches, the use amount for pulp, paper and water treatment together is calculated to 38 tonnes/annum

The figures in **Table 2.4** are derived from sales of the producers to customers which are related to an appointed industry branch. A direct correlation to the consumption volume is therefore not precise.

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 Environmental releases

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.

During production, releases occur via wastewater into the hydrosphere. According to the data submitted by the producers, the total yearly emissions into the hydrosphere are 266 tonnes/annum (see Section 3.1.3.1).

Some producers state that there would be no emission into the atmosphere pointing out the very low vapour pressure of the substance. This is plausible in the case when EDTA is handled only in aqueous solution. However, some companies report about dust particle emissions. The total yearly emissions into the atmosphere by 3 sites are 11 tonnes/annum (see Section 3.1.4.1).

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 3.1.3.2.

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 EDTA complexes, and the complete environmental risk assessment is performed on this basis. Also in the literature all figures are generally related to H_4EDTA; if the species is not stated they will be taken as H_4EDTA.

Frequently the question is raised in the literature whether EDTA can cause hazardous effects due to its property to keep heavy metal ions in the water phase of rivers. The interaction of EDTA with metal ions is elaborated in Section 3.1.3.3.

3.1.2 Environmental fate

3.1.2.1 Degradation

3.1.2.1.1 Degradation rates

Biodegradation tests

A large number of degradation tests are available for EDTA. Only a part of the available tests is shown here (cf. IUCLID). In most cases the acid or the Na salt was tested and not the complexed EDTA.

As results confirm, EDTA is not readily biodegradable. For instance an OECD Screening Test indicated 10% degradation with municipal wastewater and EDTA concentration between 7 and 50 mg/l after 19 days (Gerike and Fischer, 1979). With preacclimatisation of the inocculum only 10% carbon dioxide evolution was observed in a 28-day Sturm test (Gerike and Fischer, 1979). In closed bottle tests the oxygen consumption at day 28 was 3 and 0% of the theroretical oxygen demand as found by Gericke and Fischer (1979) and van Ginkel and Stroo (1992), respectively.

The results of different tests on inherent biodegradability are unequal. The available, not well documented tests show for instance biodegradation rates from 0 and 37% under application of pre-adapted inoculum after 14 days (Zahn and Huber, 1975; Gerike and Fischer, 1979). In a Modified Zahn-Wellens Test (OECD 302 B) a biodegradation of < 20% could be found after 28 days with non-adapted sludge (Zahn and Wellens, 1980).

Recent data suggest that under alkaline conditions EDTA can be degraded. Environmental samples from a river, a ditch and a lake were examined in the closed bottle test for their potential to degrade $CaNa_2EDTA$ in a concentration of 8.0 mg/l at pH 6.5 and 8.0 over a period of few weeks. The results show for all environmental samples that at pH 6.5 no or little biodegradation (2-12%) occurs within the first 28 days. After 49 days a biodegradation between 60 and 83% was obtained. At pH 8, rates of 53, 62 and 72% were obtained after 28 days and 75-89% after 35 days (Van Ginkel, 1999).

Different investigations show, that it is possible to obtain enrichment cultures of EDTA-utilising microorganisms. So far three strains of bacteria have been isolated breaking down EDTA completely. One of them could be identified as *Agrobacterium sp.* Counter-ions exert effects on the biodegradation of chelating agents. The different results show, that metal-EDTA complexes with a thermodynamic stability constant below 10^{12}, like Ca, Mg and Mn, were degraded. Chelates with stability constants above 10^{12}, such as Cu and Fe, were not degraded (Van Ginkel, 1999).

Results obtained at pH of 8 could be relevant because the pH value of lake and river water ranges from 7.7 to 8.5. However, in surface waters (see Section 3.1.3.3) EDTA is preferably complexed with heavy metal ions. Regarding the degradation tests cited above, no biological degradation is expected. Ca-EDTA can only occur in the environment where strong point sources release this species into a river with a low flow. Therefore, in the present exposure assessment EDTA is regarded as not biodegradable in surface waters, and a biodegradation rate constant of 0 d^{-1} is used.

Biodegradation in treatment plants

A Coupled Units Test with municipal sludge indicated degradation of 0% (-5+4%) with EDTA concentration of 30 mg/l (Gerike and Fischer, 1979).

It could be shown in three different experiments that a change of the pH-value can result in a biodegradation of EDTA. In a SCAS facility a removal by biodegradation of EDTA (65 mg/l) added to domestic wastewater could be observed at pH of 8.0 to 9.0. With a pH of 6.5 no biodegradation could be obtained. The removal at pH 8.5 starts 3 weeks after inoculation with a result up to 100% degradation after 28 days. The SCAS unit runs with sludge retention times >12 days. A maximum EDTA removal rate of 0.2 kg/m^3/day was achieved (Van Ginkel et al., 1997).

In order to confirm the biodegradation of EDTA, closed bottle tests were carried out with sludge originated from the SCAS unit. The tests were conducted at a pH range from 8.0 to 8.5. The lag period was only few days. The time to reach a BOD/ThOD ratio of 0.6 was 3 weeks after initiation of detectable biodegradation. EDTA was not biodegraded at pH 7.0 (Van Ginkel et al., 1997).

The removal of EDTA was investigated in a full-scale activated sludge plant operated at pH between 7.5 and 8.5 with dairy wastewater containing ca. 30 mg/l EDTA. The dairy wastewater was treated at a hydraulic residence time of one day and a sludge retention time of 20 days. The analysis of influent, effluent and sludge concentration results in approximately 90% removal. At a pH of 6.7 no biodegradation took place (Van Ginkel et al., 1997).

Monitoring in municipal treatment plants

During a monitoring program of one week, the elimination of EDTA was examined in a municipal WWTP in Bielefeld (Germany). 3 corresponding daily mixture samples were measured, EDTA concentrations of 130-230 µg/l (mean 193 µg/l) in the influent and 135-230 µg/l (mean 185 µg/l) in the effluent were detected (Lahl and Burbaum, 1988). The values indicate that no elimination occurs.

During a monitoring program in municipal WWTPs in Hessen (Germany) in 1988, an average elimination rate of 10% was calculated from corresponding EDTA concentrations in influent and effluent (Kröber and Häckl, 1989).

An extended and well documented study about the fate of EDTA in municipal treatment plants was conducted by Kari (1994). EDTA was measured in influents and effluents, and a mass balance was calculated. From the loads in influents and effluents of 3 plants, elimination rates of 6%, 4% and 0% were derived.

In an experimental WWTP charged with municipal sewage, EDTA concentrations in influent and effluent were measured. From the concentration figures (taken from two graphics) elimination rates of 3-30% respectively. 30-40% are calculated, with an influent's concentration range from 0.2 to 1 mg/l (BayLWF, 1990). Because of the large deviation of the single values, the result seems to be uncertain.

Monitoring in industrial treatment plants

EDTA was measured in a treatment plant dedicated to treat the sewage from a paper mill. With 50 separate samples of influent (mean 23.8 mg/l) and effluent (mean 5.8 mg/l) an elimination rate of 76% is determined. The pH in the influent was 5.3-5.8 and 7.6-7.9 in the effluent, the temperature

35-40°C over the whole year and the mean hydraulic retention time about 1 day. The total biodegradability of EDTA was verified in the laboratory with activated sludge from the treatment plant, the result shows >80% CO_2 formation and =99% DOC removal (Kaluza et al., 1998).

From EDTA measurements in influent and effluent of 3 Finnish pulp and paper mills with biological wastewater treatment, elimination rates between 17% and 30% were calculated (Sillanpää, 1996). For a Swedish mill, 58% elimination was found (Akzo Nobel, 1999). In a new long-term aerated activated sludge plant of a Swedish paper mill, EDTA was removed by 73% on average at normal operating conditions, which was further improved to a 80-85% reduction (Swedish Forest Industries Federation, 2000). In another pulp mill in Finland with biological activated sludge treatment 90% removal is established (CEFIC, 2001c).

The removal of EDTA in treatment plants receiving wastewater from industrial and institutional cleaning was evaluated by van Ginkel (1999). The elimination was determined by monitoring in influent and effluent. In **Table 3.1**, the elimination rates together with site-specific characteristics are given.

Table 3.1 Elimination rates with site-specific characteristics

Source	Removal [%]	Sludge retention [per day]	pH	Comments
dairy	90	~ 20	7.5-8.1	$C_{effluent}$ 2-8 mg/l
beer	50	~ 23	7.3-7.7	COD reduction 90%
dairy	30	~ 9	7.8-8.4	SRT low
dairy	35 95	~ 40	7.5-7.8 7.8-8.0	T= 5°C (winter) T= 20 °C (summer)
dairy and domestic	0	~ 20	6.9-7.1	neutral pH!

It can be concluded that EDTA can be biologically degraded if a number of specific conditions are present:

- a relatively high hydraulic and sludge retention time,
- an alkaline pH value of the wastewater,
- a relatively high EDTA concentration,
- EDTA is not complexed with heavy metal ions.

It is evident that these conditions are not present in municipal treatment plants (which receive the major EDTA emissions). Therefore, in the following exposure assessment it is assumed that no biodegradation occurs in municipal WWTPs. This is supported by monitoring studies, where no degradation was observed. As neither adsorption onto sludge nor volatilisation is expected, 100% of the EDTA is expected to be released into the hydrosphere.

A partial degradation is expected in some industrial treatment plants, as the favoured conditions can occur. In some industry branches EDTA is used to dissolve calcium carbonate, and the major fraction is emitted as Ca-complex. In paper mills and beverage plants, the extent of degradation is revealed by monitoring studies. In progressive long-term aerated activated sludge plants, removal rates of 90% can be reached. Those plants reflecting the best available techniques are presently available only at a limited number of sites, at many other sites either no removal or a lower removal is reached. In the exposure estimation for industrial detergents and paper mills, two scenarios are calculated: the first with no removal reflecting a worst-case scenario, and a removal of 90% reflecting the best available techniques.

As the elimination rate is based on EDTA measurements, it is only related to primary degradation. It is proven that the products of primary degradation can be finally mineralised. In tests on biodegradation in soil (see below), no metabolites could be detected, thus the first degradation step appears to be the rate-limiting step. Relevant releases of EDTA metabolites from treatment plants are not expected.

Abiotic degradation

EDTA is resistant to hydrolysis, neither strong acids nor alkalis cause any degradation (BASF, 1990 b).

Irradiation of an aqueous Na_4EDTA solution with UV light revealed a decrease of the chelating properties, which is interpreted as EDTA degradation. Formaldehyde, acetaldehyde and acetic acid were detected as degradation products (Schneider and Rump, 1981). In this publication, the UV light is not specified. Therefore, a conclusion about the environmental fate cannot be drawn. Investigations cited below reveal that uncomplexed EDTA is not degradable under environmental conditions.

The photolytic degradation of Fe(III)EDTA in aqueous solution was estimated by several authors. In a laboratory test, Frank and Rau (1990) determined the quantum yields as a function of pH (range 2.5-10.5), concentration (range $0.04 \cdot 10^{-4}$ - $1.7 \cdot 10^{-4}$ M, i.e. 1.4 - 59 mg/l) in oxygen-free and air-saturated solutions. From this, the absorption spectrum of Fe(III)EDTA, a concentration of $8 \cdot 10^{-6}$ M (i.e. 2.8 mg/l), the optical transmission of river water (Neckar, Germany), a water depth of 2 m, a flow rate of 0.5 $m \cdot s^{-1}$, and the solar irradiation data for central Europe, reaction half-lives between 5 hours in August and 480 hours in January were calculated. The half-lives correspond to flow distances from 10 to 860 km.

In a further laboratory test with Fe(III)EDTA, the quantum yield was estimated to < 0.1 (pH 8-9). From this, a half-life of 11 minutes was calculated. This value refers to the top millimeters of a waterbody in Stockholm at noon in the beginning of summer (the yearly maximum spectrum). Because of factors like the daily periodicity of incident light, weather conditions like cloudiness, shadowing of surface and shore vegetation, adsorption and scattering by suspended solids, dissolved organic compounds and planctonic organisms, the real environmental half-life is certainly longer (Svenson et al., 1989).

Complexes of EDTA with Co(III) and Mn(II) in aqueous solution were found to be in the same way instable against photolysis like Fe(III), however with lower reaction constants. The relative reaction rates of Fe(III), Co(III), and Mn(II) complex are in the ratio of 1, 0.1, and 0.05. Because of the very low environmental concentrations of the Co(III) and Mn(II) complexes (see Section 3.1.3.3.2) and their relative low reaction constants, there is no significant contribution to the degradation of EDTA in the hydrosphere. Complexes with other metal ions like Zn, Cu and Ca are inert to photodegradation (Kari, 1994).

During a field study in the Swiss river Glatt (depth 0.7 m), the photodegradation of the Fe(III)EDTA complex was analytically determined (see Section 3.1.3.3.6). If the solar irradiation would be completely available, the half-life would range from 20 to 100 minutes (summer to winter), corresponding to flow distances of 0.6, respectively 3 km. Because of the bank and water plants, only 15% of this theoretical irradiation is effective, and therefore the real degradation is slower. Also cloudiness increases the half-lives (Kari, 1994).

Following the investigation of Frank and Rau (1990), a half-life of 20 days for photolysis of Fe(III)EDTA is used as a worst-case in the following exposure calculations. Other EDTA species are considered to be persistent.

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 (Frank and Rau, 1990; Kari, 1994).

Sediment

The degradative abilities of aerobically incubated sediments were investigated by Tiedje (1975) and the results were similar to soil. The following rates of EDTA degradation per 4 weeks and total degradation after 10 weeks were found: Wintergreen lake, 3.6% and 11.3%, Clear Lake, 5.6% and 15.2%; and Mill Pond 3.2% and 9.1%. A half-life for aerobic sediment between 200 and 300 days related to mineralisation is assumed.

For the anaerobic degradation in sediment only a qualitative investigation indicates no degradation after 7 weeks (Tiedje, 1975; 1977). Therefore, no biodegradation for the anaerobic parts of the sediments is assumed.

For the exposure calculations, a mineralisation half-life of 3,000 days for the total sediment (10% aerobic, 90% anaerobic) is used.

Geosphere

Non-standard investigations under various conditions show that EDTA can be biodegraded in soil under aerobic conditions. After 4 weeks, at a concentration of 4 µg of free acid/g of soil and at 30°C, biodegradation (recorded as $^{14}CO_2$ evolution) between 4.8 and 7.9% (common agriculture soils of mid-Michigan) could be detected (Tiedje, 1975). The biodegradation of EDTA was investigated also in a variety of soils of different geographical origin, texture, various agricultural use and pH. It could be shown, that degradation was minimal in subsoil samples. EDTA degradation followed a first-order kinetic for concentrations ranging from 0.4 to 90 ppm. Degradation was observed up to 1,000 ppm EDTA, the highest concentration tested. The extent of degradation among soils was variable, common values for 2 to 4 ppm of added ^{14}C-EDTA results in biodegradation (expressed as CO_2 evolution) between 0.6-12.2% after 4 weeks, 3.5-46% after 15 weeks and 65-70.5% after 45 weeks at 25–27^{o}C (Tiedje, 1977). For the most active soil a mineralisation half-life of 120 days could be determined. From the available data a medium half-life for agricultural used soil of 300 days can be deduced.

In another study primary biodegradation of 53–60% could be proven after 173 days (25 weeks) at 22°C. Additional 39% of the substance were assumed to be eliminated by sorption and abiotic degradation (Means et al., 1980). The assumption that abiotic degradation and sorption could be relevant for the EDTA elimination is in contrast to many other investigations. Thus this is not considered in the present assessment.

Analyses of the cation-EDTA equilibria reactions suggest that EDTA will eventually predominate as the Fe(III) chelate in acid soils and as the Ca chelate in alkaline soils (Cheng et al., 1972; Norvell and Lindsay, 1969). In studies where EDTA had been added to soil in complexes with Cu, Cd, Zn, Mn, Ca, and Fe, it could be shown that all species degraded equally, whereas Ni-EDTA was degraded more slowly (Tiedje, 1975).

Adsorption and degradation properties of EDTA were investigated in the system water/soil (underground passage) by Stumpf et al. 1996. It could be shown that it is difficult to eliminate EDTA in this system. After three to four weeks a decrease of EDTA concentration was detected, but no metabolites could be found.

Summary of degradation rates

The degradation rates presented in **Table 3.2** are used in the further exposure assessment.

Table 3.2 Summary of degradation rates

Parameter	Degradation rate	Half-life	Remarks
$kbio_{water}$	0 d^{-1}	∞	
$kphoto_{water}$	0.035 d^{-1}	20 days	Fe-complex only!
$kdeg_{water}$	0.035 d^{-1}	20 days	Fe-complex only!
$kdeg_{water}$	0 d^{-1}	∞	others than Fe-complex
$kbio_{sed}$	$2.3 \cdot 10^{-4}$ d^{-1}	3,000 days	for total sediment
$kbio_{soil}$	$2.3 \cdot 10^{-3}$ d^{-1}	300 days	
$kdeg_{air}$	0 d^{-1}	∞	

3.1.2.1.2 EDTA degradation products

Photolysis

To investigate the photodegradation pathway of Fe-EDTA, an aqueous solution of the substance was irradiated with a xenon arc lamp. The reaction mixture was sampled over a period of 4 days. CO_2, formaldehyde, N-carboxymethyl-N,N'-ethylenediglycine (ED3A), N,N'-ethylenediglycine (N,N'-EDDA), N-carboxymethyl-N-aminoethyleneglycine (N,N-EDDA), iminodiacetic acid (IDA), N-aminoethyleneglycine (EDMA), and glycine were identified as major photodegradation products (Lockhart and Blakeley, 1975).

Biodegradation

Haberer and Ternes (1996) studied the metabolisation of EDTA in a soil-water-system under aerobic conditions over a 100-day period. Metabolites formed under the conditions of a soil passage (close to environmental conditions) are ethylendiamine triacetate (ED3A) and ketopiperacindiacetate (KPDA). Ethylendiaminetriacetate spontaneously polymerised to the ketopiperacine derivative. The authors assume, that the open and the cyclic form exist simultaneously in the soil solution. The metabolites could be identified by GC/MS-, GC/MS/MS-spectra and different NMR-technics.

Using pure microorganism cultures it could be found that EDTA is degraded by two pathways both of which lead to cleavage of the carbon-nitrogen bonds. In the first pathway, the cleavage of the carbon-nitrogen bond results in stepwise removal of carboxymethyl groups, i.e. EDTA is degraded to ethylenediaminetriacetic acid (ED3A), N,N'-ethylendiaminediacetic acid (N,N'-EDDA) and glyoxylic acid. In the second pathway ED3A is further cleaved into iminodiacetic acid (IDA) and iminoacetaldehyd acetate (Van Ginkel, 1999).

Nowack and Baumann (1998) examined biodegradation of the products of Fe(III)EDTA photolysis. Solutions of 138 mg/l Fe(III)EDTA were irradiated to sunlight (September, Switzerland) for 6.5 and 20 hours corresponding to a residence time in surface waters of approximately 1 and 3 days. After 6.5 hours irradiation, the EDTA has dropped to 1% of the initial concentration, while after 20 hours no EDTA could be detected. From initially

4 carboxylate moieties per molecule, on average 2.7 remained after 6.5 hours and 1.4 after 20 hours. A modified OECD 302B test with simultaneous determination of mineralisation was performed with the irradiated solutions. Elimination was determined by DOC measurement and mineralisation by carbonate titration. With non-irradiated Fe(III)EDTA no degradation was observed after 4 weeks incubation. The elimination was 53% (92%) and the mineralisation 50% (93%) after 6.5 hours (20 hours) irradiation. In a parallel experiment, the iron complex of N,N'-ethylenediaminediacetic acid (Fe(III)-N,N'-EDDA), after 30 days the DOC removal was nearly 100% and the CO_2 formation about 80% (lag-time 14 days).

Ketopiperazines

ED3A was found to react spontaneously to ketopiperazinediacetate (KPDA) by intramolecular cyclisation under neutral and especially under acidic conditions. Analogous ketopiperazine compounds are formed from N,N-EDDA, N,N'-EDDA and EDMA (Ternes et al., 1996).

The formation of KPDA was observed with uncomplexed ED3A. However, under environmental conditions ED3A is probably complexed with heavy metal ions, and this may influence the cyclisation reaction.

The biodegradation of ketopiperazinediacetate (KPDA) was investigated in closed bottle tests (OECD, 1992) and a SCAS test (OECD 302). The Closed Bottle tests were performed using unacclimated sludge from a municipal wastewater treatment plant or with sludge pre-adapted to KPDA in the SCAS test. The sludge concentration was 2 mg/l dry weight. The test substance (ketopiperazinediacetate) at an initial concentration of 2 mg/l was incubated in a mineral salt medium, without further carbon source. The bottles were incubated at 20± 1°C for 28 days. Ketopiperazinediacetate is degraded by 92% at day 28 using unadapted sludge. Starting with 10% biodegradation, a rate of 60% is accomplished within 12 days. The test result does not fulfill the 10-day time window (Van Ginkel and Stroo, 1999).

Other sources of ED3A

Beneath EDTA, diethylenetriaminepentaacetate (DTPA) was identified as a further source of ED3A. This compound was formed by biodegradation of DTPA in a soil/water suspension. DTPA is used as chelating agent in different industry branches, e.g. in pulp and paper industry. However, the use volume of DTPA is lower (Europe 1997: 13,998 tonnes DTPA, 32,550 tonnes EDTA), and DTPA forms other products of primary degradation beneath ED3A. Therefore, DTPA should be of minor importance for the environmental exposure of these metabolites.

An overview about the EDTA metabolisation pathway is shown in the following graphics:

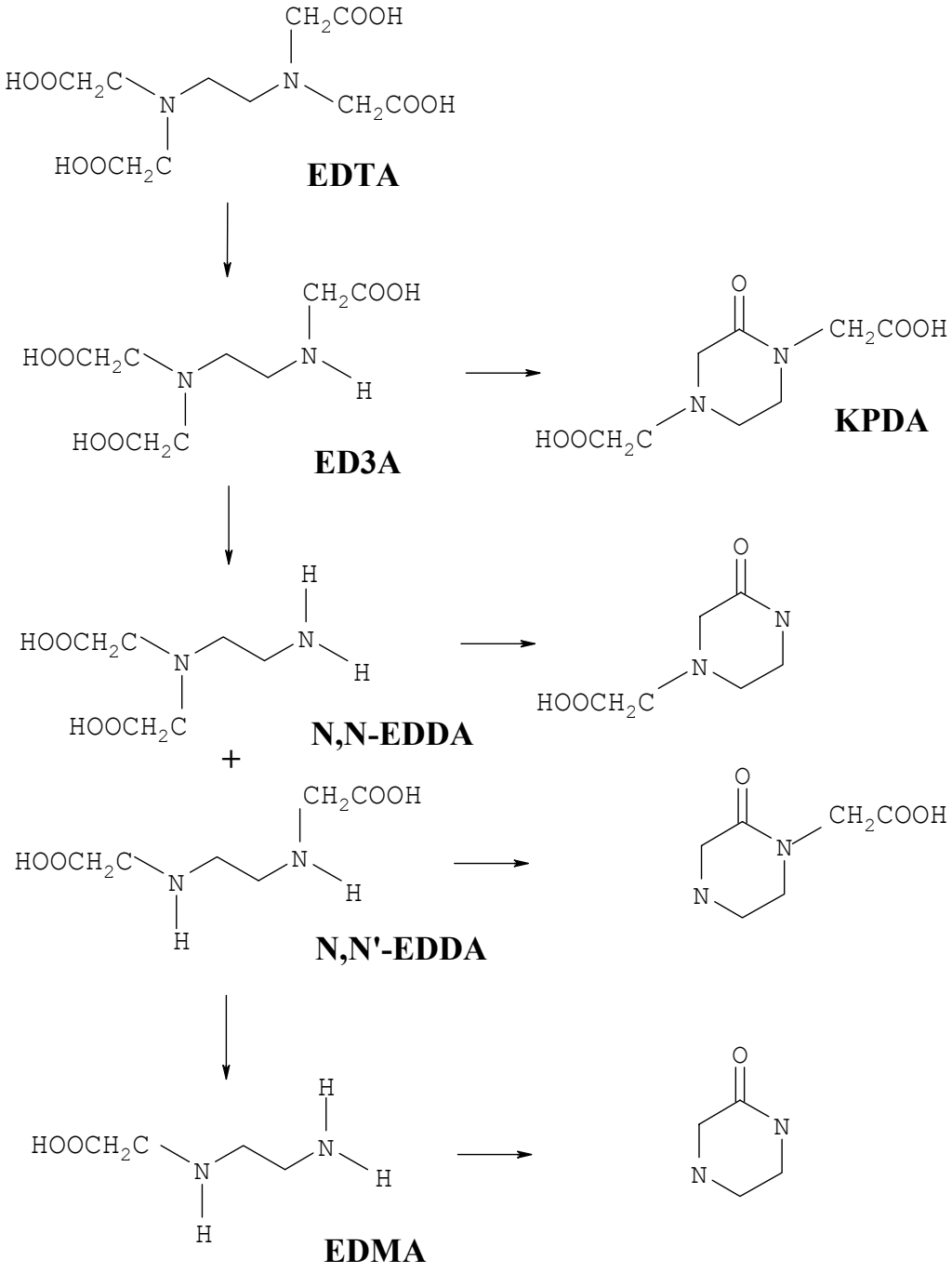


Figure 3.1 Degradation pathway of EDTA

In this graphics only those metabolites which are relevant for the present risk assessment are considered. The metal cations are omitted.

Monitoring

ED3A and KPDA were measured in several German rivers. Both substances could not be safely distinguished with the applied analytical method as under the sample preparation conditions ED3A converts to KPDA. Thus the concentrations [µg/l] presented in **Table 3.3** refer to the sum of both compounds (Ternes et al., 1996).

Table 3.3 Monitoring of EDSA and KPDA in several German rivers

Site	[KPDA+ED3A]	[EDTA]	[DTPA]
Mosel - Wehlen	3	6	1
Ruhr – Essen (2 samples)	7 / 16	11 / 7	12 / 7
Neckar - Heidelberg	3	9	2
Rhein - Wiesbaden	5.5	7.5	3.5
Rhein - Mainz	10	7	3
Main - Großkr.	0.5	14	<1
Main - Bischofsheim	1	20	<1

Measurements of ED3A and KPDA in drinking water are cited in Section 4.1.1.4.

Summary of EDTA degradation products

There are several ED3A release sources known:

- Photolysis of Fe-EDTA. According to a rough estimation about 50% of the emitted EDTA is complexed with iron (see Section 3.1.3.3.6). This source is probably the most important for the presence of ED3A in surface waters.
- Biodegradation of EDTA in industrial treatment plants. As elaborated above, the first biodegradation step appears to be the rate-limiting step, thus relevant releases are not expected.
- Degradation of DTPA. Because of its lower use volume and competing degradation reactions, DTPA is probably of minor importance than EDTA.
- According the IUCLID database, 7% ED3A and 1% EDDA are listed as impurities of Na_4EDTA. For H_4EDTA, a content of <0.3% ED3A is listed.

In the environment, ED3A reacts either to ketopiperazine diacetate (KPDA) by cyclisation, or is further degraded to EDDA etc. (as shown in the graphics). The presence of KPDA in surface waters can be explained by a balance between formation from ED3A and removal by biodegradation. In drinking water, KPDA is expected to be stable, because of the missing biological activity.

Products of further photolysis of Fe(III)EDTA like N,N'-ethylendiaminediacetic acid (N,N'-EDDA) were found to be inherently biodegradable.

From the available studies it is not possible to predict the environmental concentrations of the metabolites precisely. The reaction pathways are known, but they are not quantifiable. The environmental concentrations of the compounds being formed could only be clarified by a monitoring program.

3.1.2.2 Distribution

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 EDTA and its metal complexes, it has to be assumed that volatilisation from aqueous solution will not occur.

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

In a laboratory test, the mobility of EDTA in soil was tested. Solutions of H_4EDTA and ZnEDTA were eluted through cores of two various surface soils. H_4EDTA was found to be very slightly adsorbed and moved quite readily through both soils. The EDTA from ZnEDTA also moved readily, however, the Zn was replaced by Fe to a large extent (Cheng et al., 1972).

The influence of EDTA on the sorption of Zn onto soils was tested by Elrashidi and O'Connor (1982). The presence of EDTA in the soil suspension significantly decreased the Zn sorption on 3 investigated soils. Only a slight difference in Zn sorption was observed whether EDTA was added to the Zn containing soil before or after contact with soil.

Similar effects were found with Cd, the adsorption is significantly reduced (Elliott and Denneny, 1982; Fuji, 1978).

A model calculation of the distribution of EDTA metal complexes between water and suspended solids resulted that < 1% of the total EDTA is adsorbed. The parameters should be valid for the Swiss river Glatt: with an EDTA concentration 30 µg/l and a suspended matter concentration of 10 mg/l, only EDTA metal complexes can adsorb (Kari, 1994).

In an experiment, the distribution between water and sediment of the Swiss river Glatt was estimated for 3 different EDTA metal complexes. The EDTA concentration was measured in the water phase, from this the partition coefficients were calculated: 3 l.kg-1 for CaEDTA, 38 l.kg-1 for ZnEDTA, and 113 l.kg-1 for CuEDTA. For the real conditions of the river Glatt, the adsorbed part of the total EDTA content should generally range below 0.1% (Kari, 1994).

For the exposure calculation, values for Kpsoil, Kpsed and Kpsusp of 75 l.kg-1 are used. This is the average value between Zn- and CuEDTA, CaEDTA is not expected in most surface waters (see Section 3.1.3.3).

Based on the physico-chemical properties of H4EDTA, a calculation with the fugacity model Mackay level I predicts that the hydrosphere is the preferred environmental compartment (99.999%).

3.1.2.3 Accumulation

Bishop and Maki (1980) studied bioaccumulation of EDTA oin the fish *Lepomis macrochirus*, using the kinetic and the plateau method. Under actual requirements only the results of the plateau method can be used. After 28 days, the EDTA level in the fish, as determined by the plateau method, was of the same order of magnitude as the level in the ambient water. Depending on the used concentration BCF of 1.8±1.1 (0.08 mg/l EDTA) and 1.1±0.95 (0.76 mg/l EDTA) could be obtained. From this data it can be concluded that no bioaccumulation takes place.

There is much information about the influence of EDTA on the accumulation on heavy metals available. The concentration of metals used in the experiments is much higher than their occurrance in the environment. The influence on Cd accumulation was studied e.g. on fish (*Oncorhynchus mykiss*, Pärt and Wikmark, 1984), on the American oysters (*Crassostrea virginica*, Hung, 1982), on the barnacles *Semibalanus balanoides* (Rainbow et al., 1980) and on mussels (Gutiérrez-Galindo, 1980). All results indicate that EDTA decreases the accumulation of Cd. In an investigation with Pb and Cu it could be shown that the accumulation of these heavy

metals is also decreased by EDTA. On the other hand the absorption of Hg by mussels is promoted through complexation with EDTA (Gutiérrez-Galindo, 1981).

The influence of EDTA on the elimination of heavy metals was also studied by different authors. EDTA in concentrations of 1 or 10 mg/l had no effect on the elimination of Cadmium from American oysters after 28 days (Van Dolah et al., 1987). Mussels were exposed for 22 days in sea water but failed to find elimination of mercury in the presence of EDTA (4 mg/l Na_2H_2EDTA). The elimination of Cd, in contrast, was promoted slightly from 5% elimination without EDTA to 20% elimination in the presence of 8 mg/l EDTA (Gutiérrez-Galindo, 1981).

3.1.3 Aquatic compartment

3.1.3.1 Estimation of PEClocal during production

In the Technical Guidance Document (TGD, EC, 1996) release factors of 0.3% for production (TGD, Appendix I, Table A1.1) and 0.3% for formulation are proposed as default values.

However, considerably higher releases are calculated from specific data for 5 sites: from the emission and production volumes, release factors from 0% to 3.8% are calculated. Additionally, chemical plants may internally use EDTA for different purposes (e.g. in cooling water), the emissions from this internal consumption add to the emissions from production.

Estimation of PEClocal / Site-specific approach

For calculating the $Clocal_{aqua}$, the dilution of the wastewater in the river is considered according to

$Clocal_{water}=Clocal_{eff} \cdot D$ with $D=Q_{ww} / Q_{river}$

$Clocal_{eff}$: concentration in WWTP effluent
D: dilution factor
Q_{ww}: sewage flow
Q_{river}: river flow (10%ile value prefered)

PECregional=95 µg/l (see Section 3.1.3.4)

In **Table 3.4**, the estimated concentrations, emission volumes, and the underlying specific data (as far as available) are summarised.

Table 3.4 Estimated local water concentrations, emission volumes and specific data used for the calculations

Site	Site-specific data	Defaults	C_{eff} [mg/l]	$Clocal_{aqua}$ [mg/l]	$PEClocal_{aqua}$ [mg/l]	Release [tonnes/ann.]
A	only import	-	0	0	-	0
B	yearly emission volume, sewage and river flow	prod. period 300 days/annum	9.7	0.083	0.18	87
C	effluent conc, sewage and river flow	-	0.040	$4.7 \cdot 10^{-6}$	0.095	$2.4 \cdot 10^{-5}$
D	yearly emission volume, sewage flow, discharge into estuary, dilution modelled	prod. period 300 days/annum	No WWTP	max. 1	max. 1	24.4
E	effluent conc. (mean and 90%ile), sewage and river flow	-	1,500	0.26	0.36	117
F	yearly emission volume, sewage and river flow; no WWTP	prod. period 300 days/annum	No WWTP	0.0054	0.10	0.2
G	emission period 20 times/a for 24 h, sewage flow, no WWTP	dilution 1:10	No WWTP	0.12	0.22	0.05
H	annual and 90%ile emission, sewage and river flow	-	0.40	0.0026	0.098	38

Remarks:
Site B: The EDTA release is calculated on the basis of analytical nitrogen determination. This can be considered as a worst-case approach, as compensation the release emission amount was layed down to the PEC calculation.
Site D: The concentrations in the receiving estuary were modelled, resulting in maximum values in the range of 0.5– 0 mg/l.
Site E: Production was stopped in January 2001.

The total emission at the EDTA production sites into surface waters is 266 tonnes/annum.

3.1.3.2 Estimation of PEClocal during use

Releases into household sewage

Household detergents contain traces of heavy metals like copper, manganese and iron which catalyse the decomposition of active oxygen bleaching compounds like sodium perborate during storage and use. The addition of a chelating agent reduces the loss of the peroxyde compound (Jakobi et al., 1983; Hart, 1985). The Na_4EDTA content is about 0.8–1% (Otterbach, 1974), another reference states 0.1-0.5% (AIS, 1987).

In cosmetics the metal catalysed oxidation of olefinic compounds causes a rancid smell or taste as well as discolour. EDTA is used to prevent these effects (AIS, 1987). Further functions are the stabilisation of aromas (Otterbach, 1974), prevention of nickel and chromium allergies (Van Ketel and Bruynzeel, 1984), and supporting preservatives, especially against pseudomonades (Wilkinson, 1975).

Furthermore, EDTA is used in pharmaceuticals and as a food additive. Releases from vehicle shampoos and from amateur photographers are emitted into the household sewage as well.

For the exposure assessment, it is assumed that (in accordance to the EU standard region defined in the TGD) 10% of the European figure is consumed by 20 million people. In Europe 2,619 tonnes/annum were consumed in household detergents, 110 tonnes/annum in food,

184 tonnes/annum in pharmaceuticals, and 756 tonnes/annum in cosmetics (Σ 3,669 tonnes/annum). Thus, the regional consumption is 367 tonnes/annum. With a fraction of main source of 0.002 (TGD, Appendix I, Table B4.1), 734 kg/annum, respectively 2.0 kg/day are emitted by a treatment plant.

The resulting values are:	C_{eff}=1,000 µg/l $Clocal_{water}$=100 µg/l
PECregional=95 µg/l (see Section. 3.1.3.4)	$PEClocal_{water}$=195 µg/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 (AIS, 1987). For two rust removal formulations, Na_4EDTA concentrations of 2%, respectively 2.5% are reported (Kreuter, 1976).

There are a large number of use areas within the industrial and institutional detergents (IandI) 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 (AISE, 1999).

The total European market volume was 10,685 tonnes in 1999 (CEFIC, 2000). The industry association AISE collected market data from its larger member companies, covering 4,353 tonnes/annum. 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 tonnes/annum. One reporting company reported that across Europe, of 800 customers in the above industries, less than 5% used more than 10 tonnes/annum, and from these over 50% have treatment facilities (AISE, 1999). Due to the Dutch association of soap manufacturers (NVZ), more than 8 tonnes/annum is being used at about 25 sites in The Netherlands. The use at most of these sites is about 8–15 tonnes/annum. About 5 sites use between 20–30 tonnes/annum, from these at least 3 sites have their own industrial water treatment facility (CEFIC, 2001d).

For the exposure estimation, 3 alternative scenarios are regarded:

- It is assumed that the total amount (10,685 tonnes in 1997) is emitted into the municipal wastewater. From this, 10% (1,069 tonnes/annum) are used in the EU standard region. According to the TGD (Appendix I, Table. B3.3), the fraction for the local main source is 0.002 (i.e. 2.14 tonnes/annum) and the emission period 200 days/annum (10.7 kg/day). This scenario should reflect the situation for the majority of the sites.
- The second exposure scenario describes the exposure from large EDTA consumers. Dairy and beverage sites are known with a consumption of maximum 30 tonnes/annum. The TGD default values for the dilution model are used, which are possibly unrealistic for the largest sites. In order to avoid a chaining of worst-case assumptions, a consumption volume of 10 tonnes/annum appears to be appropriate for this scenario. The emission period is 200 days (TGD, Appendix I, Table B3.3). As a worst-case approach, no effective removal in treatment plants is assumed.
- For the third scenario, the same EDTA consumption as for the second (10 tonnes/annum) is regarded, but purification in a long-termed aerated biological treatment plant (LAS) reflecting the best available techniques is assumed (90% elimination, see Section 3.1.2.1).

Table 3.5 Data used for industrial detergents exposure scenarios and resulting local water concentrations

Scenario	1. Emission into municipal wastewater	2. Large dairy and beverage site	3. Large dairy and beverage site
Consumption	2.14 tonnes/annum=10.7 kg/day	10 tonnes/annum=50 kg/day	10 tonnes/annum=50 kg/day
Wastewater treatment	municipal (0% elim.)	no effective elim. (0%)	LAS plant (90% elim.)
Ceffluent	5.4 mg/l	25 mg/l	2.5 mg/l
$Clocal_{water}$	0.54 mg/l	2.5 mg/l	0.25 mg/l
$PEClocal_{water}$	0.64 mg/l	2.6 mg/l	0.35 mg/l

During a monitoring program in Germany, the EDTA emissions from two sites were investigated by measurements in the wastewater. At a fruit juice producer, the EDTA concentration was 5.3 mg/l and the daily load 2.3 kg. At a brewery, 49 µg/l were detected in the sewage, the load was 235 g/day. For the dairy (a site which produces whey proteins), an EDTA consumption of 180 kg/day is reported (Schlieckmann, 1996).

In the sewage of a brewery, EDTA was detected from 6 to 9 mg/l (1997). With the sewage stream, the annual emission is calculated to 3 to 4.5 tonnes (BASF, 1999).

Photochemicals

H_4EDTA, its sodium salt and the Fe(III)NH_4-EDTA complex are used in the following processing steps (Baumann, 1994; Photoindustrie-Verband, 1999):

- Bleaching: In the past, the bleaching of colour photographic film was accomplished with Fe(III)NH_4-EDTA, which oxidises the metallic silver present in the exposed image to the ionic form for removal or fixing by thiosulfate. Meanwhile EDTA is replaced by PDTA (propylenediamine tetraacetate) complexes.
- Fixing: The silver ions in the emulsion layer are removed by formation of soluble silver complexes.
- Bleachfix is a combination of both processes within one solution. The bleaching of colour photographic paper is still accomplished with Fe(III)NH_4-EDTA. Complexing agents in concentrations up to 56 g/l are applied. Meanwhile, the number of photolabs which have a separated bleach and fix instead of a bleachfix is very low.
- In different processing fleets, EDTA prevents the precipitation of calcium salts which would cause tarnishing of the photographic film or paper and incrustination of the device.

In 1999, 4,191 t EDTA were marketed to companies related to photoindustry. From several large companies, exports of formulations containing 805 tonnes EDTA are reported. Further exports from other companies (e.g. photo laboratories) may exist, and a certain amount of EDTA is used for other purposes than photography (Photoindustrie-Verband, 2001). The latter is not considered in the calculations, as no figures are available.

According to the TGD defaults, 80% of the applied EDTA is emitted via wastewater during processing (TGD, Appendix I, Table A3.9), the fraction for the main source is 0.05 and the processing period 300 days (Table B3.8). Because of the wide-spread use the 10 percentile rule can be applied. With a European consumption of 3,386 tonnes/annum, respectively a regional consumption of 339 tonnes/annum, this would lead to an emission of 13.5 tonnes/annum for the

main source. Compared with available monitoring data, these figures appear to be not appropriate for the EDTA assessment.

Data about the size of photofinishers are available for Germany and Switzerland. Annual emissions from 2.2 to 3.3 tonnes EDTA are reported for one Swiss plant (Baumgartner, 1994). In the wastewater of different German photo industry plants, EDTA was measured and the load was calculated. 9 different plants emitted EDTA amounts between 0.005 and 53 kg/day (Schlieckmann, 1994 b, 1996). These figures don`t reflect the present situation, as in the last years in bleaching baths EDTA was replaced by PDTA (propylenediamine tetraacetate) leading to lower EDTA releases.

Of more current interest are measurements from 1998/99: at two German plants emissions of 14.9 kg/day (production 7.5 million m^2 paper, the largest site in Europe) and 8.56 kg/day (production 3 million m^2 paper) were estimated from measurements in the wastewater (Photoindustrie-Verband, 1999).

In Germany, the EDTA consumption by the photoindustry was 355 tonnes/annum (1998), with the following distribution (Photoindustrie-Verband, 1999):

Table 3.6 EDTA consumption by the photoindustry in Germany

Photofinisher	190 tonnes/annum (54%)	Relevant point sources
Black and white	35 tonnes/annum (10%)	Very diffuse emission pattern
Minilabs	130 tonnes/annum (36%)	partially no wastewater

At least 95% of the European market is supplied with standard formulations (Photoindustrie-Verband, 2001). Technics and equipment are similar in European countries; therefore a representative exposure scenario can be based on the German market figures. The biggest European photofinishing plant presents 10% of the German finishing market (total 90 million m^2 paper). The second biggest one is already producing below 5 million m2, and most of the "average" labs below 2 million m^2 (Photoindustrie-Verband, 1999). For the exposure scenario, a plant with a production volume of 2 million m^2 appears to be appropriate. This site has an EDTA consumption of 2.2% (i.e. 4.2 tonnes/annum).

For large sites, a release factor of 67% was estimated (Boie, 1994). Thus, the emission of the model site is 2.8 tonnes/annum or (with a production period of 300 days/annum) 9.3 kg/day.

With the TGD standard scenario (wastewater flow 2,000 m^3/day, dilution 1:10), the resulting concentrations are

C_{eff}=4.7 mg/l
$Clocal_{water}$=0.47 mg/l
$PEClocal_{water}$=0.57 mg/l

Disposal

The bath residues are collected by disposal companies. There is contradictory information available about the final fate of the EDTA:

According to Boie (1994), the bath residues are either incinerated or evaporated and deposited.

Schlieckmann (1994a) states that the substance is generally emitted into the wastewater. EDTA concentrations up to 10 mg/l in the wastewater of disposal companies were detected.

In Germany, a large part of the residues are used by the cement industry for nitrogen oxide removal from fumes.

In the frame of the risk assessment, it was not possible to gain more information. Therefore, an exposure model based on the TGD default values is calculated:

European consumption:	3386 tonnes/annum
Regional consumption (10%)	339 tonnes/annum
Fraction recovered (TGD, App. I, Table A5.1)	0.2
Recovered amount in Europe	68 tonnes/annum
Fmain source (TGD App. I, Table B5.1)	0.2
No. of days	300 d/a
Recovered by main source	45 kg/day

C_{eff}=23 mg/l
$Clocal_{water}$=2.3 mg/l
$PEClocal_{water}$=2.4 mg/l

Existing regulations

In Germany, the use of EDTA in this field is regulated since 01/07/1993. In the wastewater of bleaching and fixing baths chelating agents which do not reach a DOC-elimination of 80% in 21 days are prohibited (Bundesanzeiger, 1994). However, the benefit of this regulation is limited as the substance is emitted via the washing water. Release factors of 50% (Schlieckmann, 1996) or 67% for large laboratories (Boie, 1994) were estimated.

There are efforts to reduce the EDTA emissions. With a voluntary engagement the German photo industry aims to reduce the EDTA consumption to about 118 tonnes/annum until the year 2000 (BMU, 1998). Thus a further reduction of the local concentrations is expected.

Textile industry

Textile dying and finishing have traditionally been a major market for chelating agents. Traces of metal ions in the fibres will cause a shade change in dyes unless a chelating agent is present. Processes like crosslinking of cellulose molecules (to produce easy care fabrics) and oxidative bleaching are supported when heavy metals are chelated with EDTA. Also catalytical damages of the fibers are prevented (AIS, 1987; Hart, 1987). Nowadays, EDTA is only used in textile finishing.

In 1999, 639 tonnes EDTA were used by textile industry. With an assumed EDTA content of 2% in the formulations, a total EU consumption of 31,950 tonnes/annum and a regional of 3,195 tonnes/annum formulation is estimated. In Appendix I of the TGD (Table B3.12), a fraction of 0.2 for the local main source is proposed.

From the European association of the textile finishing industry (CRIET) a survey on number and size of textile finishing companies for 5 EU member states is available (BASF, 2000). The size of the companies is expressed as the number of employees, and subdivided into categories. The search reveals that in most countries more than 50% of the market are covered by a few large sites. As an approximation, the TGD value is confirmed.

European consumption (1999):	639 tonnes/annum
Regional consumption (10 %)	63.9 tonnes/annum
Main source (f=0.2)	12.8 tonnes/annum
Number of operating days 300 d/a	42.6 kg/day
Emission factor 0.9	38.3 kg/day

C_{eff} (2,000 m^3/day) = 19 mg/l
$Clocal_{water}$ = 1.9 mg/l
$PEClocal_{water}$ = 2.0 mg/l

In Germany, the majority of the textile manufacturers do not use EDTA anymore. In 1993, from 11 consulted plants only 1 consumed 12 kg/a. From measurements in the wastewater of 6 further plants, daily releases of up to 1.68 kg were calculated (Schlieckmann, 1994b). In 1995, in the sewage of 7 plants loads of up to 4.1 kg/day were estimated (Schlieckmann, 1996).

In a creek downstream of a German textile manufacturer, an annual average concentration of 331 µg EDTA/l (maximum 530 µg/l) was measured (Hamm and Glassmann, 1994).

In the frame of the Joint Declaration on use reduction, The German EDTA consumption is relatively small. Thus, the German monitoring data are considered to be not representative for the EU scale.

Pulp and paper

Wood pulp is the most important raw material for paper production. It is produced from virgin fibre by chemical or mechanical means or by re-pulping of recovered paper. The European production of woodpulp is about 35 millions tonnes/annum, i.e. about 20% of the world total supply (IPPC, 2000).

In the pulping process the raw cellulose-bearing material is broken down into its individual fibres. The sulphate or kraft process accounting for ca. 80% of world pulp production is the most applied method of chemical pulping processes. The sulphite cooking process is based on the use of aqueous sulphur dioxide and a base–calcium, sodium, magnesium or ammonium. The production of sulphite pulps is much smaller than the production of kraft pulps. It is used in special purposes in papermaking. In mechanical pulping the wood fibres are separated from each other by mechanical energy applied to the wood matrix. Mechanical pulps have a low resistance to ageing which results in a tendency to discolour.

Bleaching agents are applied 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, generally with EDTA or DTPA (Hart, 1987; Baumann and Herberg-Liedtke, 1993; IPPC, 2000). EDTA is not fixed onto the paper, therefore the total use amount is emitted into the sewage.

The size structure of paper mills across Europe is unequal: From a total number of 1,064 mills, 311 mills have a production volume below 10,000 tonnes/annum, and 72 mills above 250,000 tonnes/annum (IPPC, 2000).

Different data are available concerning the EDTA application rate for hydrogen peroxide bleaching: Baumann and Herberg-Liedtke (1993) state 1.5-1.7 kg EDTA/t pulp. A survey of the Swedish Forest Industries Federation (2000) states an EDTA consumption between 0.45 and 1.65 kg/tonne pulp for 11 Swedish mills.

According to IPPC (2000), per ton pulp 0-4 kg chelators (EDTA or DTPA) are used in the kraft process, 0–3 kg/tonne pulp in the sulphite process, and 0–5 kg/tonne pulp in mechanical pulping. According to the Ministry of the Environment (1997), EDTA or DTPA are applied in amounts of about 5 kg/tonne pulp. For the exposure calculation, an EDTA application rate of 1.6 kg/tonne pulp is used.

The specific water consumption varies in a large range: Baumann and Herberg-Liedtke (1993) state a volume of 2-75 m^3/tonne pulp, depending on the type of paper. A survey of the Swedish Forest Industries Federation (2000) reports volumes between 17.3 and 155 m^3/tonne pulp at 11 Swedish mills, with an average of 76 m^3/tonne pulp. At 6 Finnish sites, the water consumption is 14.5–73 m^3/tonne pulp with an average 40 m^3/tonne (Ministry of the Environment, 1997). For the exposure calculation, a value of 40 m^3/tonne is used.

The available data on effluent flows reveal that the water consumption of pulp mills is much higher that the TGD default of 2,000 m^3/day. 11 Swedish sites with a production of 29,800-641,000 tonnes/annum have an effluent flow of 10,250–102,000 m^3/day (Swedish Forest Industries Federation, 2000). Because of the uneqal size structure, the exposure calculation is performed on the basis of EDTA and water consumption per ton pulp leading to PECs which are independent on the plants size.

Data about dilution while entering the receiving surface waters are available for 11 Swedish sites. From 11 sites, 5 release their sewage into rivers, with dilution factors of 4–660. 6 plants discharge into the sea, from the latter 4 have a diffusor equipment and 2 not (Swedish Forest Industries Federation, 2000). The TDG default value of 10 is chosen for modelling.

In Section 3.1.2.1, monitoring data for mills effluents are referred 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. However, 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, as a worst-case approach no elimination is assumed. Because of the high discharge flows it is estimated that pulp mills have no releases through municipal treatment plants. Therefore, two scenarios are calculated. (See **Table 3.7**).

Table 3.7 Data used for pulp and paper industry exposure scenarios and resulting local water concentrations

	Long-termed aerated biological treatment	**No effective treatment**
EDTA consumption	1.6 kg /tonne pulp	
Water consumption	40 m^3/tonne pulp	
Influent concentration	40 mg/l	
Elimination	90%	0%
Ceffluent	4.0 mg/l	40 mg/l
$Clocal_{water}$	0.4 mg/l	4.0 mg/l
$PEClocal_{water}$	0.5 mg/l	4.1 mg/l

During recycling of wastepaper, the deinking process is necessary for removing the dyes and various additives from the fibre. For bleaching of recovered pulp, EDTA is not used (IPPC, 2000).

Monitoring

In the sewage of 4 German paper mills, EDTA loads in the range from 0.16 to 2.24 kg/day were estimated from measurements (Schlieckmann, 1994b). In 3 further plants, 68-218 µg/l were detected in the sewage (Schlieckmann, 1996). Because of the low German consumption volume, these values are considered to be not representative for the European scale.

Kaluza et al. (1998) measured EDTA in a treatment plant dedicated to treat the sewage from a paper mill. With 50 separate samples, 18.0–28.0 mg/l (average 23.8 mg/l) were detected in the influent and 3.0–9.0 mg/l in the effluent. Sillanpää (1996) detected in 6 Finnish paper mill effluents 0.24–8.4 mg EDTA/l and 0.51–9.2 mg DTPA/l.

A survey among 11 Swedish paper mills (representing about 75% of the European EDTA consumption) refers measured EDTA concentrations before treatment of 20–40 mg/l for 2 plants and 3.7–25 mg/l after treatment for 5 plants. From site-specific EDTA consumption and effluent flow figures, influent concentrations between 4.7 and 41 mg/l can be calculated. Using site-specific dilution factors (default 10 at emissions into sea without diffusor and 100 with diffusor), Clocal values of 0.012–2.5 mg/l are calculated. At the site with the highest influent concentration (calculated 41 mg/l, measured 30-40 mg/l) a long-termed aerated biological treatment plant is available leading to a measured $C_{effluent}$ of 5-10 mg/l. For 2 further sites with Clocal of 2-2.5 mg/l, introduction of long-termed aerated biological treatment plants is planned (Swedish Forest Industries Federation, 2000).

The 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

According to the literature, EDTA was used in the galvanic and circuit boards industry in the following production steps:

- In the galvanic industry, chelating agents are a component of alkaline metal degreasing baths in concentrations of 2–4 g/l. EDTA is also used in electrolytic rust removal baths (Reichert, 1993).
- In gold plating electrolyts, concentrations of 30 g Na_4EDTA/l in one bath respectively 20 g Na_4EDTA/l and 2.5 g Cu-EDTA in a further bath are stated (Reichert, 1993). Na_4EDTA causes the total blocking of copper which would segregate simultaneously (Kreuter, 1976).
- EDTA is applied in copper electrolytes (no concentration reported). In baths for chemical copper plating, EDTA concentrations of 25 g/l, respectively 30 g/l are described, while with 2 measurements concentrations of 7.6, respectively 3.9 g/l were detected (Kreuter, 1976; Reichert, 1993).
- In nickel plating baths, Na_4EDTA is applied to bind other metal ions selectively (Kreuter, 1976).
- From time to time, the galvanised metals have to be removed from the electrical contacts. The respective baths can contain EDTA (Reichert, 1993).

Recently, in the European galvanic industry EDTA is exclusively used for the production of printed circuit boards, which are indispensable components in many kinds of electronic

equipment. EDTA (30-40 g/l) is mainly used in electroless copper plating, when copper is deposited on the board by catalytic reduction of complex copper compounds in the presence of formaldehyde and a variety of catalysts such as palladium, copper, or other metals. After pretreatment with electroless copper plating, the surfaces are inforced by applying a layer of copper using electrolysis; the latter process is performed EDTA-free (BASF, 1996b).

With a European consumption of 470 tonnes/annum and a mean content of 3.5%, 13,400 tonnes/annum formulations are used in Europe and 1,340 tonnes/annum in the model region. According to the TGD (Appendix I, Table B3.2), the fraction of main source is 0.4 and the release period 134 days/annum.

The number of circuit board producing sites in Europe is known, but not quoted here to keep confidentiality. The average EDTA consumption of one site is 31 tonnes/annum. For the exposure estimation, this figure is used as the most realistic one.

The TGD emission factor of 0.005 (Table A3.4) is not used, as it is not appropriate for chelators. As a worst-case assumption, 100% release into wastewater is taken.

Local main source	31 tonnes/annum
Emission period 134 days/annum	231 kg/day
Sewage flow 2,000 m^3/day	C_{eff}=116 mg/l
Dilution 1:10	$Clocal_{water}$=12 mg/l
PECregional=95 µg/l (see Section. 3.1.3.4)	$PEClocal_{water}$=12 mg/l

As EDTA is applied in high concentrations in galvanic baths, it can simply be regenerated. For this purpose, the complexed metals have to be removed by catalytical reduction or electro-chemical partition. Subsequently H_4EDTA is removed by crystallising at a pH of 1.6-1.8. The residual wastewater contains theoretically 100-200 mg EDTA/l (Reichert, 1993). However, suspended particles remain, thus the total EDTA concentration is about 1,500 mg/l. 97% of the EDTA can be recycled by this procedure. Further possible purification or EDTA recycling techniques like ion exchange and electric dialysis are described in the literature; however these techniques are not commonly applied (Erlmann, 1994). This process is directed in Germany (see below), however it is not known whether it is representative for the European situation.

In Germany, the EDTA application in the metal processing industry has been regulated since 01/01/1990 (GMBl, 1989):

- In baths for chemical copper plating and the rinsing baths, EDTA and its salts have to be recycled (the process is described above).
- In the wastewater from degreasing baths, baths for metal removing from the electrodes and nickel plating baths, EDTA is prohibited.

Because of this regulation, we assume that the emission data for German plants cited below are not representative for the European scale.

During a monitoring study in the wastewater of 3 German circuit board producers, the following concentrations presented in **Table 3.8** were detected (Reichert, 1993):

Table 3.8 Results of EDTA monitoring in the waste water of 3 German circuit board producers (Reichert, 1993)

Site	Production volume	H_4EDTA conc. (number of measurements)	Sewage flow
A	350 m^2/day	< 0.2 mg/l (2)	20 m^3/h
B	60 m^2/day	< 0.2-45 (mean 21) mg/l (5)	9 – 12 m^3/day
C	700 – 800 m^2/day	3 mg/l (1)	55,000 m^3/annum

As grab samples were taken for the measurements, the detected concentrations are highly variable.

In the sewage of 16 German metal treating plants, EDTA concentrations of < 0.1 to 6.3 mg/l were detected (Schlieckmann, 1994). Two years later, a pickling plant with a daily emission of 3.3 kg EDTA was identified. At 30 further plants, concentrations in the range of < 1 to 391 µg/l were detected in the sewage (Schlieckmann, 1996). The results reveal that EDTA has been replaced by most of the companies.

In an investigation about EDTA emitters into the Swiss river Wiese, a circuit board producer with a consumption volume of 1,950 kg/annum was identified. The EDTA emissions of this plant are not continuous. Due to the batch procedures, the baths are renewed in periods of 6 to 8 weeks, the emissions last one week in each case. The measured concentrations are max. 850 mg/l in the plants sewage, max. 4.8 mg/l in the municipal WWTP effluent into which the plants sewage is discharged, and max. 56 µg/l in the mouth of the receiving river Wiese (Rath, 1994). Since 1993 no EDTA is used by this plant (Schlieckmann, 1994).

Water treatment

Chelating agents are 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. For the preventive use, an amount of 1–5 kg Na_4EDTA/m^3 water is stated (Kreuter, 1976; Hart, 1987; AIS, 1987).

As no site-specific data have been provided by industry, the exposure cannot be calculated. However, we assume that the 215 tonnes EDTA yearly used in Europe for this purpose are widespread and will not lead to a high local exposure.

In Germany, poorly degradable chelating agents like EDTA in the wastewater from cooling systems of power plants and industrial processes as well as steam generators are prohibited (Bundesanzeiger, 1994).

Polymer and rubber production

EDTA is used in the production of Styrene Butadiene Elastomers (SBR) which are mainly manufactured by emulsion polymerisation (CEFIC, 2001a). EDTA is a sequestering agent for Fe(II)/Fe(III) ions in the initiator system. A typical recipe for the production of SBR contains 0.025 parts of Na_4EDTA (=190 g H_4EDTA) per 100 parts of polymer. Under the assumption that all EDTA will end up in the aqueous effluent of the SBR production, the main source producing 50,000 tonnes of SBR per year has an EDTA emission of about 9.5 tonnes H_4EDTA per year. With a production period of 300 days/annum (TGD, Appendix I, Table B1.14) the daily release is 32 kg.

Sewage flow 2,000 m^3/day	Ceff=16 mg/l
Dilution 1:10	$Clocal_{water}$=1.6 mg/l
PECregional=95 µg/l (see Section. 3.1.3.4)	$PEClocal_{water}$=1.7 mg/l

Oil production

A major problem encountered in oil field operations is the occurrence of scale both downhole and in pipelines. EDTA is being used in oil production in scale removal (CEFIC, 2001b). The cleaning process is applied discontinuously. In a typical well cleaning process the oil well is closed and treated with a cleaning formulation. In the cleaning process about 1 tonne of EDTA is used during a 24-hour period to clean the well. Subsequently the well would be started up again and run for about 1 year before the next cleaning process will be started. Such cleaning procedure would fit the "intermittent release" definition of the TGD (less than once per month and for not more than 24 hours).

During cleaning as much water is pumped into the well as oil is pumped out (typically about 1,000 barrels per day=158,000 l/day). This would result in an intermittent EDTA discharge from a typical well cleaning of 1 tonne of EDTA /day in 158,000 liter resulting in a EDTA concentration of 6.3 g/l.

In about 50% of the wells the discharge water is pumped into the oil reservoir to maintain the pressure resulting in a closed system with no emission of EDTA to the surface waters. This is becoming standard practice in all new wells / production platforms. At older platforms normally the spent cleaning liquids are being diluted further by combination with the discharge waters from the other operating wells. A typical platform would include about 10 wells. This results in a typical dilution factor of about 10 (depending on the number of wells) before emission. In a typical cleaning situation the intermittent EDTA concentration in the effluent would be 630 mg/l.

According to the TGD, Chapter "marine risk assessment", a dilution factor of 100 for discharges to a coastal zone may tentatively be assumed, which seems to be representative for a realistic worst-case. Additionally, for substances released from offshore platforms, a harmonised mandatory control system for the use and reduction of the discharge of offshore chemicals is already agreed within OSPAR. For this specific exposure situation within the EU legislation, the methodology proposed by OSPAR (CHARM-model) can be taken into consideration. It can be assumed that dilution is higher near offshore platforms than in coastal zones. Therefore we propose a dilution factor of 1,000 according to the CHARM-model. Using this dilution factor a PEClocal of 0.63 mg/l can be calculated.

In Western Europe 96% of oil production is 'off-shore' and about 4% is 'on-shore'. 'On-shore' situations are all closed systems where the discharge water is pumped into the oil reservoir to maintain pressure. In 'off-shore' situations the intermittent release of EDTA will be to the open sea.

Fuel gas cleaning

During fume desulfuration at coal power plants and waste incineration plants according to the Wellmann-Lord-process, SO_2 is adsorbed from a Na_2SO_3 solution, subsequently released and further processed. Heavy metal ions would catalyse the oxidation of the Na_2SO_3 to sulfate, this is prevented by chelating with EDTA (BASF, 1988). The EDTA containing solution is run in a circle. As a by-product, thiosulfate is formed which has to be removed from the circle. In a German power plant (which uses yearly 300 tonnes EDTA) a partial stream containing thiosulfate and EDTA is incinerated, thus there are no emissions into the wastewater (Hüsch,

1998). All known plants using the Wellmann-Lord-process do not release EDTA into the sewage (VGB, 1999).

By another process, nitrogen monoxide can be removed from fumes simultaneously with SO_2. With Fe(II)EDTA, NO forms the complex [Fe(II)(NO)EDTA], which is able to oxidise sulfite to sulfate, meanwhile NO is reduced to elementary nitrogen (BASF, 1988; Sada et al., 1984; Schrod et al., 1985; Heiting, 1984). This process was discussed earlier, but not commercially realised (VGB, 1999).

Disposal

From different uses, EDTA containing wastes come up from the industrial processes. From photoindustry it is known that minilabs are (partially) run wastewater-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 are several strategies for the waste treatment. The bath residues can be evaporated with subsequent incineration or deposition of the remaining solids. Monitoring data reveal that there are releases into the hydrosphere from disposal sites. Concentrations up to 10 mg/l (Schlieckmann, 1994a), respectively 0.69-1.78 mg/l, and respectively 1.6-4.3 mg/l for two further German sites were detected (Schlieckmann, 1996). The emission volumes were not determined. There is no information about the original EDTA use.

In Section 3.1.3.2 (photochemicals), an exposure model for residues from photoindustry was calculated resulting in a $C_{effluent}$ of 23 mg/l and a PEClocal of 2.4 mg/l. Because of the lack of data, the model was mainly based on TGD default values.

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.

$C_{effluent}$=23 mg/l
PEClocal=2.4 mg/l

Sediments

No monitoring data for sediments are available. The EDTA concentration could be modelled using the equilibrium partitioning method. As also no effect tests are available, a risk assessment for sediments would lead to identical PEC/PNEC ratios like for the aquatic compartment.

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 WWTPs

During an extended monitoring program, EDTA was measured in German municipal WWTP effluents (Schlieckmann, 1994; 1996). The number of samples from each plant varied from 1 to 10. In the following evaluation, presented in **Table 3.9** the results are sorted into different concentration ranges. The highest concentration is considered when several samples were taken at one site.

Table 3.9 EDTA measured in German municipal waste water treatment plant effluents (Schlieckmann, 1994; 1996)

Period	1993	1994-1995
< 60 µg/l	13	25
60 – 600 µg/l	25	25
> 600 µg/l	1	5
total number of WWTPs	39	55

The EDTA in the WWTP with the highest concentration in 1993 has probably its origin in a photography manufacturer (Schlieckmann, 1994). The emission sources into the WWTPs with the highest concentrations in the period 1994-1995 are not reported.

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 (Kari, 1994).

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. Most locations were sampled over 1 or 2 years within the 3-year period (Hamm and Glassmann, 1994-1996). Presented in **Table 3.10**, the results are sorted in concentration ranges, the highest concentration at each location found in the 3 years was considered.

Table 3.10 EDTA measured in German surface waters from 1993 to 1995 (Hamm & Glassmann, 1994-1996)

Maximum concentration [µg/l]	Number of sites
< 6	21
6-60	90
> 60-500	30
> 500	2
total	143

The highest detected concentration in a creek was 2,000 µg EDTA/l, however this was a singular result (simultaneously a high NTA concentration was detected). In the range between 100 and 1,000 µg/l the substance was detected more frequently. The following conclusions can be drawn from the measurements:

- From 1991 to 1995, the EDTA concentrations in German rivers decreased by about 23% (Hamm and Glassmann, 1996), and from 1991 to 1998 by 33% (Nitschke and Glassmann, 1999). The decrease is caused by the German EDTA declaration (see Section 2).
- The EDTA concentrations in the river Rhine at Bimmen (which can be regarded as representative for large rivers) were in the range between <1 and 19 µg/l (1993-1995). The average was 9.5 µg/l and the yearly load 697 tonnes in 1995.
- The concentrations in the Ruhr at different localities were <1–103 µg/l (1993-1995). This river can be regarded as representative for a densely populated region in Germany. Drinking water is produced there by bank filtration.

– The highest EDTA pollution was detected in small rivers or creeks. Often the maximum concentrations alternate with negative detections. This indicates that the pollution is caused by one or few sources with intermittent releases.

Because of the large number of measurements, the data reported by Hamm and Glassmann (1994-1996) give a good overview to the actual EDTA pollution in Germany. However it should not be regarded as representative for the European scale, as

1. The German EDTA consumption (1995: 4,030 tonnes/annum) is lower than the European average (1995: 29,560 tonnes/annum; see Section 2), and
2. In the years since 1991 (in conjunction with the joint declaration) strong emission sources have replaced EDTA by other complexing agents.

In 1994, EDTA was measured by RIWA (1995), the concentrations were 4.1-17.6 (mean 8.69) µg/l in the Rhine at Lobith and 3.5-11.4 (mean 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 (RIWA, 1996-1998).

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 (Schick, 1994). The lake is an important reservoir for drinking water.

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 (Kari, 1994). For the interpretation it has to be considered that the EDTA consumption also in Switzerland (ca. 200 tonnes/annum) is below the European average (ca. 30,000 tonnes/annum). Thus in some other countries the concentrations should be higher.

In the river Odiel near Huelva (Spain) EDTA was measured at two sites (Kowalik and Einax, 2000). 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.

3.1.3.3 EDTA metal complexes in the hydrosphere

In natural waters, both natural and anthropogenic heavy metals are present, which are able to form complexes with EDTA. The environmental risk assessment is confronted with some problems (e.g. photolysis of complexes, remobilisation of sediment-bound metals, effects of heavy metals) which are related to the speciation under environmental conditions. Therefore the main features of the EDTA complex chemistry have to be elaborated.

3.1.3.3.1 Stability of EDTA complexes

(See Ringbom and Wänninen, 1979).

The most important property of EDTA is to form complexes (usually 1:1-complexes) with multivalent metal ions. The stability of these complexes is usually described by the mass action law:

$$K_{MeZ} = \frac{[MeZ^{(m-n)-}]}{[Me^{n+}] \cdot [Z^{m-}]}$$

with $[MeZ^{(m-n)-}]$ the concentration of the metal complex
$[Me^{n+}]$ the concentration of the metal ion
$[Z^{m-}]$ the concentration of the $EDTA^{4-}$ anion (active complexing species)
K_{MeZ} the stability constant of the metal complex

The stability constants for the most important metal ions are given e.g. by Martell and Smith (1974). However, the distribution of the specific metal complexes in the hydrosphere cannot be derived from this equation, because of the following reasons:

- In aqueous solution, EDTA can in principle occur as a neutral molecule or as ions with different charges. With increasing pH, ionisation increases and the formation of complexes is enhanced. There are high proportions of $EDTA^{4-}$ only at pH values above 10 or 11.
- Metals can form unsoluble hydroxydes (especially in alkaline medium), phosphates and carbonates, complexes with other ligands (e.g. humic substances) or can be adsorbed onto suspended solids, which decrease the concentration of free metal ions. Some of these reactions are also dependent on pH.
- Both effects are accounted by the conditional complex-formation constant. These constants pass for all metal complexes through a maximum as a function of pH value.

The metal with the highest complex-formation constant is Fe(III), and iron is the most frequent heavy metal in river water. This would suggest that the major product formed under environmental conditions is the Fe(III)EDTA complex. Nevertheless, studies on the EDTA speciation in surface waters (see below) reveal that no significant amounts of FeEDTA are present in the thermodynamic equilibrium state, as unsoluble $Fe(OH)_3$ and Fe(O)OH are formed which are adsorbed or form colloids.

3.1.3.3.2 Speciation of EDTA metal complexes in the hydrosphere

EDTA monitoring generally does not differentiate between the individual species (acid, salts, metal complexes) in the environment. During sample preparation, the metal complexes are destroyed, and the sum of all different species is determined which is generally referred as H_4EDTA. A limited number of publications are available in which individual EDTA species are identified:

- Some EDTA species, especially the iron complex, are photolysable (see Section 3.1.2.1). The photolysable fraction can be determined by measuring the EDTA content of a sample before and after irradiation. Kari (1994) determined this fraction in wastewater and in a river (see Section 3.1.3.3.6).
- Nowack et al. (1997) estimated the speciation in river water and an aquifer by a combination of experimental methods (e.g. voltametry) and equilibrium calculations (see Section 4.1.1.4).

Another way to estimate the EDTA speciation is model calculations which describe the state of thermodynamical equilibrium. Several investigations are available.

Gardiner (1976) investigated the influence of water hardness to the complexation of trace metals in a model system with few components. The extent of complexation of Cd with different EDTA

concentrations was calculated. In the presence of 0.1 µg Cd/l and 100 mg Ca/l (which are typical concentrations in rivers), the concentration proportions of Cd-EDTA (related to total Cd) are presented in **Table 3.11**.

Table 3.11 Extent of complexation of Cd at different EDTA concentrations (Gardiner, 1976)

[EDTA]	[Cd-EDTA]:[Cd_{tot}]
1.46 µg/l	67%
14.6 µg/l	95%
146 µg/l	100%

As the cadmium concentration is increased, the ratio [Cd-EDTA]:[Cd_{tot}] begins to decrease only until the EDTA concentration is approached and then exceeded. The results are virtually independent of pH value in the range of 6-8. The author concluded that, despite the competitive effect of calcium in hard water, most of the important trace metals would be complexed by EDTA.

The same author investigated the complexation of copper in the presence of bicarbonate ions. With an increasing pH, the Cu-EDTA concentration is decreasing, and $CuCO_3$ (dissolved complex) and $CuOH^+$ are formed. A similar effect was found for iron. These results reveal that EDTA is in competition with other anions.

With a more complex model, the chemical interactions and the competition between trace metals and different constituents in natural waters were investigated (Vuceta and Morgan, 1978). The fresh water model considered the following components:

- the major cations Ca, Mg, K, Na
- the trace metals Pb, Cu, Ni, Zn, Cd, Co, Hg, Mn, Fe
- the inorganic ligands CO_3, SO_4, Cl, F, Br, NH_3, PO_4, OH
- the organic ligands EDTA, citrate, aspartic acid, histidine, cysteine
- the adsorbant SiO_2 to represent suspended solids.

The concentrations of the metal-EDTA complexes were calculated as a function of the EDTA concentration. The following results, presented in **Table 3.12** are taken out of a graphic.

Table 3.12 Chemical interaction and competition between EDTA, trace metals and different natural water contituents

Me	Me_{tot} [µg/l]	MeEDTA : Me_{tot} with 30 µg EDTA/l [%]	MeEDTA : Me_{tot} with 300 µg EDTA/l [%]	MeEDTA : Me_{tot} with 3 mg EDTA/l [%]
Cd	110	0	2	100
Co	6	0	8	100
Cu	60	4	70	100
Fe	560	0	0	45
Hg	0.2	0	0	33
Mn	170	0	0	0
Ni	20	20	90	100
Pb	20	3	70	100
Zn	6.5	0	10	100

Additionally, Ca (16 mg/l) and Mg (4.1 mg/l) were considered, the pH value was 7. The proportions of the MeEDTA complexes (%) listed in the table are related to the total metal concentrations (Me_{tot} is the sum of dissolved complexed and uncomplexed ions, and the adsorbed fraction). Hg(II) and Fe(III) are only partially complexed at very high EDTA concentrations. Mn remains precipitated as MnO_2.

The concentrations of these components were taken from publications from 1966 and 1963, respectively. In **Table 3.13**, their values are compared with recent measured concentrations in some rivers (all values are yearly averaged, [µg/l]):

Table 3.13 Metal concentration used by Vuceta and Morgan (1978) compared to monitoring values (all values are yearly averaged [µg/l])

Metal	Vuceta and Morgan (1978)	Elbe at Schmilka (1994)*	Rhine at Lobith (1994) **	Ruhr at Essen (1995) ***
Cd	110	0.16	0.1	0.2
Co	6	nd	nd	nd
Cu	60	9.1	5	12
Fe	560	nd	1,110	670
Hg	0.2	0.31	0.03	nd
Mn	170	200	70	71
Ni	20	7.0	4	nd
Pb	20	4.9	4	nd
Zn	6.5	43	24	48

nd not determined
* Schmilka is near the German-Czech frontier. Source: Arge Elbe (1995)
** Lobith is near the German-Dutch frontier. Source: RIWA (1995)
*** Source: AWWR (1996)

It is obvious that the cadmium concentration used by Vuceta and Morgan is unrealistically high compared with the recent, but not with the former situation. More than 15 years ago, the Cd concentrations in the Rhine were one hundred times above the recent levels (Kerdijk and Salomons, 1990).

The results at the mean concentration of 300 µg EDTA/l reveal that cadmium is not complexed to a high extent. This metal competes only in a low extent and the proportions for the other metals should not change significantly if the Cd concentration is changed. This result should be valid for both the present and the past Cd concentrations.

In the model, significantly higher concentrations of Cu, Ni and Pb (those metals which are preferably complexed) are used, and the Zn concentration is lower than measured in the rivers. However, these deviations may be in the range of the variations in different real surface waters. In the case of lower concentrations of Cu, Ni and Pb, their complex proportions should be in the same range.

A model calculation performed by van Dijk-Looyaard et al. (1990) resulted in the following distribution of metal species, presented in **Table 3.14**, related to the total EDTA and the total metal concentration.

Table 3.14 Metal complexation according to model calculations (van Dijk-Looyaard et al., 1990)

Metal	[Me-EDTA]/[EDTA] (%)	[Me-EDTA]/[Me] (%)
Zn	2.1	0.5
Ca	2.0	< 0.01
Fe	0.1	0.03
Cu	1.1	2.4
Cd	0.01	1.0
Ni	94.4	76.4

This calculation was based on an EDTA concentration of 20 µg/l, a pH of 7.9, and the metal concentrations occurring in Maas water (values not reported). Ni ions are complexed to the major part, and the major part of the EDTA is available in form of the Ni complex. This may be an explanation for the unusual behaviour of Nickel, which is the only metal which was to a slight extent remobilised by EDTA even under anaerobic, sulfidic conditions (see Section. 3.1.3.3.7).

Similar results are reported from a model calculation by Hennes (1989).

Lorenz (1997) carried out speciation calculations which were accompanied by corresponding experiments: in order to check the remobilisation of heavy metals by EDTA in a well defined system a quartz matrix, representing the sediment body, was spiked with pure metal compounds (sulfides, oxides and basic carbonates of Zn, Cu and Pb) in a contamination degree of 10,000 mg heavy metal per kg of the quartz matrix.

The experiments showed that regarding sulfides, oxides, and basic carbonates of lead, copper and zinc, EDTA achieved a nearly stoichiometric remobilisation of the bound heavy metals. A comparison of these experiments with calculations showed, that, in most cases, a carbonatic solid phase was generated as the solubility determining solid. This phase, in fact, was remobilised by EDTA to a degree of 100%. The effective heavy metal concentration in the aqueous phase, which was analytically determined, was very well confirmed by the calculations with a deviation of only 1-2%. According to the calculations the experimental measurable heavy metal concentration is a multiple sum which mainly consists of the EDTA-species, the metal carbonato species and, in the case of zinc, the free metal cation. In all cases EDTA was completely bound to the heavy metal. Depending on the metal the measurable heavy metal concentration in the aqueous phase was caused to a different extent by EDTA (> 90% regarding Pb and Cu compounds, 10-25% for Zn-compounds) and increased thereby the heavy metal concentration stoichiometrically.

These speciation calculations were performed by an actual version of the AWASANT4 programme, which was developed by Eberle (1989) taking into consideration the major cations and anions including carbonate, Pb, Cu, Zn, EDTA and the species formed by these constituents.

For the sulfides, it was shown in a detailed experiment with PbS as example, that even traces of oxygen cause a partial oxidation of the sulfide which leads via formation of non-sulfidic compounds to a nearly stoichiometric remobilisation (97-102%) of lead to be achieved by EDTA. The compounds formed were $PbCO_3$, elemental sulfur, and sulphate which were analytically detected; but, no formation of hydrocerrussite ($Pb_3(CO_3)_2(OH)_2$) was observed, on the other hand.

The result of these studies which are valid for natural fresh waters (not for sea water) can be summarised as follows: At the thermodynamic equilibrium, the complex formation is selective. The most preferred metal being complexed is Ni, followed by Cu, Zn, or Pb. The succession of the latter is strongly dependent on the water-specific conditions. At low EDTA concentrations, almost all of the EDTA is bound to Ni. With increasing EDTA concentrations, other metal ions are complexed successively. With EDTA concentrations exceeding the heavy metal equivalents, the Ca-complex is formed. In the thermodynamic equilibrium, there is no uncomplexed EDTA in the hydrosphere.

It has to be noted, however, that in the investigations cited in this Section degradation processes as well as the kintetics of metal exchange reactions (see below) are generally not taken into account. The speciation in wastewaters is quite unequal (see Section 3.1.3.3.5). EDTA is emitted as complex with Ca or heavy metals like Fe. Because of the low metal exchange reaction constants of metal exchange and degradation processes (e.g. photolysis of the iron complex), in surface waters the thermodynamic equilibrium is only approximately reached.

3.1.3.3.3 Exchange reactions of metal complexes

Usually EDTA is emitted as metal complexes with speciation patterns different from those estimated for river waters at thermodynamic equilibrium. Therefore, metal ion exchange reactions occur.

The exchange kinetics of Fe(III)EDTA with other cations were studied under the conditions of natural river water. Fe(III)EDTA was added to a sample of river water, and its decrease as a function of time was determined. The test reveals that Fe is outcompeted by other cations, preferably with Ca and Zn. The dissociation of the Fe complex appeared to be the rate-limiting step for the exchange reaction, with a first-order rate constant of $4 \cdot 10^{-7}$ s^{-1}, corresponding to a half-life of 20 days. The exchange of Zn(II) with Ca-EDTA is much faster with a half-life of 2 hours (Xue et al., 1995).

The stability of the Fe(III)EDTA against ion exchange was tested in water of the Swiss river Glatt. The decrease of the Fe-complex in the dark (to prevent photolysis) was estimated by determination of the photolytically unstable EDTA part (for the method see Section 3.1.3.3.6). In the river water, a half-life for the ion exchange of 17.5 days was estimated (Kari, 1994).

The Fe(III)EDTA complex is important for the exposure assessment because its instability against photolysis (see Section 3.1.2.1). As predicted by model calculations cited above, no Fe(III)EDTA is present at the thermodynamic equilibrium. However, significant amounts of the EDTA are emitted as Fe-complex. As its metal ion is exchanged only slowly, the equilibrium speciation may not be reached within the time scale of the river flows. Significant EDTA amounts will be degraded by photolysis under favourable conditions.

3.1.3.3.4 Effect on heavy metals in treatment plants

The effect of EDTA on the fate of Cd was studied in a semi-batch activated sludge reactor (Huang and Kao, 1981; Kao et al., 1982). Cd (2 mg/l) and variable amounts of EDTA were added into synthetic wastewater. If no EDTA is added, Cd accumulated on the sludge. When EDTA was present concurrently, the accumulation was drastically decreased: The amounts of accumulated Cd were 5.7, 0.8, 0.24 and 0.13 mg Cd/g sludge, respectively, for Cd/EDTA molar

ratios of 1:0, 1:1 (i.e. 5.2 mg EDTA/l), 1:5, and 1:10. When Cd was pre-accumulated, and then EDTA added, the major part of the adsorbed Cd was removed.

Further investigations on the effect of EDTA to the adsorption of heavy metals onto activated sludge used unrealistic high concentrations of EDTA and heavy metals; therefore they are not used in this risk assessment.

The cited investigation is interpreted as follows: if heavy metals without chelating agents reach a WWTP, significant amounts would be adsorbed onto sludge and subsequently, if the sludge is applied as fertiliser, would reach agricultural soils. The presence of EDTA causes a higher tendency of the metals to the water phase, the agricultural soil is less contaminated, and instead of this the metal (in form of the EDTA complex) is emitted into the hydrosphere. The strength of this effect is strongly dependent on the EDTA concentration.

3.1.3.3.5 Speciation of EDTA in wastewater

Because of the ubiquitary presence of metal ions, it has to be assumed that EDTA is always emitted as metal complex, although precise information as to which metal is bound is not available. An approximation can be tried by regarding the technical uses. The use of EDTA can be divided into 3 categories:

1. Prevention or dissolving of calcareous precipitations, e.g. applied in food and beverage industry. The complexing agents are released preferredly as Ca-complex, however traces of heavy metals are ubiquitous and thus complexed.
2. Sequestering of heavy metal ions. Metal ions can catalyse chemical reactions thus disturbing technical processes, e.g. heavy metals decompose peroxide which is needed for pulp bleaching. Sometimes the complexing agent is (related to heavy metals) applied to overstoichiometric amounts. From the Kraft pulp process, per ton pulp about 280 mmol heavy metals (sum of Cd, Pb, Cu, Cr, Ni, Zn) and 5.5 mol EDTA are discharged (IPPC, 2000). In the sewage from those industries, the complexing agents are expected to be emitted as a mixture of both Ca- and heavy metal complexes.
3. Use as metal complex, e.g. in the photo industry, the iron complex is used, thus EDTA is mainly emitted as Fe-complex.

When complex-containing wastes are mixed with other wastewaters, the metal composition changes thus leading to metal exchange reactions. The Ca-complex is relatively unstable (see above), the Ca ion is rapidly exchanged with other heavy metal ions being present in the wastewater. Strong sources may emit the Ca-complex, if few heavy metals are present. The thermodynamical equilibrium is influenced by many parameters: beside the technical use, parameters like pH, redox potential, the trace metal composition which may vary with the regions etc. In treatment plants, a combination metal exchange reactions and (with favourite conditions) degradation takes place. Therefore, in the effluent always an incessant variable mixture of different metal complexes is present. In the receiving surface waters, in almost every case a surplus of heavy metals is present, leading to a further exchange of Ca.

In treatment plants, phosphate is often precipitated with Fe(III) salts. Because of the high iron concentration, the very high stability constant of the Fe(III)EDTA-complex and the relatively low pH (locally, upon addition of iron salts), Fe(III)EDTA-complex can be formed and emitted (Xue et al., 1995). This is confirmed by the investigation of Kari (1994), who detected an

increasing part of photolytically unstable EDTA species (i.e. Fe(III)EDTA) in a WWTP effluent (see below).

3.1.3.3.6 Photostability of EDTA species in wastewater and rivers

In the hydrosphere, the only relevant degradation pathway is photolysis, especially of the iron complex (see Section 3.1.2.1). For the exposure assessment, it is important to differentiate between photolytically stable and instable EDTA species. A method to perform this differentiation was developed by Kari (1994). Wastewater samples from three Swiss treatment plants were irradiated with sunlight or a Hg-lamp with a broad emission spectrum for 2 hours until no further change of the EDTA concentration was observed. The photolytically unstable part is the difference between the EDTA concentrations before and after the irradiation. The results are:

- In the treatment plant of Niederglatt, a relatively high part (about 50%) of the EDTA in the influent was photolytically unstable. This is interpreted by the fact that EDTA is discharged as Fe(III)-complex by the photo industry in the catchment area. In the effluent, about 80% of the EDTA was unstable, and this is interpreted by complex change reactions caused by the application of iron salts for phosphate elimination.
- In the treatment plant of Opfikon, in the influent is about 50% of the EDTA unstable, while in the effluent this part is only slightly increased. The author concluded that the photolytically stable part in the influent is composed by (heavy) metal complexes with a high complex constant, which undergo ion exchange reactions only slowly.
- In the treatment plant of Uster, which purifies mainly household wastewater, the unstable part is only 20-25% in the influent and 30-40% in the effluent. The cause of these low values is not clear.

The same experiment was performed with water of the Glatt which is the receiving river of the above mentioned WWTPs. The total EDTA concentration was 26.8 µg/l, from this 8.8 µg/l (=33%) are photolytically unstable (Kari, 1994). Probably a part of Fe(III)EDTA was photolytically degraded before sampling.

3.1.3.3.7 Influence on the partitioning of heavy metals in sediments and water

In several model experiments, the influence of EDTA on the partitioning of heavy metals adsorbed onto sediments was tested. Several studies using EDTA amounts far above the environmental relevant concentrations are not cited here.

In a mobilisation experiment, 1 g of river sediment containing 1.7 g Zn/kg and 0.5 g Cu/kg was shaken with 1 l of Na_2H_2EDTA solutions with different concentrations. Zn was remobilised with 10 mg Na_2H_2EDTA/l, while Cu was only mobilised with 100 mg Na_2H_2EDTA/l. With 1 mg Na_2H_2EDTA/l, no significant desorption was found (Müller and Förstner, 1976).

During an extensive study, both adsorption of heavy metals onto river sediments and remobilisation of adsorbed metals with uncomplexed EDTA were examined. With Rhine sediment and artificial Rhine water (containing only anorganics) at a pH of 6.5, the adsorption of Cd and Zn is almost unaffected by $\leq$ 250 µg EDTA/l. Increasing the pH to 8.5 however, only a little amount of EDTA (50 µg/l) is needed to prevent substantial amounts of the metals from adsorption. In a similar experiment with Elbe sediment suspended in natural Elbe water at pH

7.8, the effects became noticable at EDTA concentrations > 100 µg/l. In the experiment with artificial water (representing a very clean river system) the effect of EDTA becomes noticeable at much lower concentrations compared with the more realistic experiments representing present-day conditions of surface waters (Kerdijk and Salomons, 1990).

Similar effects were observed in the experiments in which the remobilisation of metals from sediments was studied by the same authors. It was shown that EDTA addition affects the remobilisation of the metals. An EDTA concentration of $\geq$ 50 µg/l influences the remobilisation of adsorbed Cu and Zn. Further experiments show that the adsorption process is not completely reversible. After the initial adsorption the metals become more strongly attached to the sediments with time. After equilibration over a 2-week period, the increase in dissolved Cd and Zn is lower compared with the increase in the adsorption experiments.

Based on the experimental results, a computer model was run simulating the concentrations of dissolved metals in the river Rhine at Lobith with various fictitious EDTA concentrations. In **Table 3.15**, the real and the calculated dissolved metal concentrations [µg/l] are given (Kerdijk and Salomons, 1990):

Table 3.15 Comparison between modelled and measured concentrations of dissolved metals [µg/l] in the river Rhine at Lobith (Kerdijk & Salomons, 1990)

Metal		Cd	Cu	Ni	Pb	Zn
Real concentration	dissolved	0.032	3.0	3.2	0.45	11
	total	0.118	5.3	4.3	4.2	47
Calculated dissolved concentration	without EDTA	0.031	2.8	3.1	0.46	11
	with 100 µg EDTA/l	0.044	4.6	3.9	0.92	20

The results reveal that the heavy metal ion concentrations are considerably increased when EDTA is present.

A further study on the effects of metal solubilisation was conducted by Gonsior et al. (1997). A system of sediment and water from Rouge River (USA) was amended with different concentrations of Na_2H_2EDTA and shaken in the dark at 23°C for 28 days to allow equilibration. The metal concentrations were analytically determined. A no observed effect level (NOEL) was statistically determined to identify the EDTA concentration below which the solubilisation of metals did not enhance. The NOELs were 120 µg H_2EDTA/l for Ni, 180 µg/l for Co, 290 µg/l for Cu and Zn, 880 µg/l for Cd and Fe, and 2,300 µg/l for Pb, respectively.

An extended study on heavy metal remobilisation by EDTA from 8 natural lake and river sediments was performed by Lorenz (1997). Bottom-layered sediment bodies were overflown by artificial river water containing 390, respectively 1,600 µg H_4EDTA/l (i.e. 1.34, respectively 5.37 µmol/l), and the increase of heavy metals in the water phase was detected. During the test time (up to 42 days) about 30% of the EDTA degraded, probably by photolysis. Typical concentration patterns specific to each element were found, which generally were independent of the choice of sediment.

Under aerobic conditions (8 mg O_2/l) a 2 mm deep oxic sediment layer developed out of which mainly Zn was remobilised (2-5 µmol), while with Cd, Cu, Ni and Pb concentrations only from 0.1 to 0.3 µmol/l were detected. The remobilisation yield was nearly stoichiometric, the equilibrium was reached after 20 to 40 days.

Anaerobic conditions were received by overflowing the sediment with oxygen-free water. No substantial remobilisation of the toxic metals Pb, Cd, Cu and Ni was observed (the only exception is Fe, which is reduced to Fe[II] and remobilised). This is explained by formation of sulfide which forms heavy metal salts with an extreme low solubility. Thus, in nature even highly loaded sediments cannot emit heavy metals as long as they are burried in deeper sediment layers. However, if anoxic sediment layers come into contact with oxygen (naturally this occurs by whirling up during high water flows or by shipping traffic), sulfide is oxidised to sulfate and the metals are again available for remobilisation.

The author concludes that the extent of remobilisation is not primarily determined by the complex formation constants. Higher influences have the sediment load and the form of binding of the metals (Lorenz, 1997).

The influence of EDTA on the heavy metal concentrations was studied for the river Rhine by comparing the concentration fluctuations. In 1993, the heavy metal concentrations (sum of Cd, Cr, Cu, Hg, Ni, Pb, Zn) were in the range of 0.42 to 0.99 µmol/l, while EDTA was in the range of 0.02 to 0.04 µmol/l. The fluctuation of the heavy metal concentrations is greater than the range of EDTA concentrations. This underlines that EDTA has no visible impact on remobilisation under the conditions of the river Rhine (Potthoff-Karl et al., 1996).

The influence of EDTA on the complexation capacity of different waters was studied by Kowalik and Einax (2000). With four kinds of filters with different pore size a molecular-size fractionation was conducted, and the metal content in the filtrates was analysed. The fractionation allowed separation of different complexing substances like humic and fulvic acids, and complexing agents like EDTA. The samples were from a wastewater of a German treatment plant (EDTA 0.77 mg/l in influent and 0.70 mg/l in effluent) and water from a Spanish river (EDTA 2.46 and 0.60 mg/l). The results reveal that the fraction of EDTA complexation from the total complexing capacity in the 4 samples was 0.15-1.2% for Zn, 0.75%-7.8% for Cd, and 0.03-0.15% for Cu. The complexation of the metals was mainly determined by organic substances with a high molecular size like humic and fulvic acids or amino acids. The heavy metal concentrations, however, were extremely high in most samples; thus it is questionable whether the results are representative for “typical” surface waters.

Summary

We interpret the remobilisation studies as follows: The presence of EDTA in environmental relevant concentrations can cause an increase in soluble levels of heavy metals. Two mechanisms have to be distinguished:

1. There is a tendency to prevent the adsorption of recently emitted heavy metals onto sediments and suspended solids. Without strong complexing agents like EDTA, a lower fraction of these metals would remain in the aqueous phase. Simultaneously, sediments and suspended matter would be higher contaminated.
2. There is a tendency to remobilise the metals from highly loaded sediments which remain from high metal emissions in the past. Simultaneously, the highly loaded sediments would be relieved in the course of time.

For the evaluation of the remobilisation process, the following topics need to be considered:

- EDTA always occurs as metal complex in the hydrosphere. In German rivers, heavy metal concentrations in the order of range of 10-20 µmol/l (predominantly Fe and Mn) are detected. The stoichiometric EDTA equivalent is 2.9-5.8 mg/l. In most rivers, the EDTA

concentration is lower. Therefore, all EDTA is bound onto actually emitted heavy metal, and there is no free EDTA available to remobilise metals from sediments. Only metal exchange reactions may occur.

- In remobilisation tests with freshly adsorbed heavy metals, some metals begin to remobilise when the EDTA concentration exceeds a range of about 50 to 100 µg/l.
- Old highly loaded sediments remain in deeper (anoxic) sediment layers. Remobilisation from the deeper layers is limited by formation of nearly unsoluble metal sulfides. Only if the sediments are whirled up during high water flows, a significant increase of heavy metal abundance in the water phase can occur.
- The more time has gone since the reduction of high metal emissions, the lower is the probability that these old sediments come into contact with the river water being available for metal remobilisation.
- 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.

It can be concluded that significant remobilisation processes can only occur in extreme cases, i.e. when high EDTA amounts are released. This leads to an increase of metals with high conditional complex-forming constants. In this case they are completely complexed with EDTA. Simultaneously, the sediments are deloaded.

Further investigations dealing with the mobility of heavy metals during bank filtration are cited in Section 4.1.1.4.

3.1.3.4 Regional exposure

For the regional exposure assessment it is assumed that the total EDTA consumption volume is emitted into the environment, as only in rare cases EDTA waste is deposited or incinerated. In some industrial treatment plants, the substance is partially eliminated. However, the fraction discharged in those plants is not known, thus it is not considered here. To compensate the latter, releases by EDTA producers are not considered.

In 1999, 34,546 tonnes EDTA were used in Europe. From this, 5,592 tonnes were applied in acriculture, which is released into soils. The rest (28,954 tonnes/annum) is assumed to be released into the hydrosphere.

Following the investigations of Kari (1994; see Section 3.1.3.3.6), it is assumed that 50% of the EDTA is emitted into the hydrosphere as Fe-complex. While the other metal species have to be considered as persistent in the hydrosphere, Fe(III)EDTA undergoes both photodegradation (see Section 3.1.2.1) and ion change reactions with other metal atoms leading to persistent EDTA species (see Section 3.1.3.3.3). The constant for each reaction is 0.035 d^{-1} ($t_{1/2}$=20 days). To take account the latter process, the initial Fe(III)EDTA concentration available to photolysis is lowered by a factor of 0.5. Thus it is assumed that 25% of the EDTA releases into the hydrosphere are degradable with a half-life of 20 days, while 75% would be persistent.

Furthermore, the following substance-specific parameters are used, as presented in **Table 3.16**.

Table 3.16 Substance-specific parameters used in the regional exposure estimation

Parameter	Value	Remark
$kdeg_{water}$ [d^{-1}]	0.069	Fe(III)EDTA decay
$kdeg_{water}$ [d^{-1}]	0	Other complexes than Fe
$kbio_{sediment}$ [d^{-1}]	$2.3 \cdot 10^{-4}$	$t_{1/2}$=3,000 days; see Section 3.1.2.1.2
$kbio_{soil}$ [d^{-1}]	$2.3 \cdot 10^{-3}$	$t_{1/2}$=300 days; see Section 3.1.2.1.2
Kp_{susp} [l/kg]	75	See Section 3.1.2.1.3
Kp_{sed} [l/kg dw]	75	See Section 3.1.2.1.3
Kp_{soil} [l/kg dw]	75	See Section 3.1.2.1.3

In accordance to the TGD, 10% of the European releases are taken for the regional and 90% for the continental scenario. In **Table 3.17**, EDTA release amounts and the resulting PECs of the EUSES calculation are presented (See Euses calculations as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it).

Table 3.17 EDTA release amounts and the resulting PECs of the EUSES calculation

	25% Fe(III)EDTA		75% other species		Sum	
Parameter	**Regional**	**Continental**	**Regional**	**Continental**	**Regional**	**Continental**
Emission hydrosphere [tonnes/ann.]	724	6,515	2,171	19,544	2,895	26,059
Emission soil [tonnes/ann.]	0	0	582	5,239	582	5,239
PECwater [µg/l]	9.6	1.4	85	27	95	28
PECsediment [mg/kg dw]	0.69	0.10	6.2	2.0	6.9	2.1
PECagr.soil [µg/kg dw]	0	0	210	22	210	22

In all cases, the concentrations in the atmosphere are negligible

3.1.4 Atmosphere

3.1.4.1 Production

As the vapour pressure of EDTA is extremely low, the substance (as acid or salt) can be emitted in dust form only. Site-specific data are available for 5 production facilities, as presented in **Table 3.18**.

Table 3.18 Site-specific data for air emissions of production facilities

Site	Emission into air
A	Import only
B	950 kg/a (dust)
C	3 tonnes/annum
D	0 (only liquid handling)
E	Not detected, liquid scrubbed
F	Not submitted
G	0 (only liquid handling)
H	7,260 kg/a (dust)

The local exposure is calculated for the strongest point source. With a release of 7,260 kg/annum and a production period of 300 days/annum, the daily release is 24.2 g/day. The local exposure is:

$Clocal_{air}$=6.7 µg/m^3

To calculate the deposition flux, the fraction adsorbed to aerosol is set to 1, as EDTA is not volatile.

DEPtotal = 0.242 mg/m^2/day

3.1.4.2 Use

Generally, EDTA is used in aqueous solutions, so releases into the atmosphere will not occur.

3.1.5 Terrestrial compartment

3.1.5.1 Production

Significant amounts of EDTA dust are emitted during production. This dust will reach the soil in the vicinity of the production sites by wet and/or dry deposition. According to the TGD model, the local exposure around the strongest emission source is calculated, as presented in **Table 3.19**.

Table 3.19 Calculation of the local soil concentration around the strongest emission source

Parameter	Value	Remarks
Kp_{soil}	75 l/kg dw	See Section 3.1.2.2
Henry's law constant	$4 \cdot 10^{-10}$ Pa · m³/mol	fictitious low value
$k_{bio\ soil}$	$2.3 \cdot 10^{-3}$ d^{-1}	$t_{1/2}$=300 days; see Section 3.1.2.1
$PEClocal_{soil}$	0.31 mg/kg dw	endpoint: terrestrial ecosystem
$PEClocal_{agr.soil}$	0.31 mg/kg dw	endpoint: crops for human consumption
$PEClocal_{grassland}$	0.61 mg/kg dw	endpoint: grass for cattle
$PEClocal_{soil,porew}$	4.6 µg/l	endpoint: terrestrial ecosystem

3.1.5.2 Use

Trace elements in agriculture

Cu-, Fe-, Mn-, Mg-, Mo- and Zn-EDTA complexes are mixed into fertilisers if there is a lack of trace elements in agricultural soil. The metals are applied in chelate form in order to prevent their precipitation as biological inactive compounds and to allow their conversion through the soil medium to the root zone for uptake into the plant (Hart, 1987; AIS, 1987; BASF, 1988).

To a low extent, powdery leaf fertilisers are applied in a quantity of 0.3-1.5 kg EDTA/ha. The major part is applied in liquid leaf fertilisers in a quantity of 0.004-0.15 kg EDTA/ha (Lübbe, 1989).

Plant protection agents

Active substances of plant protection agents like 2,4-dichlorophenoxyacetid acid form poorly soluble calcium salts if they are dissolved in hard water. Without chelating agent, the effect of the agent diminishes, and nozzles can be blocked. Chlorine containing insecticides degrade more rapid in the presence of iron and in hard water, chelating agents have a stabilising effect. A herbicide with dichlorophenoxyacetic acid as the active agent contains 1% EDTA (Kreuter, 1976). Application figures were not submitted.

Sewage sludge

EDTA was measured in digested sludge of a German WWTP which received yearly about 13 tonnes EDTA. The concentration in the sludge was 0.29 mg/kg dw, and the yearly load 12 kg (Schlieckmann, 1994 b).

With an application rate of 5 tonnes sludge/ha and year, 1.45 g EDTA/ha are released into agricultural soil.

Calculation of $PEClocal_{soil}$

As little information on application figures is available, for a worst-case approach a release of 1.5 kg/ha onto agricultural soil is assumed following the maximum figure of Lübbe (1989). For the PEC calculation, the TGD model for sewage sludge is used provisionally as no model for fertilisers is available. In **Table 3.20**, the substance-specific input parameters and the resulting PECs are listed.

Table 3.20 Substance-specific input parameters used in the TGD model for sewage sludge and the resulting PECs in soil

Parameter	Value	Remarks
Kp_{soil}	75 l/kg dw	see Section. 3.1.2.13
Henry's law const.	$4 \cdot 10^{-10}$ Pa·m³/mol	lowest value accepted by EUSES
$k_{bio\ soil}$	$2.3 \cdot 10^{-3}$ d^{-1}	$t_{1/2}$=300 days; see Section. 3.1.2.1
$C_{agr.soil}(0)$	0.3 mg/kg	$C_{agr.soil}(0)$=1.5 kg/ha / (DEPTH · RHO)
$C_{grassland}(0)$	0	no application of EDTA on grassland
$PEClocal_{soil}$	0.51 mg/kg dw	endpoint: terrestrial ecosystem
$PEClocal_{agr.soil}$	0.43 mg/kg dw	endpoint: crops for human consumption
$PEClocal_{grassland}$	0 mg/kg dw	endpoint: grass for cattle
$PEClocal_{soil,porew}$	7.6 µg/l	endpoint: terrestrial ecosystem, drinking water

3.1.6 Secondary poisoning

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

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION)-RESPONSE (EFFECT) ASSESSMENT

3.2.1 Aquatic compartment

A result of the exposure assessment was that in the environment always overstoichiometric amounts of metal ions are present, thus there is no uncomplexed EDTA. In Section 3.1.3.3, it is elaborated that always a mixture of different metal complex species occurs in surface waters. As shown below, there is a large influence of the speciation to the ecotoxicity of EDTA. Therefore, tests with EDTA metal complexes have to be considered as well.

In the tests, either H_4EDTA, the sodium salt or metal complexes were used as test substance. In order to present comparable results, all effect values are calculated as H_4EDTA.

3.2.1.1 Single species test

3.2.1.1.1 Vertebrates

Short-term toxicity

The toxicity of H_4EDTA on *Pimephales promelas* was tested by Curtis and Ward (1981). As test medium a reconstituted soft water (40-48 mg/l hardness as $CaCO_3$, pH 7.2-7.9) was used. For a test period of 96 hours, a LC50 of 59.8 mg/l is reported. During the test, the pH was recorded, but not reported. The pH value of the dilution water was in the range allowed by test guidelines, but the pH measurements in similar media as Batchelder (see below) indicate that the pH might have been decreased when the test substance was added. Therefore the validity of the result is doubtful.

The following tests (Batchelder et al., 1980) show the influence of water hardness, pH and metal speciation on the fish toxicity of EDTA. None of the substances were neutralised prior to testing. The dilution water from Lake Huron exhibits the following main chemical characteristics: dissolved oxygen: start of test 8.2 mg/l, end of test 4.2 mg/l, pH 7.6, total hardness 103 mg/l as $CaCO_3$ (medium hard water). The very soft (10-13 mg/l as $CaCO_3$, pH 6.4-6.8) and very hard water (280-320 mg/l as $CaCO_3$, pH 8.0-8.4) were reconstituted from distilled water as recommended in Marking and Dawson (1973).

Table 3.21 Acute toxicity to *Lepomis macrochirus* in static waters of different hardness, values in mg/l after 96-hour exposition, all concentrations in H_4EDTA equivalents

Water Hardness	NOEC (pH-value)	PK* (pH-value)	LC 100 (pH-value)	LC 50
H_4EDTA **				
Very soft (10-13 mg/l $CaCO_3$)	24	32	75	41
Medium hard (103 mg/l $CaCO_3$)	100 (5.8)	135 (4.1)	240 (3.7)	159
Very hard (280-320 mg/l $CaCO_3$)	420 (4.4)	560 (4.0)	750 (3.5)	532

Table 3.21 continued overleaf

Table 3.21 continued Acute toxicity to *Lepomis macrochirus* in static waters

Water Hardness	NOEC (pH-value)	PK* (pH-value)	LC 100 (pH-value)	LC 50
Na_4EDTA **				
Very soft (10-13 mg/l $CaCO_3$)	88 (7.0)	104 (7.0)	138 (7.7)	121
Medium hard (103 mg/l $CaCO_3$)	669 (9.4)	769 (9.5)	861 (9.6)	792
Very hard (280-320 mg/l $CaCO_3$)	1,380 (9.5)	1,615 (9.6)	1,846 (9.6)	1,592
Zn- EDTA **				
Very soft (10-13 mg/l $CaCO_3$)	460 (8.1)	616 (8.1)	1,109 (8.2)	772
Medium hard (103 mg/l $CaCO_3$)	263 (7.9)	345 (8.0)	822 (8.4)	563
Very hard (280-320 mg/l $CaCO_3$)	263 (8.4)	345 (8.4)	616 (8.5)	422

* Partial kill
** Batchelder et al. (1980)

The test results of H_4EDTA and Na_4EDTA show that there is a relation between water hardness and ecotoxicity. Tests performed in very soft (10-13 mg/l $CaCO_3$) and medium hard water (103 mg/l $CaCO_3$) showed a higher toxicity than those performed in very hard water. As the hardness increased, more of the chelator was converted to the Ca-complex, thus more chelating agent was required to exert a toxic effect-less uncomplexed EDTA is available.

On the other hand, the Zn-EDTA exhibited a greater toxicity at higher hardness levels. Although the conditional stability constants at pH 8 would greatly favour zinc, the observed increased toxicity at higher levels of hardness can possibly be due to the mass action effect of Ca and Mg, which allows the release of minute amounts of zinc. Zinc is known to be toxic to bluegill at 10-12 mg/l (Batchelder et al., 1980).

The influence of the pH is demonstrated in **Table 3.22**. All tests were performed in medium hard water, concentrations in mg/l, in parathesis: pH-values, effect values are given as H_4EDTA (Batchelder et al, 1980).

Table 3.22 Influence of the PH on ecotoxicity

Species	NOEC	LC50	LC100
H_4-EDTA	100 (5.8)	159	240 (3.7)
Na_4-EDTA	669 (9.4)	792	861(9.6)
Na_4-EDTA	351(8.1)	374	521(8.9)

Most waters containing fish have pH values between 6.7-8.6, with extremes of 6.3 and 9.0. The acid kills 100% of the bluegill at 240 mg/l in medium hard water at a pH of 3.7, at which acidity alone is lethal to bluegill. If the sodium salt is used, a 100% mortality occurs at 401 mg/l with a resultant pH of 8.9 which is not itself toxic to bluegill, and at 861 mg/l in medium hard water at a pH of 9.6, respectively (Batchelder et al., 1980).

In the tests presented in **Table 3.23** the influence of different complexed metal ions on the toxicity of EDTA is investigated with *Lepomis macrochirus*. In all tests medium hard water with a water hardness of 103 mg/l $CaCO_3$ is used. Effect values are given as H_4EDTA (Batchelder et al., 1980).

Table 3.23 Influence of complex metal ions on EDTA fish toxicity

EDTA Species	96-hour NOEC	96-hour LC50	96-hour LC100
Na_4-EDTA	351 mg/l (pH 8.1)	374 mg/l	401 mg/l (pH 8.9)
Cu-EDTA	264 mg/l (pH 7.8)	458 mg/l	620 mg/l (pH 7.9)
Zn-EDTA	263 mg/l (pH 7.9)	563 mg/l	822 mg/l (pH 8.4)
Mn-EDTA	6,350 mg/l (pH 7.5)	11,940 mg/l	27,100 mg/l (pH 8.0)
$CaNa_2$-EDTA	781 mg/l (pH 7.5)	1,827 mg/l	3,280 mg/l (pH 7.4)
Mg-EDTA	1,256 mg/l (pH 7.6)	2,344 mg/l	3,906 mg/l (pH 7.6)

In all tests medium hard water (water hardness 103 mg/l $CaCO_3$) is used. Effect values are given as H_4EDTA (Batchelder et al., 1980)

The results show that the toxicity of complexes with the toxic metals Cu and Zn is in the same concentration range as the uncomplexed EDTA. Chelates with non-toxic metals (Mn, Ca, Mg) are much less toxic.

Our interpretation is that the complexing agents can cause either nutrient deficiency by reducing the essential concentration of different ions, or the metal metabolism in the organisms is disturbed (In Section 4.1.2.1, the depletion of essential metal ions e.g. zinc is elaborated). This could already be demonstrated in the tests with H_4EDTA and Na_4EDTA. The higher the water hardness (which causes complete complexation with Ca), the higher the concentration necessary to exert a toxic effect.

Chelating EDTA with Mn, Ca or Mg leads to LC50 values (referred as H_4EDTA) between 1,827 and 11,940 mg/l. This shows that previously complexed EDTA has only minimal acute toxic effects on fish. The chelated metal ions are exchanged slowly against essential metals, therefore the toxicity (compared with uncomplexed EDTA) is reduced. The higher toxicity from chelates with Zn or Cu is assumed to be caused by the metal ions which are set free by metal exchange reactions.

Long-term toxicity

A test on early life-stage toxicity of $CaNa_2$EDTA on embryos, larvae and young fish of the zebrafish (*Danio rerio*) following the OECD 210 guideline was conducted by BASF (2001). The study was performed under flow-through, unaerated conditions with 5 concentrations of the test substance (1.0–35.1 mg/l) and a dilution water control. Each concentration group consisted of four replicates. The mean measured concentrations were 91–105% of the nominal values. Measured and/or determined biological parameters were the mortality of the embryos at the beginning of hatch (day 1), the number of surviving healthy larvae at the end of hatch (day 5) and of the young fish at the termination of the study (day 35), time to hatch and swim-up, toxic signs (symptoms), the wet weight and the total length of surviving fish. The survival at start of hatch (days 0-1) was slightly lower in all concentration groups (84–87% vs. 91% in the control). Compared to the control group survival from start of hatch to the termination of hatch (day 1–5) was statistically significantly reduced in the concentration group 3 (7.7 mg/l) and following the results of the log rank test also in concentration group 2 (3.3 mg/l) but not in the 2 highest concentration groups (16.4 and 35.1 mg/l). No concentration dependent tendency was observed. The deviations are not considered to be caused by the test substance. Survival from the end of the hatch to the end of the study (day 5–35) was not statistically significantly decreased in comparison to the control group in any of the concentration groups. In the further endpoints (time to hatch and swim-up, toxic signs (symptoms), the wet weight and the total length of

surviving fish) no relevant differences related to the control were observed. Thus the NOEC is determined to > 37 mg/l $CaNa_2EDTA$ (> 26.8 mg/l H_4EDTA) based on analytically determined concentrations.

3.2.1.1.2 Invertebrates

Short-term toxicity

Daphnia magna 24-hour EC50 = 625 mg/l Na_4-EDTA (i.e. 480 mg/l H_4-EDTA)

(effect: immobilisation, used EDTA-species: Na_4-salt, water hardness: 160 mg/l CaO, Bringmann and Kühn, 1977)

Daphnia magna 24 hour-EC50 = 1,033 mg/l Na_4-EDTA (i.e. 790 mg/l H_4-EDTA)

(effect: immobilisation, used EDTA-species: Na_4-salt, water hardness: 160 mg/l CaO (285 mg/l $CaCO_3$), DIN 38412 T27, Bringmann and Kühn, 1982)

In these short-term tests, Ca was present in overstoichiometric amounts. Thus, in the test system the Ca-complex was formed.

Long-term toxicity

Daphnia magna	21-day NOEC	=25 mg/l Na_2H_2EDTA (i.e. 22 mg/l H_4EDTA)
	21-day LOEC	=50 mg/l Na_2H_2EDTA (i.e. 43 mg/l H_4EDTA)
	21-day-LC0	$\geq$100 mg/l Na_2H_2EDTA (i.e. 87 mg/l H_4EDTA)

(effect: reproduction, mortality, semistatic, BASF 1996a)

Daphnia magna was exposed for 21 days to seven nominal concentrations of Na_2H_2EDTA ranging from 1.56 to 100 mg/l in synthetic M4 medium. At the beginning of the test and before changing the test solution a stock solution (100 mg/l) was freshly prepared. The test solution was changed three times per week. The nominal concentration 0, 1.56, 12.5 and 100 mg/l were analysed in the 1st, the 2nd and the 3rd week of the test. For each concentration the freshly prepared test solution (unstocked) and the corresponding 48-hour or 72-hour old test solution (stocked with daphnids) were analysed. With regard to the precision of the analytical method (RP-HPLC and post column derivatisation with Fe(III)-nitrate, UV/VIS detection) and taking into account deviation of the blank value (M4 medium contains 2.5 mg/l Na_2H_2EDTA and causes a background value of about 1 mg/l) the measured concentrations approximately correspond to the expected values, except for the samples at 1.56 and 12.5 mg/ level, whose concentrations are too low. The endpoints are based on the nominal values. Oxygen and pH was measured at the start of the test and at each change of the test solution in the 48- or 72-hour old solutions at each concentration. The pH-value ranged between 7.3 and 8.5 and the oxygen content between 8.0 and 9.6 mg/l. The total hardness of the medium is 2.2-3.2 mmol/l. The concentration of Na_2H_2EDTA (NOEC=25 mg/l=0.074 mmol) in relation to metal ions is chosen in a manner, that nutrient deficiency can probably be excluded. In the control the first rising generation was observed at day 7. In the highest concentration tested, the daphnids produced young (100 mg/l) at day 13.

24-hour exposure to 0.33 mmol/l Na_2H_2EDTA (i.e. 96 mg/l H_4EDTA) in artificial sea water (salinity 28 ppt) had no influence on both the survival rate and the metamorphosis of the decapode *Penaeus stylirostris*. At 0.67 mmol/l (195.8 mg/l H_4EDTA) metamorphosis was

inhibited by about 45%. 1.34 mmol/l (391.6 mg/l H_4EDTA) caused a mortality rate for the nauplii of 100% after 12 hours (Castille et al., 1981).

Mollusca

The number of fertile eggs of *Crassostrea gigas* (American oyster) developping to veliger larvae in 24 hours rose by 42 and 47% when 1 and 2 mg/l Na_2EDTA (i.e. 0.87 and 1.74 mg/l H_4EDTA) was added to natural sea water (salinity: 28 ppt, pH: 8.0) (Utting and Helm, 1985).

Echinodermata

Concentrations > 29.2 mg/l EDTA (unknown which EDTA species was used) had an inhibiting effect on the motility of sperm of the sea urchin *Arbacia punctulata* in sea water at 22-23°C. 58.5 mg/l EDTA decreased motility by 17%, 116.9 mg/l by 36% and 175 mg/l by 79% (Young and Nelson, 1974).

3.2.1.1.3 Plants

Scenedesmus quadricauda 8 d-EC3 (TGK)=11 mg/l Na_4EDTA (8.5 mg/l H_4EDTA)

(effect: growth inhibition caused by reduced nutrient, used EDTA-species: Na_4EDTA, pH 7.0; medium contains additionally 7.8 mg/l H_4EDTA; Bringmann and Kühn, 1978)

A growth inhibition test with Na_4EDTA on *Scenedesmus subspicatus* according to the guideline 79/831/EEC was conducted. For the biomass development, an EC50 of 1.01 mg/l (=0.78 mg/l H_4EDTA) and an EC10 of 0.48 mg/l (=0.37 mg/l H_4EDTA) was determined. The concentration-effect curve has a bi-phasal shape indicating that the effects are caused by nutrient deficiency. EDTA forms chelates with essential trace elements in the test medium, and these are available only to a smaller extent. The test medium (identical with OECD 201) contained a large stoichiometric surplus of Mg and Ca (BASF (1994).

Further tests on *Scenedesmus subspicatus* with equimolar amounts of Na_4EDTA and Fe(III) failed to reveal an inhibitory effect on algae growth up to a nominal concentration of 100 mg/l Na_4EDTA (i.e. 77 mg/l H_4EDTA) (BASF, 1995a;b). As Fe-EDTA is instable to photolysis, the test substance concentration was probably not constant.

A test with *Pseudokirchnerella subcapitata* (formerly *Selenastrum capricornutum*) with Fe(III)EDTA as active test substance following OECD 201 was performed by Geurts and van Wijk (2001). Nominal concentrations of 60, 80, and 100 mg/l (expressed as H_4EDTA) were used, during the test the concentrations were measured by HPLC. The extinctions measured at 60 and 80 mg/l are higher than the controls, indicating growth stimulation which is not regarded as an adverse effect. The EC_b50 and EC_r50 are both higher than the highest concentration tested. The NOEC based on nominal concentration was determined to 79.4 mg/l based on mean measured concentration to 48.4 mg/l.

Dufková (1984) demonstrated with *Scenedesmus quadricauda* that not the absolute EDTA concentration, but rather the ratio of the EDTA to the bivalent cations is crucial to algae growth. Higher concentrations (400 mg/l $Na_2H_2EDTA \cdot 2\ H_2O$=310 mg/l H_4EDTA), when in surplus over trace elements in the nutrient solution, inhibited cell division, chlorophyll synthesis and the production of algal biomass, especially in the earlier phase of algae growth. No negative influence was observed when the concentration of trace elements in the nutrient solution was increased corresponding to the increased EDTA concentration. Besides the micronutrients, the

concentration of Mg is of importance for the growth of algae. With an excess of EDTA, a large portion of Mg was complexed and Mg ions thus became less available.

Muggli and Harrison (1996) examined the influence of EDTA on growth of the oceanic algae *Emiliana huxleyi* and *Actinocyclus sp*. The added EDTA concentrations were 1, 10, and 100 µM (=0.29–29 mg/l), the amount of nutrient metals was increased with the EDTA amount thus the resulting free metal ion concentrations (calculated with the equilibrium program MINEQL) was approximately constant. With 10 µM (=2.9 mg/l) EDTA, the growth rate was reduced respectively by 8% (*E. huxleyi*) and 16% (*A. sp.*). At all test concentrations there was a large excess of EDTA when compared to the essential ions. The authors mentioned that caution is warranted when working with newly isolated oceanic phytoplankton, because they are difficult to culture. Therefore these test results are not used for the PNEC derivation.

For [S,S]-Ethylenediamine disuccinate ([S,S]-EDDS), a strong chelator for transition metals, it was demonstrated that algae toxicity is an indirect effect of complexing the trace metals in the medium, resulting in limitation of essential nutrients (Schowanek et al., 1996). *Chlorella vulgaris* was tested according OECD 201, water hardness and trace metal concentrations were varied. In standard media with different water hardness (24-375 mg/l $CaCO_3$), addition of 1 mg/l [S,S]-EDDS reduced the growth rate by 53%, independent on the water hardness. Speciation calculations showed that in the standard medium [S,S]-EDDS is mainly associated with Zn, Cu, and Co. To test the hypothesis that the apparent toxicity was caused by nutrient deficiency, growth experiments in metal-enriched medium were performed. With increasing concentrations of Zn, Co, and Cu, the algal growth increased, reaching a maximum and then falling. The maximum growth was obtained with 1 mg/l (=3.4 µM) [S,S]-EDDS, 0.62 µM Co, 0.051 µM Cu, and 2.9 µM Zn, where the levels of free Cu, Co and Zn were the same as in standard medium without the chelator. With lower [S,S]-EDDS concentrations, growth is decreased, mainly caused by Zn toxicity.

The apparent toxicity of complexing agents to algae in standard tests is related to essential trace metal bioavailability. Trace metal levels tend to be more important in algal growth tests than in other short-term tests (e.g. on fish or daphnia); the main reason is the rapid increase of biomass during the test. In standard tests using uncomplexed agents, the concentrations of free essential metal ions decrease drastically, leading to nutrient deficiency and relatively low effect concentrations. Addition of stoichiometric amounts of nutrients results in detoxification of the agent. 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.

Eutrophicating effects

The growth of natural phytoplankton populations is studied in more than 380 trials (Pöhlmann et al., 1989). It was demonstrated that water temperature and nutrient concentration of phosphorus, silicate, nitrate, ammonia and carbon dioxide have a substantial influence to the growth rates of algae. An increased availability of essential nutrients caused by the complexing agent EDTA is able to stimulate the eutrophication considerably. The influence of EDTA on algae growth was studied in water from river Regnitz and river Wiesent at laboratory scale. Addition of EDTA (maximum 1.5 µmol/l) to water from the river Regnitz with an intrinsic level of 0.13 µmol/l complexing agent, was found to cause 20% increase of the growth. Addition under the same conditions to water from the river Wiesent with an intrinsic level of 0.01 µmol/l complexing agent produced an increase of 48%. The concentration of soluble trace elements is the critical point. Given a high enough concentration of trace elements in synthetic nutrient medium, algae growth was increased only slightly by 12%. Generally, a significant increase in phytoplankton production was found following an addition of 0.1 to 0.35 µmol/l EDTA (30 to 300 µg/l

H_4EDTA). The authors believe that nutrient metals are remobilised from suspended particles stimulating phytoplancton growth. The observed growth increase varied with algae species, preloading of the water with trace elements and other complex former e.g. humic acids from 22 to 50%.

Summarising, 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 only insignificantly after addition of EDTA.

Blue algae

A test on growth inhibition of *Microcystis aeruginosa* resulted in a EC3=76 mg/l Na_4EDTA (i.e. 58 mg/l H_4EDTA) (Bringmann and Kühn, 1978). In the test medium, the molar Ca concentration was above EDTA, but trace metals like Mn, Zn, Cu, Mo, and Co were present in lower concentrations. Additionally, 10 mg/l 1, 2-cyclohexanediaminetetraacetic acid, which is also a complexing agent, was added. Taking account of the above referred results of Dufková (1984) with *Scenedesmus quadricauda*, the observed effects were probably caused by nutrient deficiency.

In studies on *Nostoc muscorum* 9.9 mg/l H_4EDTA reduced growth by 8% after 14 days (Raizada and Rai, 1985). The authors suppose that this effect may have been caused by a decrease in calcium concentration, which is known to stimulate both heterocyst formation and nitrogenase activity.

Higher plants

It was demonstrated that supplementing the medium with a complexing agent like EDTA resulted in healthy growth of the frond; plants not only multiplied rapidly but were also greener. The addition of up to 29.2 mg/l H_4EDTA was responded by *Spirodela polyrhiza* (greater duckweed) with a growth increase of up to 50%. A concentration of 292.2 mg/l H_4EDTA is responded by growth inhibiting of 35% relative to the control. The cultures were incubated at pH 5.5 for 10 days (Khurana and Maheshwari, 1986). According to the authors the presence of a chelator like EDTA is a prerequisite for vegetative growth of the plant. The described effects were obtained under laboratory conditions and not in real environmental situations.

3.2.1.1.4 Microorganisms

A test on growth inhibition on *Pseudomonas putida* with Na_4-EDTA as test substance resulted in a 16-hour-TGK (EC3) of 105 mg/l (i.e. 81 mg/l H_4EDTA). There is no information about test conditions available (Bringmann and Kühn, 1976).

In an oxigen consumption test according Robra with Na_2H_2EDTA, a 30-minute EC10 of 55 mg/l (i.e. 48 mg/l H_4EDTA) was found. There is no information about test conditions available (BASF, 1990a).

A test on cell multiplication inhibition with different protozoa was performed using identical experimental conditions. Stock and preliminary cultures of the test organisms were fed with living bacteria, whereas the test cultures were fed with inactivated bacteria. Na_4EDTA was used as test substance. The test medium (pH 6.9) contained 290 mg/l $Ca(NO_3)_2 \cdot 4\ H_2O$ and 70 mg/l $Mg(NO_3)_2 \cdot 6\ H_2O$, therefore EDTA is completely complexed with Ca and Mg. After a test

period, the cells were counted, and the TGK (i.e. EC5) was determined. In **Table 3.24**, the concentrations are given as H_4EDTA equivalents

Table 3.24 Results of a test on cell multiplication inhibition with protozoa. (EDTA completely complexed with Ca and Mg, concentrations given as H_4EDTA equivalents; TGK = EC5)

Organism	Test duration	TGK	Reference
Uronema parduczi	20 hours	13 mg/l	Bringmann and Kühn (1980)
Chilomonas paramaecium	48 hours	510 mg/l	Bringmann, Kühn, Winter (1980)
Entosiphon sulcatum	72 hours	28 mg/l	Bringmann (1978)

These tests are not well-documented. It is unclear whether the test organisms are sufficiently supplied with trace nutrients. It cannot be excluded that, similar to algae, the effects were caused by nutrient deficiency.

A respiration test with activated sludge collected from a domestic sewage treatment plant was performed in accordance to OECD Test Guideline 209 (Van Ginkel and Stroo, 2000). Na_2H_2EDTA was used in concentrations of 125, 250, and 500 mg/l (referred as H_4EDTA). Equimolar amounts of $CaCl_2$ were added, thus CaEDTA was formed in the stock solutions. At the highest test concentration (500 mg/l) a significant inhibition of the respiration rate could not be detected after 30 minutes. It can be concluded that both the EC10 and NOEC values are above 500 mg/l.

3.2.1.2 Effects on ecosystems. Pond studies

The influence of EDTA on pond ecosystems was investigated by Kucklentz (1991) and Hamm (1991). The ponds simulate a natural system with macrophytes and littoral vegetation, stocked with fresh water crayfish and fish. Two types of ponds were used, one having a minimal water exchange and a retention time of six weeks, and the others are equipped with a water-batcher, providing a continous inflow of the test substance, with a retention time of two weeks. One pond of each type is not charged with EDTA and served as control. Only one control and one test pond are used. The experiments took place over two vegetation periods. Under stagnant conditions the concentration of H_4EDTA varies in winter between 53–331 µg/l and in summer between 51-288 µg/l. The variation of the H_4EDTA concentration under flow-through conditions are in winter 17-96 µg/l and in summer 19-51 µg/l. It is probable, that there is no significant difference in zooplankton between the control pond and the EDTA in summer. The winter population in all ponds is much smaller than in summer. The EDTA pond has extremely few organisms, they appeared to be inhibited. Under flow-through conditions no essential changes in the biocoenosis could be detected. The concentration of chlorophyll a-as a value of algae growth-was never higher in the EDTA-flow-through pond than in the control. Under stagnant conditions the growth of algae was in 2 of 5 investigation periods higher as the control pond, with the result it is not possible to reliably infer an eutrophicating effect exerted by EDTA. These two periods were characterised by high EDTA concentrations of 288 µg/l and 331 µg/l respectively.

3.2.1.3 Influence of EDTA on the toxicity of heavy metals

There is a large number of investigations available dealing with the decrease of heavy metal toxicity by EDTA. Only the following is discussed in detail, because the results of the other

studies are mainly in line with these results (see Section results obtained by Batchelder et al., (1980) for *Lepomis macrochirus*).

Sorvari and Sillanpää (1996) compared the toxicity (24-hour EC50, *Daphnia magna*) of different heavy metal ions complexed by EDTA with those of the respective uncomplexed metals and free EDTA. The results are shown in **Table 3.25**. To examine the effect of complexation, an equimolar amount of solid Na_4EDTA was added to each metal stock solution, there was no need for pH adjustment. EC50 values of the metals are counted as the total amount of the metal ion. EC50 values of EDTA complexes are expressed as the amount of the free anionic species $EDTA^{4-}$.

Table 3.25 Influence of EDTA on the toxicity of heavy metals

Substance	24-hour EC50 (mg/l)	Confidence interval (95%)
Na_4EDTA	610	570- 640
Mn (II) Mn (II) + EDTA	56 960	45-67 800-1,000
Cu (II) Cu (II) + EDTA	0.022 38	0.014-0.035 31-45
Zn (II) Zn (II) + EDTA	5.5 910	3.4-18 840-980
Hg (II) Hg (II) + EDTA	0.0016 0.00032	0.001-0.0022 0.00022- 0.00052
Cd (II) Cd (II) + EDTA	0.98 310	0.82-1.1 290-330

As the results show, the toxicities of the heavy metals were 17 to 1,700 times decreased, except for mercury. There is a high correlation between conditional stability constant and the relative toxicity reduction (in log-scale) accomplished by EDTA complexation, with exception of mercury. This result indicates a different toxicity mechanism in the case of mercury.

On the other hand, compared with the toxicity of uncomplexed EDTA, equimolar heavy metal complexation with Cu, Hg and Cd increased the toxicity of EDTA. Because of the test design it must be assumed that this is caused by uncomplexed metal ions.

3.2.1.4 Determination of Predicted No Effect Concentration (PNEC)

Determination of $PNEC_{aqua}$

According to the results from different ecotoxicological studies discussed above, 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. In Section 3.1.3.3, the main features on complex chemistry in the environment are elaborated. The reactions in the test media are similar.

Beside Ca and Mg, test media contain a certain amount of heavy metal ions being necessary as trace nutrients. The complex forming constants of heavy metal complexes are by several orders of magnitude higher than that 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 present when it is present in overstoichiometric concentrations.

The choice of the complex species being relevant for effect testing should consider their different ecotoxicological properties. As shown in Section 3.1.3.3.5, always a mixture of metal complexes is released or is being formed in surface waters. Effect tests should be conducted with a complex for which metal toxicity can be excluded. We propose to use the Ca-complex as test substance for all release scenarios. Effects from complexes with a higher toxicity are caused by the dissociated metal ions and should be covered by the risk assessment of the respective metals.

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, as demonstrated by Batchelder et al. (1980). The higher the water hardness the higher was the concentration of EDTA necessary to cause a toxic effect expressed as mortality. 96-hour LC50 values for H_4EDTA between 41 mg/l and 1,590 mg/l were found. The lowest acute toxicity recorded with H_4EDTA for the fish *Lepomis macrochirus* in very soft water with LC50 of 41 mg/l should not be used because it is probably influenced by pH effects. In the test result obtained with Na-EDTA and a water hardness of 103 mg/l $CaCO_3$ (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 $CaNa_2$EDTA as test substance, a LC50 of 1,827 mg/l was obtained being in a concentration range where unspecific effects are expected. The test with *Pimephales promelas* (96-hour LC50=59.8 mg/l, Curtis and Ward 1981) obtained in water hardness of 40-48 mg/l $CaCO_3$ are doubtful, as the effects might have been caused by a low pH value. 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. $CaNa_2$EDTA 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. Trace metal levels tend to be more important in algae tests than in short-term tests on fish or daphnia, the main reason is the rapid increase of biomass during the test. 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.

A standard growth inhibition test on *Scenedesmus subspicatus* resulted in an EC10 of 0.37 mg/l H_4EDTA. The effect is probably caused by nutrient deficiency, as essential metal ions like Cu,

Zn and Co are largely complexed leading to drastically reduced concentrations. It could be demonstrated by Geurts and van Wijk (2001), that in a test with *Pseudokirchnerella subcapitata* (formerly *Selenastrum capricornutum*) with Fe(III)EDTA as activ test substance following OECD 201, ECb50 and ECr50 higher than 100 mg/l were found. The NOEC based on nominal concentrations was determined to 79.4 mg/l and to 48.4 mg/l when based on mean measured concentration.

Therefore, this inhibition of algae growth is an artefact which is caused by the drastic increase of biomass during the test. Indirect effects cannot be quantified from the laboratory tests, thus only theoretical considerations can be made. In German and Dutch rivers, heavy metal concentrations in the range of 10-20 µmol/l (predominantly Fe and Mn) are detected. In the environment heavy metals are generally present in over-stoichiometric amounts, thus those effects are not expected in low concentrations like in the tests. Nutrient deficiency in surface waters can only occur when essential metal ions are overchelated by high EDTA amounts. On the other hand, plant growth is influenced by many limiting parameters; probably the presence of macronutrients like phosphate or nitrate is of greater importance. Therefore, it is unlikely that nutrient deficiency occurs in the environment, although it cannot be excluded absolutely.

In addition to the discussed adverse effects, like growth inhibition, mortality and immobilisation of EDTA the growth stimulating effects like eutrophication occurs. Standard media for algae tests contain EDTA (OECD 201: 100 µg/l) to prevent precipitation of nutrient metals as hydroxide. For two different river waters a significant increase in phytoplankton production was observed after addition of 30 to 300 µg/l EDTA. The observed increase in growth varied with algae species, preloading of the water with trace elements and other complexing agents e.g. humic acids from 22 to 50%. Thus, 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 cannot be assessed quantitatively with the available methods.

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.

Therefore, a $PNEC_{aqua}$ of 2.2 mg/l is determined.

The assessment of intermittent releases for fresh water is based on the 24-hour EC50 values of 480 and 790 mg/l obtained for daphnids. Both results were obtained under very similar conditions and are within the uncertainty range of effect test results. Therefore, the mean value (640 mg/l) together with an assessment factor of 100 is used. The PNECintermittent is calculated to 6.4 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 philosophy of 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.

Besides the monospecies tests used for the discussion of the PNEC a study on pond ecosystems (Kucklentz, 1991; Hamm, 1991) is available. Although field studies with aquatic ecosystems may provide a better insight into the effects, these studies were not used for the derivation of the PNEC, because due to the relative large deviation the evidence of the results is limited. The

applied concentration of ± 100 µg/l cannot be used as a real NOEC, therefore the value has indicative character.

Influence on the toxicity of heavy metals

In surface waters, EDTA causes an increase of heavy metals in the water phase (see Section 3.1.3.3.7). The influence of EDTA on the toxicity of heavy metals is demonstrated in a test on Daphnia (Sorvari and Sillanpää, 1996). 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.

Determination of $PNEC_{microorganism}$

There are tests on different protozoa available with a 20-hour TGK of 13 mg/l with *Uronema parduczi* as the lowest effect value. However, similar to the algae tests, it cannot be excluded that the effects in these tests were caused by nutrient deficiency by reduction of the concentrations of essential metals. Therefore, these tests are not used for the PNEC derivation.

The sludge respiration test performed by Van Ginkel and Stroo (2000) is more relevant. CaEDTA was the effective test substance, and we assume that sewage sludge contains sufficient adsorbed metal ions which are essential for microorganisms. Therefore the PNEC for microorganisms is calculated from an EC10 of > 500 mg/l and an assessment factor of 10.

$PNEC_{microorganism} > 50$ mg/l

Determination of $PNEC_{sediment}$

There are no test results available with sediment dwelling organisms. A determination of the PNEC sediment is not possible. Based on the properties no adsorption of EDTA onto the sediment has to be expected, thus the assessment of this compartment will be covered by the aquatic assessment.

Ecotoxicity of EDTA Metabolites

A semistatic test on acute toxicity of KPDA on the zebrafish *Brachidanio rerio* was carried out in accordance with OECD 203 guideline (van Wijk and Garttener-Arends, 2000a). Fish were exposed for 96 hours, the test medium was replaced after 48 hours. The test was carried out as a limit test at 100 mg/l nominal concentration of the test substance. At this test concentration there was one dead fish, which is equal to the mortality allowed in the control. Sublethal effects such as deviations in behavior or the appearance were not observed. It can be concluded that the LC50 (96 hours) value is above 100 mg/l.

A 48-hour static test on acute toxicity of KPDA on the *Daphnia magna* was carried out in accordance with OECD 202 guideline (van Wijk and Garttener-Arends, 2000b). The test was carried out as a limit test at 100 mg/l nominal concentration of the test substance. At the test concentration, 2 daphnids (from 20) were immobile and 1 (from 20) in the control, thus the percentage immobility was within the quality criterium of ≤ 10%. It can be concluded that the EC50 (48-hour) value is above 100 mg/l.

The toxicity of KPDA to exponentially growing *Pseudokirchnerella subcapitata* (formerly known as *Selenastrum capricornutum*) was carried out in accordance with OECD 201 guideline (van Wijk and Garttener-Arends, 2000c). The test was carried out as a limit test at a nominal concentration of 100 mg/l over an exposure period of 72 hours. At this concentration the inhibition was calculated to 10.4% based on the biomass and 3.4% based on the growth rate,

both were significantly different from the control. EC50 and NOEC values cannot be determined, but the results allow the conclusion that both EC50 values are above 100 mg/l.

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, a tentative PNEC can be calculated:

PNEC (KPDA) > 100 µg/l

For the further EDTA metabolites (see Section 3.1.2.1.2) no ecotoxicological investigations are available.

3.2.2 Atmosphere

Because there are no fumigation tests available, an effects assessment for this compartment cannot 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.

3.3.1.1 Production

The results for the site-specific scenarios are presented in **Table 3.26**.

Table 3.26 Site-specific scenarios for production

Site	$PEClocal_{aqua}$ [mg/l]	PECaqua / PNECaqua	Ceffl [mg/l]	Ceffl. / PNECmicro
A	only import			
B	0.18	0.08	9.7	<0.19
C	0.095	0.04	0.040	<0.0008
D	max. 1.0	<0.45	no WWTP	-
E	0.36	0.16	1,500	<30
F	0.10	0.045	no WWTP	-
G	0.22	0.1	no WWTP	-
H	0.098	0.04	0.40	< 0.008

Site E has stopped its production in January 2001.

Conclusion (ii).

3.3.1.2 Use

Releases into household sewage

The exposure assessment for the EDTA uses in household detergents, food additives, pharmaceuticals and cosmetics resulted in a PEClocal of 195 µg/l, leading to a PEC/PNEC ratio of 0.09. With a $C_{effluent}$ of 1,000 µg/l, a $PEC/PNEC_{microorganism}$ of < 0.02 is reached.

Conclusion (ii).

Industrial detergents

For the exposure estimation, 3 alternative scenarios were regarded:

For Scenario 1, it is assumed that the total application amount is emitted into the municipal wastewater. This scenario should reflect the situation for the majority of the sites.

Scenarios 2 and 3 describe the exposure from large EDTA consumers. Sites are known with a consumption up to 30 tonnes/annum. In order to avoid a chaining of worst-case assumptions, a volume of 10 tonnes/annum was chosen for both scenarios. For Scenario 2 no effective WWTP

purification is assumed, while for Scenario 3 wastewater purification in a long-termed aerated biological treatment plant (LAS) reflecting the best available technique is assumed.

Table 3.27 Risk characterisationfor the use of industrial detergents

	1. Emission into municipal wastewater	2. Large site without LAS	3. Large site with LAS
$PEClocal_{water}$	0.64 mg/l	2.6 mg/l	0.35 mg/l
PEC/PNEC	0.29	1.2	0.16
$C_{effl.}$	5.4 mg/l	25 mg/l	2.5 mg/l
$C_{effl}/PNEC_{micro}$	< 0.11	< 0.5	< 0.05

The resulting ratio for the aquatic assessment is above 1 for large users without effective wastewater treatment: **conclusion (iii)**.

For the majority of the sites with a low EDTA consumption no risk is expected: **conclusion (ii).**

Photochemicals

The exposure assessment for photo-finishing sites was based on branch-specific information and resulted in a PEClocal of 0.57 mg/l, leading to a $PEC/PNEC_{aqua}$ ratio of 0.26. With a $\mathbf{C}_{effluent}$ of 4.7 mg/l, a $PEC/ PNEC_{microorganism}$ of < 0.09 is reached: c**onclusion (ii)**

Releases from recovery of photochemicals are considered in Section 3.3.1.2.

Textile industry

The exposure estimation based on the European use volume and information on the size structure of the sites resulted in a PEC_{local} of 2.0 mg/l, leading to a PEC/PNEC ratio of 0.9. With a $\mathbf{C}_{effluent}$ of 19 mg/l, a $PEC/ PNEC_{microorganism}$ of < 0.38 is reached: c**onclusion (ii).**

Pulp and paper

For the exposure estimation, 2 alternative scenarios were regarded. For the first scenario wastewater purification in a long-term aerated biological treatment plant (LAS) reflecting the best available technique is assumed, while the second scenario is based on available monitoring data in plants effluents.

Table 3.28 Risk characterisation for the use in the pulp and paper industry

	Long-termed aerated biological treatment	No effective treatment
$PEClocal_{water}$	0.5 mg/l	2.6 mg/l
$PEC / PNEC_{aqua}$	0.23	1.2
$C_{effluent}$	4 mg/l	40 mg/l
$C_{effl}/PNEC_{micro}$	< 0.08	< 0.8

The result indicates that for pulp and paper mills without an effective industrial wastewater treatment, a risk to the aquatic environment is expected: **conclusion (iii)**.

For sites where the sewage is purified with long-term aerated biological treatment plants, a risk is not expected: **conclusion (ii)**.

Metal plating

The exposure estimation based on the European use volume and site-specific consumption data resulted in a PEC_{local} of 12 mg/l, leading to a $PEC/PNEC_{aqua}$ ratio of 5.5. With a $C_{effluent}$ of 116 mg/l, a $PEC/PNEC_{microorg}$ of < 2.3 is reached. A risk to aquatic organisms cannot be excluded: **conclusion (iii) .**

Water treatment

Because of the lack of data, an exposure model could not be calculated. However, it is assumed that this use is widespread and will not lead to a high local exposure: **conclusion (ii)**.

Polymer and rubber production

The exposure calculation based on site-specific data resulted in a PEC_{local} of 1.7 mg/l, leading to a $PEC/PNEC_{aqua}$ ratio of 0.77. With a $C_{effluent}$ of 16 mg/l, a $PEC/ PNEC_{microorg}$ of < 0.32 is reached: **conclusion (ii).**

Oil production

For the discontinous (a few days per year) cleaning process during oil production a PEC_{local} of 0.63 mg/l was calculated using a dilution factor of 1,000 according to the CHARM model. The PEC/PNEC ratio using the $PNECintermittent_{marine}$ of 0.64 mg/l is 0.98. It is recognised, that the PEC/PNEC ratio is very close to one, however, any further measures of data improvement or risk management does not fall under the scope of existing chemicals regulation.

Conclusion (ii).

Fuel gas cleaning

Releases into the environment from this use are not expected: **conclusion (ii).**

Disposal

In the frame of the present risk assessment, it was not possible to gain site-specific information about environmental releases for this life-cycle step. Therefore, the results from photochemical recovery are used for the risk characterisation.

With a PEC_{local} of 2.4 mg/l, a $PEC/PNEC_{aqua}$ ratio of 1.1 is calculated. With a $C_{effluent}$ of 23 mg/l, a $PEC/PNEC_{microorganism}$ of < 0.46 is reached.

Conclusion (iii).

3.3.1.3 Influence on the distribution of heavy metals

EDTA and its metabolites are wide-spread in the hydrosphere and in drinking water where it occurs in considerable concentrations. Because of its chelating properties, EDTA has an influence on the heavy metal distribution in the environment. The concentrations of heavy metals in drinking water gained from surface waters or by bank filtration is probably increased by EDTA.

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. Simultaneously, the sediment is deloaded. On the other hand, the aquatic effects assessment resulted that the EDTA complexes of heavy metals are less toxic than the uncomplexed metals. The only exception is Hg-EDTA, which is more toxic than Hg, however Hg has a very low tendency to form EDTA complexes in the hydrosphere. Overall, a risk for the aquatic environment due to the influence of EDTA on the mobility of heavy metals is not expected.

Conclusion (ii).

3.3.1.4 EDTA metabolites

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.

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 PEClocalair for the strongest emission source was estimated to 6.7 µg/m3. No appropriate effect tests are available, so a risk characterisation ratio for this compartment cannot 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 Secondary 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 General discussion

The uses of edetic acid H_4EDTA and its tetrasodium salt Na_4EDTA are determined by their high capacity for complexing metal ions. Diluted aqueous preparations with EDTA concentrations below 5% are mainly used.

In the Swedish product register, 17 out of a total of 118 products are listed as consumer products.

The literature frequently only reports generally on the use of EDTA without distinguishing between H_4EDTA and Na_4EDTA.

The substances, summarised as EDTA, are used in small quantities as intermediates, mainly, however, as additives in the following areas (percental, breakdown for western Europe, CEFIC, 1998):

– Cleaning products for industry and skilled trades	28.7%
– Photochemicals	14.3%
– Agriculture	13.5%
– Pulp and paper industry	12.9%
– Household laundry and cleaning products	7.0%
– Textile industry	1.2%
– Electroplating industry	0.7%
– Cosmetics	1.2%
– Water treatment	0.5%
– Other uses	7.6%
– End uses unknown	12.2%

Further areas of use include the leather industry, the printing industry, the industrial use of oils and greases, the rubber production and processing, the treatment of metal, the construction industry as well as the analytical chemistry.

As a rule, H_4EDTA instead of Na_4EDTA is used when particular demands are made on the purity of the complexing agent. The solubility of the complexing agent can be influenced by the selection of the neutralising agent (NaOH, KOH, amines).

A small proportion of EDTA is used as an intermediate in the production of metal complexes which may be components of, for example, micronutrient fertilisers, photochemicals or cosmetic products.

For workers the inhalative exposure route is the most likely.

4.1.1.2 Occupational exposure

In the following, the description and assessment of occupational exposure is made for both substances, Na_4EDTA and H_4EDTA, summarised as EDTA. If information is related only to one of the substances, this is mentioned in the text.

EDTA is a colourless, crystalline substance and is mainly handled in the form of aqueous preparations. According to information provided by one manufacturer, in the case of H_4EDTA 15% of the powder particles have a diameter under 63 µm and in the case of Na_4EDTA 30% of the powder particles have a diameter < 63 µm.

With regard to the handling of powdery EDTA, exposures to dusts in the production of the substance and its further processing to aqueous solutions during transfer and filling activities are mainly to be expected. Due to the physico-chemical properties of the substance (solid at room temperature, low vapour pressure), inhalative exposures to vapour during the handling of solutions without formation of aerosols are assumed to be negligible. Exposures to droplet aerosols during spray-application of aqueous preparations may additionally occur.

On account of the low dermal absorption of the substance (0.001%), dermal exposure is regarded to be of minor relevance for occupational risks. A theoretical worst-case estimate might serve as 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 of 21.8 mg/kg/day for H_4EDTA (28.2 mg/kg/day for Na_4EDTA). Taking into account that the resulting MOS of > 36,000 is clearly beyond concern, dermal exposure is not assessed quantitatively.

Occupational exposure limits have not been established.

Occupational exposure scenarios may occur in:

- Production and further processing as a chemical intermediate (Scenario 1),
- Formulation (Scenario 2),
- Uses of formulations incl. formulation of preparations on-site (Scenario 3).

Detailed information on the size of the collectives of exposed workers is not available.

4.1.1.2.1 Scenario 1: Production and further processing as a chemical intermediate

EDTA is produced by large-scale chemical companies. The further processing to different products (e.g. detergents, photochemicals ...) predominantly occurs in the large-scale chemical industry, too. These fields are clustered in Scenario 1. The production of formulations by formulators is described in Scenario 2 (see Section 4.1.1.2.2).

The most common process for the production of EDTA is based on alkaline cyanomethylation of ethylene diamine with sodium cyanide and formaldehyde. In this, EDTA is formed directly in aqueous solution. The synthesis takes place continuously in closed systems.

A second, technically utilisable method for the production of EDTA is the two-stage Singer synthesis, which can be performed continuously or batch-wise. In this method, hydrogencyanic acid and formaldehyde first react to form water-insoluble ethylenedinitrilotetraacetonitrile. The nitrile is then separated, washed and hydrolysed with NaOH to form Na4EDTA in an aqueous

solution. After the conversion of Na4EDTA using sulphuric acid, the hardly soluble acid H_4EDTA is precipitated and filtered off.

According to information provided by industry the greatest part of the produced EDTA (H_4EDTA+Na_4EDTA) is placed on the market in the form of aqueous solutions which contain typically 40% EDTA. The solutions are mainly handled in closed systems. However, a powdery good is also produced by means of spray drying. According to information provided by one manufacturer, the filling of the powders into 25 kg paper sacks or big-bag containers is performed automatically and local exhaust ventilation (LEV) is used.

As a rule, the production of the metal complexes and of different liquid preparations consists of a process in which liquid or solid substances are mixed. Information on the production of the metal complex NH_4Fe(III)EDTA has been provided by one manufacturer: The production of the complex as well as the handling of the solutions take place exclusively in closed systems. In the production of preparations, the Na_4EDTA salts are filled into the starting vessels, in part by means of pneumatic conveyance. Local exhaust ventilation systems are present here.

For the production of widespread detergents a level of protection similar to the production and further processing of EDTA is assumed. The concentration of EDTA in detergents amounts to 1%.

In rubber synthesis, EDTA or the disodium salt of edetic acid is added in a quantity of 0.02% to create a redox catalyst system (Winnaker et al., 1982; BASF, 1988). The large-scale production of cold rubber using these catalyst systems takes place in continuously operating, closed system.

In Germany, the use of Na_4EDTA to soften boiler feedwater and cooling water as well as to dissolve and remove condensates and scale is on the decrease. No information is available with regard to uses in other Member States. Na_4EDTA is typically added in amounts of 0.1-0.5% (Kreuter, 1976).

It is assumed that the continuous or batchwise processes occurring in the chemical industry are mainly performed in closed systems and/or at workplaces equipped with local exhaust ventilation systems. For the large-scale chemical industry high standards of control at workplaces are assumed to be practised even if the containment is breached during taking of samples, maintenance, repair and cleaning. On account of the low vapour pressure of EDTA low inhalative exposure is to be expected if liquid EDTA is handled compared to exposure to dust during filling of powdery EDTA. For workers who handle EDTA continuously (e.g. filling, loading and unloading) exposure to dust is assessed assuming that the duration and frequency of exposure are daily and full shift length.

Inhalation exposure

Workplace measurements

Information on exposure has only been provided by 1 of 7 manufacturers. The company provided measurement results relating to the production of the substance, mixing it with other solid substances and adding it to liquid reaction solutions during the production of the NH_4Fe(III)EDTA complex. Total dust samples were taken during the above-mentioned processes. On a worst-case basis, it was assumed that the total dust consists exclusively of EDTA. The measurement value range amounts to 0.002-0.14 mg/m^3 (n=10), the mean being 0.008 mg/m^3 (the item of data relates to Na_4EDTA). No information is provided on the duration and frequency of exposure or on the collective of exposed persons. In the case of workers who, due to the continuous process, handle the substance on a permanent basis, the duration and frequency are assumed to be daily and for the total length of the shift.

A second company provided measurement results on EDTA exposure during the production of metal chelates. It is described that a maximum of 1 batch was charged per shift and that one batch is got through with EDTA. The shift averages described as representing the normal working conditions were at 0.1 mg/m³. The duration of exposure and the duration of sampling were lower: about 15 minutes. During this time, exposure levels were between 2.7 and 4.8 mg/m³ (n=3). Four more results were taken at non-normal conditions in order to exceed the detection limit. The corresponding shift averages were between 0.2 and 0.4 mg/m³.

EASE estimation

The Version EASE for Windows 2.0, Aug. 1997 was used.

EASE estimation for handling the powdery substance with local exhaust ventilation (LEV):

Input parameters: T=20 °C, exposure-type is dust, dry manipulation, LEV present
Level of exposure: 2-5 mg/m^3

Conclusions

Based on the available information, it is to be assumed, that most of the substance is produced in the form of liquid formulations. For this case, based on the low vapour pressure (partially ionic substance), inhalative exposure is assessed as negligible. The formation of aerosols is regarded to be unlikely.

A smaller amount of the substance is produced in the form of a powder. The measurement data provided by 1 of 7 companies are taken to describe an individual case and cannot be regarded as representative for all producers and further processing companies. One user producing metal chelates provided measurements, too. In this case, only one batch per shift during 15 minutes was charged. It is to be assumed, that during the production of EDTA, considerable longer durations of exposure are realised (e.g. drumming during the whole length of a shift). For this reason, the shift averages cannot be regarded as representative for the production of the substance. But it is worth recognising that the short-term values representing exposure during handling EDTA may be representative for shift averaged exposure, if exposure relevant activities are performed during the whole shift. This asssumption is supported by the correspondence between the EASE estimates (2–5 mg/m³) and the measured values (2.7–4.8 mg/m³).

For the purpose of assessing the risks resulting from inhalative exposure to dust in the area relating to the production and the filling of the powdery substance, its further processing as well as the production of preparations in the chemical industry, 2–5 mg/m^3 (EASE estimation, supported by measured results) should be considered as an 8-hour time-weighted average for daily exposure. For batchwise production and use, lower durations of activities relevant for exposure are expected and, therefore, lower shift averages are probable.

Dermal exposure

For the production and further processing of EDTA dermal exposure is assessed as low since direct skin and eye contact can be largely excluded in the chemical industry due to the prevalence of closed process technologies and the use of suitable personal protective equipment. High areas of the skin may be exposed if occasional cleaning and maintenance activities are performed. On account of the low dermal absorption of the substance, dermal exposure is not assessed quantitatively.

4.1.1.2.2 Scenario 2: Formulation

In this section, the production of powdery and liquid products containing EDTA is described. These products are applied in different industrial and skilled-trade sections:

- Water treatment
- Rubber processing
- Phototechnology
- Paper industry
- Textile industry
- Leather industry
- Printing works
- Chemical laboratories
- Use of laundry and cleaning products including high pressure cleaning
- Metal-cutting with cooling lubricants
- Pre-treatment of metal
- Electroplating industry
- Use of herbicides and insecticides (only H4EDTA).

The maximum EDTA concentration in the produced aqueous preparations amounts to < 1% in the main and to 5% in case of photochemicals.

During the use of liquid EDTA for the preparation of formulations, on account of the physico-chemical properties of the substance, inhalative exposure to vapour is assessed as negligible. In the following, the formulation process is described for powdery EDTA.

It is to be assumed, that the preparations are produced in specialised formulation companies or at the users site. In this, possibilities of inhalative and dermal exposure exist during weighing and filling of the powdery substance. It must be assumed that in small and medium-sized companies these activities are performed without local exhaust ventilation and without the use of suitable personal protective equipment (Kliemt, 1995). According to information provided by the monitoring authorities of the Federal States of Germany, the duration (1 minute-1 hour) and frequency of the activities of relevance to exposure vary widely. Mostly, durations far below 1 hour (not daily) are given. Sometimes, tasks are performed repeatedly during the given duration. In one case (production of photochemicals, mixing in closed mixers with LEV present at filling) the daily duration of mixing is 1 hour, but loading the mixer is shorter. The small amounts EDTA used result from the low concentrations in the finished products (mostly < 1%, in photochemicals up to 5%). For the production of 1 tonne of a formulation containing 2% (5%) EDTA, 20 kg (50 kg) EDTA are needed. For example during electroplating a chemical bath (1,200 litres) is prepared containing 42 kg EDTA (BASF, 2000). In this, 2 sacks of powdered material are emptied into a galvanic bath once a day leading to exposure duration far below 1 hour. This activity is not performed on a daily basis. This is by far the highest amount of EDTA used for formulating processes.

Taken all the individual information into account, it is derived that the daily duration is 1 hour at the most and that small amounts are used during this time interval.

Because of the similarity of the exposure relevant activities (handling the powdery substance during filling, weighing, loading, unloading) the scenarios relating to the production of formulations used in the different industries listed above are clustered.

Inhalation exposure

Workplace measurements

No workplace measurements are available.

The Netherlands provided results of a study relating to dumping of powdery goods in different formulating facilities (Marquart et al., 1999). The study was aimed neither at very good nor at very bad equipment. The measurements were taken during continuous dumping of powders into mixers equipped with LEV. The measurement values of 1.9–27.6 mg/m³ (shift averages: 0.8-12.1 mg/m³) refer to the handling of 330–11,369 kg of powders.

Within the framework of an EASE validation study it turned out that exposure levels are below 1 mg/m³ (8-hour TWA), if low amounts of powdery substances are handled. This was shown at workplaces in the textile industry, where printing inks are mixed by adding and mixing powdery substances (colour kitchen, typical amounts a few kg) (Bredendiek-Kämper, 1999).

EASE estimation

The Version EASE for Windows 2.0, Aug. 1997 was used.

a) EASE estimation for handling the powdery substance (non-fibrous, not readily aggregating) with local exhaust ventilation (LEV):

Input parameters: T=20 °C, exposure-type is dust, dry manipulation, LEV present
Level of exposure: 2-5 mg/m^3

b) Handling the powdery substance (non-fibrous, not readily aggregating) without local exhaust ventilation (LEV)

Input parameters: T=20 °C, exposure-type is dust, dry manipulation, LEV absent
Level of exposure: 5-50 mg/m^3

Conclusion

Since no measurement results relating to the formulation of preparations on site using the powdery substance are available, an estimation of the exposure is undertaken using the EASE model. It produces values of 2-5 mg/m^3 with LEV and 5-50 mg/m^3 without LEV. Since the quantities of the substance which are handled to formulate diluted preparations are small, the lower exposure levels of the assessed exposure ranges should be taken for risk assessment. These values (2 mg/m^3 with LEV and 5 mg/m^3 without LEV) should be considered as exposure levels for the duration of the above-mentioned activities. Assuming that inhalative exposure occurs daily and for the duration of one hour, the corresponding 8-hour TWA amount to 0.3 mg/m^3 with LEV and 0.6 mg/m^3 without LEV. This assessment is supported by the low exposure levels observed in the EASE validation study for the handling of small amounts of powdery substances.

Due to the short duration of the activities carried out, the above mentioned Dutch study (Marquart et al., 1999) seems to be only applicable with limitations. Possibly the lower end of the range of measurement values or shift averages is related to the handling of low amounts of powders (as a rough prediction). Taking the lower end of the ranges (measurement value: 1.9 mg/m³, shift average: 0.8 mg/m³) a good agreement with the assessed level is observed.

For the use of EDTA in chemical laboratories, on account of the physico-chemical properties of the substance and the small amounts in use, inhalative exposure to vapour is assessed as negligible.

During the use of liquid EDTA for the preparation of formulations, on account of the physico-chemical properties of the substance, inhalative exposure to vapour is assessed as negligible.

Dermal exposure

For the formulation of preparations containing EDTA it cannot be excluded, that substances and preparations are handled without using suitable personal protective equipment (here gloves and eye protection) (Kliemt 1995). Therefore direct skin contact is probable. On account of the low dermal absorption of the substance, dermal exposure is not assessed quantitatively.

4.1.1.2.3 Scenario 3: Uses of formulations

Powdery formulations containing EDTA (concentrations < 1%) are mainly detergents and fertilisers. For detergents it is assumed, that professional use results in short-term application comparable to consumer exposure. Fertilisers are used seasonally in low dust form. For assessing inhalative exposure, the attention is focused to liquid formulations, especially at workplaces with possible formation of aerosols.

Liquid formulations containing EDTA are used in a variety of industrial and skilled-trade sectors (see Section 4.1.1.2.2). The applications can be subdivided into activities with and without the formation of aerosols.

Use of liquid formulations without formation of aerosols

In the following, those areas are listed at which exposure to aerosols is unlikely:

- Water treatment
- Rubber processing
- Phototechnology
- Paper industry
- Textile industry
- Leather industry
- Printing works
- Chemical laboratories.

Based on the available information on the processes, aerosols are normally not formed at the workplaces. At the most, bath or containers with the solutions inside are applied. At workplaces where aerosols are not formed, on account of the physico-chemical properties of the substance (solid at room temperature, low vapour pressure), inhalative exposure to vapour is assumed to be negligible.

Use of liquid formulations with formation of aerosols

In the following, those areas are listed at which exposure to aerosols may occur:

- Use of laundry and cleaning products including high pressure cleaning
- Metal-cutting with cooling lubricants
- Pre-treatment of metal
- Electroplating industry
- Use of herbicides and insecticides (only H4EDTA).

EDTA is a component of numerous laundry and cleaning products which are mainly used in the skilled-trade area (UBA, 1994b). One area of use is cleaning with high-pressure or steam-jet equipment, e.g. in the food industry and in metal working. Further cleaning products containing EDTA include cleaners intended for skilled-trade use, e.g. floor cleaners, car-cleaning products for brush and high-pressure washing and car shampoos (UBA, 1994b; BASF, 1988). For the purpose of washing and cleaning, diluted solutions are taken. As a rule, the Na_4EDTA concentrations in the cleaning solutions amount to 0.1–2%. The concentrated cleaners containing up to 20% Na_4EDTA are only used directly in rare exceptional cases. In case where high-pressure cleaning is a fundamental step of a production e.g. in bottle filling, stationary high-pressure cleaning working automatically are installed.

Preparations for the cleaning and degreasing of surfaces of materials may contain H_4EDTA. The metal parts are sprayed down with the cleaning solutions or brushed clean in baths.

EDTA may be added to oils and greases which are used in industry to prevent metal-catalysed decomposition. In water-miscible cooling lubricants the part of H_4EDTA in the concentrate may be up to 5% (Baumann and Herberg-Liedke, 1996).

In metal working Na_4EDTA is also used in pickling baths, in agents for stripping lacquers and paints and in galvanic baths. The effect of these baths can be increased by the movement or brushing of the metal parts as well as by the stirring of the solutions.

Spray application of herbicides and insecticides containing H_4EDTA may be performed manually or semi-automatically. As a rule the use of PPE (gloves, respiratory protection) is highly accepted. It is to be assumed that this work is not done daily and not for the entire length of the shift.

Among the above-mentioned fields, manual high-pressure cleaning in different industrial and skilled-trade areas is considered to be the most important exposure scenario. The exposure assessment is performed for this scenario exemplary. Spray-cleaning is often not performed during the whole shift. For assessing inhalative exposure it is to be assumed, that low levels of protection are realised at the workplaces.

Inhalation exposure

Workplace measurements, analogous substances

No workplace measurements relating to EDTA are available. In the following, an estimation of exposure levels is performed by analogy.

The Federal Institute for Occupational Safety and Health (BAuA, Germany) conducted workplace measurements during high pressure cleaning of cars in a washing bay (worst-case: closed room, ventilation only during the exchange of cars). A component of the cleaning agent, linear alkylbenzene sufonate (LAS, concentration in the cleaning product about 0.7%) was detected using ion chromatography. From 20 measurement results (sampling duration 15-210 minutes) 18 were below the detection limit (0.17 mg/m³, sampling time 210 minutes). Two results amount to 0.18 mg/m³ and 0.3 mg/m³. The analogy of LAS and EDTA is justified because both substances are solid at room temperature and both are used in low concentrations in cleaning agents. As a rough estimation an exposure level for EDTA can be derived if the different concentrations of LAS (0.7%) and EDTA (2%) in cleaning products are considered. This leads to exposure levels of EDTA of ca. 0.6 and 0.9 mg/m³. Taking into account that most of the measurement results are lower than the detection limit and that the high pressure cleaning was performed in a room without permanent ventilation, the lower value of 0.6 mg/m³ is

regarded to represent a reasonable worst-case. A request at petrol stations and car washing premises revealed that in Germany high pressure cleaning is not carried out during the whole shift, but irregularly and only for a few hours. For the assessment of an 8-hour-shift average, a daily duration of 4 hours/day is assumed. This leads to a shift average of 0.3 mg/m^3.

EASE estimation

The EASE model is not applicable to this scenario.

Conclusion

For the assessment of risks of inhalation exposure to EDTA during the high-pressure cleaning, 0.3 mg/m^3 (determined by analogy) should be taken as an 8-hour-shift average, and 0.6 mg/m^3 should be taken as an exposure level for the duration of spray-cleaning. It is assumed, that the estimated values can be regarded to represent a reasonable worst case. For the other sections (metal-cutting, pre-treatment of metal, electroplating and use of herbicides and insecticides) exposure levels are assumed to be lower. Exposure to dust during the use of powdery formulations is in the same range or lower, because the concentration of EDTA in detergents and fertilisers is very low (< 1%).

Dermal exposure

It cannot be excluded, that preparations and products containing EDTA are handled without using suitable personal protective equipment (here gloves and eye protection) (Kliemt, 1995). Therefore, during high-pressure cleaning, dermal exposure may occur. On account of the low dermal absorption of the substance, dermal exposure is not assessed quantitatively.

4.1.1.2.4 Summary of occupational exposure

The uses of edetic acid H_4EDTA and its tetrasodium salt Na_4EDTA are determined by their high capacity for complexing metal ions. Diluted substances with EDTA concentrations below 5% are mainly used.

Due to the physico-chemical properties of the substance (solid at room temperature, low vapour pressure), inhalative exposures to vapour during the handling of solutions are assumed to be negligible. On account of the low dermal absorption of the substance (0.001%), dermal exposure is regarded to be of minor relevance for occupational risks. A theoretical worst-case estimate might serve as 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 of 21.8 mg/kg/day for H_4EDTA (28.2 mg/kg/day for Na_4EDTA). Taking into account that the resulting MOS of > 36,000 is clearly beyond concern, dermal exposure is not assessed quantitatively.

The relevant inhalation exposure scenarios are given in **Table 4.1**.

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. For this case exposure is assessed as negligible. If powders are produced, exposure of dusts occurs if the closed systems are breached for certain activities e.g. filling (Scenario 1, **Table 4.1**).

If formulating of products is performed using the powdery substance, possibilities of inhalation exposure occur during weighing and filling (Scenario 2, **Table 4.1**).

Inhalation exposure has to be considered if droplet aerosols are formed during the application of aqueous preparations. Among the different fields of applications (see Section 4.1.1.2.3) high-pressure cleaning is considered to be the most important exposure scenario (Scenario 3, **Table 4.1**). Exposure is negligible if aerosols are not formed.

Table 4.1 Summary of exposure data concerning inhalation exposure relevant for the occupational risk assessment

Exposure by inhalation								
Area of production and use	**Form of exposure**	**Activity**	**Duration**	**Frequency**	**Shift average [mg/m³]**	**Method**	**Exposure duration < shift length [mg/m³]**	**Method**
Production and further processing								
Production and further processing of powdery EDTA	dust	transfer, filling, mixing	shift length	daily	2–5 (1), (2)	EASE	--	--
Preparation and use of formulations								
Preparation of formulations, handling of the powdery substance	dust	transfer, filling, mixing	1 hour (assumed)	daily	0.3 (3) 0.6 (3)	EASE (with LEV) (dilut. ventil.)	2 (3), (4) 5 (3), (4)	EASE (with LEV) (dilut. ventil.)
High pressure cleaning (diluted solutions, < 2% EDTA)	droplet aerosols	spraying	4 hours (assumed)	daily	0.3 (5)	determined by analogy	0.6	determined by analogy

1) EASE estimate because of non-representative measurement results, estimate supported by measurement results
2) Most of the substance is produced as a liquid formulation. In this case inhalative 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) EASE estimation for the duration of the activity
5) Exposure assessment exemplary for all uses of formulations (liquid, powdery) where the formation of aerosols are probable
Exposure is negligible, if aerosols are not formed.

4.1.1.3 Consumer exposure

According to the Swedish product register, EDTA is used in photochemicals, fixing agents, developers, and detergents. The consumer products are offered in wholesale and retail trade, as products for personal and household use and in stores for photographic equipment and similar services (as per February 1995). As outlined under Section 4.1.1.1, the most important exposure of EDTA for consumers should be expected from use of household detergents and cosmetics. The use in textiles cannot be discussed because of lacking data, which has been already discussed under occupational exposure.

In the Federal Republic of Germany, EDTA is used as a component of cosmetics (skin creams and lotions, after care products for hair in concentrations of <0.2%, 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% (voluntary notification to the Federal Institute for Health Protection of Consumers and Veterinary Medicine (BgVV), as per September 1996).

Furthermore, the consumer may be exposed to EDTA by migration of the substance from plastics coming into contact with foods.

Thus, the consumer may be exposed to EDTA via dermal and oral routes.

Dermal exposure

Exposure to cosmetics

When using 16 g of a lotion per day containing 0.2% of EDTA (=0.032 g), the total exposure can be estimated to ≈ 0.5 mg/kg bw/day (=16,000 mg · 0.002/60 kg bw).

For hair bleaching an amount of 5-6 ml (≈5-6 g) of a hair bleaching agent containing 1% of EDTA (=60 mg of EDTA) is used. Taking into account the retention factor of 10, then 6 mg of EDTA would contact skin, which is 0.1 mg/kg bw.

Exposure to household cleansers or dish washing agents

The following assumptions, presented in **Table 4.2** were used to estimate exposure of consumers to household cleansers. This example is supposed to cover all of the subcategories of household cleansers. The value of weight fraction was set to 10% as a worst-case estimate because this is the highest concentration found among 427 products in the BgVV database. The most probable concentration of EDTA in household cleaners, however, is below 1%.

Table 4.2 Parameters for estimation of dermal exposure to EDTA

Weight fraction of chemical in product	10	%	Worst-case estimate
Density of formulation	0.86	g/cm³	
Dilution fraction	0.01		TGD default
Amount of product used per event	100	g	worst-case estimate
Film thickness of liquid on skin surface	0.01	cm	TGD default
Skin surface area exposed per event	795	cm²	TGD default
Body weight	60	kg	TGD default
Frequency of events per year	360	times	days per year

According to the equations given in the appendix of the TGD, the worst-case estimate of the daily dermal exposure was calculated as 0.12 mg/kg bw/day.

Oral exposure

Because Fe(II)EDTA is used in the emulsion polymerisation of styrene-butadiene rubber, it might be assumed that consumers are exposed to EDTA from migration of residues of the substance from food packing material coming into contact with foods. There is no specific EU harmonised legislation for rubber materials and articles intended to come into contact with food. Article 2 of Council Directive 89/109/EEC lays down general rules about the migration of substances from food contact materials that are not covered by specific rules. Plastic materials and articles intended to come into contact with food have to comply with the rules laid down in Commission Directive 2002/72/EC. EDTA is listed in that Directive as an additive that may be used for technical effect in the manufacture of the plastic material without limit of migration.

Because no data exist about the amounts used for this purpose and how much is migrated from plastic materials, an estimation of exposure is not possible.

Additionally, oral exposure may result from the use of cleansers of tooth brackets that contain maximum concentrations of 5% (=50 mg/ml) of EDTA. Assuming that brackets having an area of~6 cm², and the thickness of the layer after cleansing is 0.01 cm, without rinsing with water as a worst-case, the residual amount of EDTA on the bracket would be 3 mg (= $6 \cdot 0.01 \cdot 0.05$). Because tooth brackets are normally used in childhood, the body weight assumed was related to the bodyweight of a 10 year old child, accounting for 30 kg (5^{th} percentile), the exposure is 0.1 mg/kg bw.

In summary, the exposure of EDTA is as follows, as presented in **Table 4.3**.

Table 4.3 Total exposure of consumers to EDTA

Cosmetics	External exposure	Internal exposure	
Lotions	0.5 18	0. 000005 0.00018	mg/kg bw/day mg/kg bw/year
Hair bleach	0.1	0.000001	mg/kg bw/event
Household cleansers	0.12 4	0.0000012 0.00004	mg/kg bw/day mg/kg bw/year
Plastic material		Unknown	
Tooth brackets	0.1	mg/kg bw/day	

The calculation of dermal exposure of consumers results in a value of ~0.72 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. The internal exposure from dermal contact may result in a maximum amount of 0.0000072 mg/kg bw/day.

The calculation of oral exposure (only for tooth brackets wearing children) is 0.1 mg/kg bw/day.

4.1.1.4 Indirect exposure via the environment

As EDTA does not accumulate in biota, a significant intake via fish, plants or meat is not expected. The only significant indirect exposure for human occurs via drinking water.

Production and treatment of drinking water

The behaviour of EDTA at different drinking water purification techniques was studied in several investigations; a summary is given by Schick (1994).

Bank filtration

Near a drinking water work at the Rhine, EDTA was measured in the ground water at different distances from the river. Up to 30 m, no elimination was observed. Only at a distance of 70 m the concentration was lower, the author interprets this as dilution with groundwater coming from the land side. EDTA is not eliminated in the filtration zone (Schick, 1994).

Based on measurements in river water (Elbe) and bank filtrate, a very slow degradation of EDTA during bank filtration was found under both aerobic and anaerobic conditions. The elimination rate was 20% after 1-8 days in a both aerobic and anaerobic zone, 47% after 20-40 days and 53% after 150-300 days under anaerobic conditions. The EDTA concentration in the river was 15.3 µg/l (50 percentile values) (Grischek et al., 1997).

At a further site at the same river with a retention time in the aquifer of only a few days, no significant elimination was found (Guderitz et al., 1993).

Slow sand filtration

In a test apparatus, no EDTA elimination was observed (Schick, 1994).

Charcoal

EDTA is adsorbed on charcoal. However, a breakthrough occurs with relatively low water volumes (< 15 m3/kg) (Schick, 1994).

Oxidation

While chlorine and chlorine dioxide did not react with EDTA, it is oxidised by ozone. Oxalic acid, glyoxylic acid, iminodiacetic acid, glycine, nitrate and ammonium were identified as reaction products. After subsequent chlorination, trichloronitromethane is formed (Schick, 1994). Gilbert and Hoffmann-Glewe (1990) found ethylenediamine N,N'diacetic acid, formic acid and small amounts of nitrilotriacetic acid additionally.

In laboratory experiments, a more effective oxidation was found with UV/H_2O_2 and O_3/H_2O_2. These techniques are not in practice.

Measurements at drinking water works showed different results: in the water work at Düsseldorf-Flehe, the EDTA concentration decreased from 28 µg/l in the Rhine to 4 µg/l in the drinking water (after bank filtration, ozone oxidation, filtration, and charcoal adsorption), i.e. an elimination of 86%. In water from Lake Constance, the decrease was from 2.5 µg/l in the lake to 1.5 µg/l (elimination 40%) after sieve, ozone oxidation, and sand filtration (Schick, 1994).

Monitoring

In drinking water produced from Rhine water, EDTA concentrations up to 31 µg/l were measured in 1988/89 (Bayer AG, 1989).

In drinking water produced by bank filtration from the river Ruhr, EDTA concentrations up to 19 µg/l were measured (Brauch, 1988). In 1992/93, the median value was about 10 µg/l, 5% of the measurements were above 20 µg/l (Klopp and Pätsch, 1994). In the period 1997 to 1998, EDTA concentrations between 2.8 and 12.7 µg/l were measured at 6 water works at the same river (AWWR, 1998, 1999). With this drinking water, a densely populated region with several million inhabitants is supplied.

In drinking water from the Lake Constance, 1.5 µg/l were detected (Schick, 1994).

In 1996/97, EDTA annual average concentrations from 0.5 to 9.6 µg/l were analytically determined in drinking water of 18 water works gaining from surface water and bank filtration. Two further water works gaining drinking water from groundwater and well water, EDTA was not detected with a detection limit of dl=0.5 µg/l (DVGW 1997).

The analysis of 47 samples of 14 water supply companies in The Netherlands confirmed the presence of EDTA in drinking water prepared from surface water, with or without dune filtration or bank filtration, in concentrations of 10 to 30 µg/l (van Dijk-Looyard et al., 1990).

Model calculation

As a worst-case approach it is assumed that no elimination during purification occurs as ozone oxidation is not an overall spread technique. According to the TGD model, the intake is calculated for all exposure scenarios:

Table 4.4 Calculation of indirect exposure via the drinking water

Scenario	$PEClocal_{aqua}$ [mg/l]	$DOSE_{tot}$ [mg.kg $bw^{-1}.d^{-1}$]
Producer B	0.18	0.0057
Producer C	0.095	0.0030
Producer D	max. 1	max. 0.032
Producer E	0.36	0.011
Producer F	0.10	0.0032
Producer G	0.22	0.0069
Producer H	0.098	0.0031
Household sewage	0.195	0.0061
Industrial detergents 1 2 3	0.64 2.6 0.35	0.020 0.082 0.011
Photochemicals	0.57	0.018
Textile industry	2.0	0.063
Pulp and paper 1 2	0.5 2.6	0.016 0.082

Table 4.4 continued overleaf

Table 4.4 continued Calculation of indirect exposure via the drinking water

Scenario	$PEClocal_{aqua}$ [mg/l]	$DOSE_{tot}$ [mg.kg $bw^{-1}.d^{-1}$]
Metal plating	12	0.38
Polymer / rubber production	1.7	0.054
Recovery	2.4	0.076
Agriculture	PECs see Section 3.1.5.2	0.0024
Regional	PECs see Section 3.1.3.4	0.0039

In the regional scenario, 70% of the intake is via drinking water, 7% via fish and 23% via aboveground plants. From the agricultural use, the intake is nearly 100% from aboveground plants. In all other scenario EDTA is released into surface waters, leading to 90% intake via drinking water and 10% via fish.

EDTA metabolites

In surface waters, Fe(III)EDTA is photolytically degraded, the known transformation products are listed in Section 3.1.2.1 During bank filtration, N-carboxymethyl-N,N'-ethylenediglycine (ED3A) and its subsequent product ketopiperazinediacetate (KPDA) is formed by biological transformation. In accordance to the TGD, the metabolites have to be included in the risk assessment.

KPDA was measured in drinking water gained from bank filtration in Wiesbaden (Germany). ED3A and KPDA cannot be safely distinguished by the applied analytical method, but the author's state that KPDA was probably dominating in the samples. The concentrations [µg/l] during the subsequent purification steps, as presented in **Table 4.5**, were (Ternes et al., 1996):

Table 4.5 Concentrations during subseaquent purification steps

Step	[KPDA + ED3A]
Rhine water	5.5
Flocculation	3.5
Charcoal	1.2
soil passage	1.9
slow sand filtration	1.3
Disinfection	1.5

KPDA was detected in 10 different drinking waters and in 2 of 15 mineral waters, the single concentrations are not reported.

As no more data are available, the drinking water concentration of 1.5 µgl for the sum of KPDA and ED3A is considered for the exposure estimation, having in mind that this is no worst-case scenario. According to the TGD model, the intake for a person with 70 kg body weight and a daily consumption of 2 l drinking water is calculated:

$\Rightarrow DOSE_{drw}=0.043\ \mu g \cdot kg\ bw^{-1} \cdot d^{-1}$ (ED3A + ketopiperazinediacetate, KPDA)

Furthermore, the following photolysis products are known to be formed, and it is probable that they occur in drinking water:

- N,N'-ethylenediglycine (EDDA-N,N')
- N-carboxymethyl-N-aminoethyleneglycine (EDDA-N,N)
- N-aminoethyleneglycine (EDMA)
- the respective ketopiperazine compounds formed from EDDA-N,N', EDDA-N,N, EDMA

Because of the lack of exposure data, intake doses for these substances cannot be estimated. A monitoring program is needed to clarify the exposure of these compounds.

Heavy metals

The investigations cited above do not distinguish between uncomplexed and complexed EDTA species. As described in Section 3.1.3.3.2, EDTA mainly occurs as heavy metal complex in river water. It has to be expected that during bank filtration the presence of EDTA will increase the heavy metal concentration, since there is a tendency to prevent adsorption and precipitation of the metal ions, and no mechanism breaking the heavy metal complexes and eliminating the metals is obvious.

The behavior of Cadmium in slow sand filters used in artificial recharge of groundwater was studied by Schmidt (1977). Cadmium (50 µg/l, about 100 times higher than recent environmental concentrations) was dosed into the filter influent. The metal ions were held back totally over a period of 60 days. During the following 40 days the Cd concentration in the effluent rose up to one tenth of the dosage, showing a wash effect over 30 days after the dosage had been stopped. The addition of 1 mg EDTA/l increased the effluent concentration up to the level of the inflow during the dosage time.

The behavior of dissolved metals, EDTA and natural ligands during infiltration of river water to the adjacent aquifer was investigated at the Swiss river Glatt (Nowack et al., 1997). The speciation of EDTA was determined by a combination of experimental methods and of equilibrium calculations. Results for some metals are:

Fe: The fraction of EDTA that is present as Fe(III)-EDTA decreases from the river with 35% to 11% in groundwater. In the thermodynamic equilibrium, nearly no Fe-EDTA is expected. The Fe cation is exchanged by other metals.

Ni: The fraction of Ni-EDTA is slightly increasing during infiltration. However, only a minor fraction of Ni is complexed with EDTA. Natural ligands have possibly a greater influence on the Ni concentration in bank filtrate.

Zn: The fraction of Zn-EDTA is in all samples between 40 and 60% of total EDTA.

Mn: The fraction of Mn-EDTA is increasing during infiltration from 20% in the river to 40% in the filtrate. Mn is not complexed by natural ligands, thus EDTA has a significant influence on its abundance.

Ca: The fraction of Ca-EDTA is increasing from 13% to 40% in the deeper groundwater where the metal concentrations are low.

Pb: The fraction of Pb-EDTA is always below 3%. 93% of the Pb are complexed with EDTA, and this explains the high mobility of Pb.

Cu: The fractions are always below 1% of total EDTA. Less than 0.1% of the Cu are complexed with EDTA, so EDTA has no influence on the abundance of this metal.

From these results we conclude that EDTA can increase the concentrations of Mn, Ca and Pb in the drinking water gained from bank filtration. An absolute increase cannot be determined, as this is strictly dependent on the EDTA concentrations, and probably dependent on other parameters like the geological nature of the bank zone.

4.1.1.5 Combined exposure

It is possible for an individual to be exposed to EDTA/Na_4EDTA at work, from consumer products and indirectly via the environment. Occupational exposure may occur via inhalation, whereas the dermal exposure is low due to the poor absorption of EDTA (internal body burden 0.6 µg/kg bw/day). For different scenarios an inhalation exposure of 0.3 to 0.6 mg/m^3 (see **Table 4.1**) was estimated as reasonable worse case. The corresponding values for internal body burdens were calculated to be 43 to 86 µg/kg bw/day. The internal exposure levels resulting from dermal exposure to consumer products were estimated as a worse case up to about 0.0072 µg/kg bw/day. The levels that would be received indirectly from environmental sources via drinking water range from 0.003 to 0.38 mg/kg bw/day.

4.1.2 Effects assessment: Hazard identification and Dose (concentration)-response (effect) assessment

Introductory remarks: Justification for cross-reading from different EDTA compounds

In general, edetic acid (H_4EDTA) and tetrasodium EDTA show similar properties and exposure pattern. With respect to acute toxic and local effects both substances show different effects. Thus, the hazard effects of the two substances are evaluated separately for the endpoints acute toxicity, irritation, corrosivity and sensitisation indicating the test substances used in the respective toxicity assays. Therefore, the description of the health effects (Effects assessment) is presented in two separate reports to distinguish between the two substances.

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 (Becke-Göhring and Fluck, 1961). 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 ($CaNa_2$EDTA) were discarded from all sections of the report except the section on toxicokinetics and reproductive toxicity. Taking into account the stability constant of the calcium EDTA complex (about $10^{10} \cdot M^{-1}$) the concentrations of free anionic EDTA species in $CaNa_2$EDTA solutions can be estimated to amount < 0.01% according to the mass action law (see Section 3.1.3.3.1). Thus, almost all proportion of the $CaNa_2$EDTA complex is still present as $CaEDTA^{2-}$ species, whereas only a very minor proportion of the $CaNa_2$EDTA 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 Na_4EDTA.

The $CaNa_2$EDTA will chelate any other metal that has a higher binding affinity than Ca^{2+} (e.g. lead, iron, zinc, and copper). For instance, lead chelates with $CaNa_2$EDTA to form a complex that is 10^7 times greater than that of the calcium complex. Due to these chelating properties $CaNa_2$EDTA is administered intravenously for therapy of heavy metal poisoning. On the other hand, zinc chelates with $CaNa_2$EDTA to form a complex that shows a 10^4 times higher binding affinity than that of the calcium complex. Therefore, application of $CaNa_2$EDTA will result in complexation of zinc ions thus interfering with the zinc homeostasis and leading finally to developmental toxicity (see Section 4.1.2.9).

4.1.2.1 Toxico-kinetics, metabolism and distribution

Studies in animals

Following oral administration of the calcium salt of 14C-EDTA (50 mg/kg bw) to rats the chelate was poorly absorbed from the gastrointestinal tract (2 to 18% within 24 hours). After parenteral injection of a comparable dose, 95 to 98% radioactivity was excreted in the urine within 6 hours with an elimination half-life of approximately 50 minutes. A very small amount of the radioactivity, less than 0.1% of the dose, appeared in the respiratory CO_2 (Foreman et al., 1953).

Ten i.p. injections of $CaNa_2$-14C-EDTA salt (300-500 mg/kg bw/day) were applied to rats. 66 to 92% of the total activity injected was recovered in the urine. The activity of both kidneys

24 hours following the last injection was less than 0.1% of the total injected dose (Doolan et al., 1967; Miller et al., 1986).

The effects of $CaNa_2EDTA$ salt (280 mg/kg bw/6h for 54 hours, application s.c.) on the metabolism of Zn, Cu and Mn were investigated in dogs. The substance increased significantly the urinary excretion of Zn, Cu and Mn (Ibim et al., 1992).

Inhalation studies are not available.

Studies in humans

Foreman and Trujillo (1954) have studied the toxicokinetics of 14C-EDTA, ($CaNa_2EDTA$; 2 mg) using young healthy adult men. Studies were carried out after peroral and parenteral application and after application on the skin. EDTA is poorly absorbed from the gastrointestinal tract. 24 hours after oral application, a maximum of 5% of the dose was detected in the urine; faeces still contained the substance up until day three. Overall, 93% was recovered. Intravenously injected Calcium-14C-EDTA (2 mg with 2 g unlabelled $CaNa_2$ EDTA) is excreted within 24 hours in the urine, 50% of it in the first hour, 90% within 7 hours. The dose used in skin absorption studies (2 mg calcium salt of 14C-EDTA and 1 g unlabelled $CaNa_2EDTA$) was prepared in a water-soluble base. In one study the sodium salt of 14C-EDTA was used in the place of the calcium salt. Because of the very low activity, the urine from skin absorption studies required special treatment with the sodium salt of EDTA as carrier. The maximum of activity in the urine after application over an area of 100 cm² was 0.001%.

Inhalation studies are not available.

Conclusion on 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. In whatever salt EDTA is administered it is likely to chelate metal ions in vivo. 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 $CaNa_2EDTA$.

Calcium salts of EDTA are poorly absorbed from the gastrointestinal tract (2 to 18% within 24 hours), a maximum of 5% was detected in the urine. Only 0.001% is absorbed after dermal application. Intravenously injected EDTA is excreted within 24 hours in the urine, 50% of the substance in the first hour and 90% within 7 hours.

4.1.2.2 Acute toxicity

Studies in animals

Oral exposure

For the rat LD50 values of >2,000 mg/kg bw (Akzo Chemicals, 1987) and of approximately 4,500 mg/kg bw are reported (BASF AG, 1973b). After treatment of 5 female and 5 male rats (Wistar) with the limit dose of 2,000 mg/kg bw of edetic acid (99% purity, vehicle water) in a test according to international guidelines no deaths, no clinical signs and no autopsy findings

were reported (Akzo Chemicals, 1987). In the test with the LD50 being approximately 4,500 mg/kg bw (edetic acid (no data on purity) administered as 30% preparation in an aqueous solution of carboxymethylcellulose) clinical signs consisted of dyspnoea, diarrhoea and spastic gait. Autopsy revealed general hyperaemia, dilatation of the heart, bloody ulceration of the stomach and fluid contents of the intestine (BASF AG, 1973c).

Inhalation exposure

In a test system similar to the inhalation hazard test, 12 rats/group were exposed for 8 hours to a dust atmosphere containing edetic acid (no data on purity) heated to 20 or 80˚C.

In the test chamber no concentration was measured. A mild irritation of the mucous membranes was observed. There were no mortalities and no autopsy findings (BASF AG, 1973c).

Dermal exposure

No animal data are available

Studies in humans

See Section 4.1.2.5

Conclusion on acute toxicity

In rats the acute oral toxicity is low. In two tests LD50 values of > 2,000 mg/kg were reported. There is no need for classification and labelling for acute oral toxicity.

In a test system similar to the inhalation hazard test there was no mortality (12 rats) after an 8-hour exposure of an unknown test concentration of the substance that was heated to either 20 or 80˚C.

This result is considered to be sufficient for the risk assessment of acute inhalation toxicity. There is no need to conduct an LC50 test and no need for classification and labelling for acute inhalation toxicity.

No data are available on acute dermal toxicity. Taking into account the poor dermal absorption (Foremann, 1954), there is reason to assume that the result of an acute dermal toxicity test would not reveal toxic properties warranting a classification and labelling for acute dermal toxicity.

4.1.2.3 Irritation

Studies in animals

One rabbit was exposed for either 1, 5 or 15 minutes or 20 hours on the back or for 20 hours on the ear to a 50% aqueous preparation of edetic acid (no data on purity). At 24 hours the ear showed a mild irritation after a 20-hour exposure time. There were no other findings (BASF AG, 1973c).

Instillation of 50 mg of solid edetic acid (no data on purity) to the eye of one rabbit resulted in mild irritation, strong oedema, mild opacity and blood formation at one hour. At 24 hours there was a strong irritation, mild oedema and strong opacity. Irritation scores are not mentioned. At 8 days there were no findings (BASF AG, 1973c).

Studies in humans

No data on humans are available.

Conclusion on irritation

A 50% aqueous preparation of edetic acid (no data on purity) resulted in a mild irritation of the skin after a 20-hour exposure time. It can be concluded that these findings do not warrant a classification and labelling for skin irritation.

Instillation of 50 mg of solid edetic acid (no data on purity) to the rabbit eye resulted in strong but reversible irritant effects that led to a classification as "Xi, Irritant" and labelling as "R 36, Irritating to eyes".

4.1.2.4 Corrosivity

Studies in animals

The substance is not corrosive to skin but irritating to eyes (BASF AG, 1973b).

Studies in humans

No data on humans are available.

Conclusion on corrosivity

The animal data obtained for skin and eye irritation demonstrate a weak effect on the skin and an irritating effect on the eye (see Section 4.1.2.3). There is no need to classify the substance as corrosive.

4.1.2.5 Sensitisation

Studies in animals

In a Magnusson Kligman Test according to OECD Test Guideline 406 Na_2EDTA (Trilon BD; purity 99%) 10 test animals and 5 control animals were used. A 0.5% substance concentration was used for intradermal induction and for topical induction the substance concentration was 30% in test animals. Control animals were treated with the vehicle corn oil. The challenge was conducted with a 30% substance concentration in corn oil. 3/10 (30%) test animals showed a discrete patchy erythema 24 hours after patch removal; after 48 hours 0/10 test animals showed a positive reaction. Control animals were negative. A second challenge was conducted 7 days later with a 30% substance concentration in corn oil. 1/10 (10%) test animals demonstrated a discrete patchy erythema after 24 hours, but not after 48 hours. Control animals exhibited no skin reactions (BASF AG, 2000a).

With Na_3EDTA a Repeated Insult Patch Test gave a negative result (0/10 guinea pigs). Within 10 days the animals received 4 topical treatments (0.1 ml) of Na_3EDTA (10%) in dipropyleneglykolmethylether; after the third treatment 0.2 ml FCA was injected. 14 days after the last treatment the challenge was conducted with Na_3EDTA (10%) in dipropyleneglykolmethylether. Cross-reaction with ethylenediamine was not observed (Henck et al., 1980). This test is not an OECD adopted test.

Studies in humans

Skin sensitisation

Three out of 50 subjects showed a positive reaction to EDTA (patch test concentration 1%, Raymond and Gross, 1969). In another study after patch testing with a 1% EDTA concentration (Rudner, 1977), an incidence of 0.9% (positive responses of 215 subjects) was reported by the North American Contact Dermatitis Group without data on exposure to EDTA or other tested substances. Positive incidences of 1.7-2.8% (13/743 or 10/345 patients) were reported by Pevny and Schäfer (1980) and by Pevny et al. (1981). However the usual test concentration of 1% in either petrolatum or water (de Groot, 1986) was not used but a 10% concentration in petrolatum. Therefore, these data may not only suggest a contact allergy but also an irritating response. In 529 patients with eczematous dermatitis 2 (0.4%) showed a positive reaction to EDTA. It was not mentioned if the patients were exposed to EDTA (Angelini et al., 1985).

According to Fisher (1986) not a single positive reaction in hundreds of patients who were tested with EDTA was observed. He concludes that EDTA is not a sensitiser and also does not cross-react with ethylenediamine hydrochloride.

Respiratory sensitisation

Six out of 22 patients with stable asthma developed bronchoconstriction after inhaling 4 ml of a nebuliser containing EDTA (0.5 g/l) and benzalkonium bromide (0.25 g/l) as preservatives together with the bronchodilatator ipratropium bromide. When these six subjects inhaled 4 ml EDTA and benzalkonium bromide free ipratropium bromide solution all subjects showed bronchodilatation. Inhalation of EDTA and benzalkonium bromide administered separately (EDTA solutions containing 0.25–10 g/l) produced dose related bronchoconstriction which persisted for longer than 60 minutes. The cumulative geometric mean (range) of a 20% fall in FEV_1 (forced expiratory volume) was 2.40 g/l (1.2-12.8) for edetic acid. Although the mechanism by which edetic acid causes bronchoconstriction is uncertain, it probably relates to its action as a chelator of calcium ions (Beasley et al., 1987). In another study with asthma patients Beasley (1989) could not reproduce the result in that EDTA (0.5 g/l) did not influence the bronchodilator effect of a single dose of inhaled Duovent with fenoterol (0.31 g/l) and ipratropium bromide (0.13 g/l). However, the airway effects of repeated inhalations of EDTA were not investigated.

The use of these data for even a qualitative risk assessment is limited due to unclear experimental details with regard to the dissolved amount of edetic acid.

In letters from industry (BASF, Dow, Akzo Nobel, CEFIC) it was reported that no adverse acute or chronic respiratory health effects from exposure to EDTA or Na_4EDTA have been observed in workers (BASF-Letter, 2001). However, this information is not valid because no details were given on the effects on the respiratory tract and on the methodolgy of the exposure measurement (duration, intervals).

Conclusion on sensitisation

In a Magnusson Kligman Test with Na_2EDTA according to OECD 406 3/10 (30%) of the guinea pigs showed a positive response after a first challenge and 1/10 (10%) after a second challenge. There are only two reports on humans. 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 is too low to warrant a labelling with R 43 “May cause sensitisation by skin contact”.

Taking into account that the result of the study of Beasley et al. could not be reproduced, we do not recommend a labelling as R 42 "May cause sensitisation by inhalation".

4.1.2.6 Repeated dose toxicity

There are no repeated dose studies with EDTA itself or the tetrasodium salt available. In whatever salt EDTA is administered it is likely to chelate metal ions in vivo. Under the assumption of these biomechanism, investigations on Na_2EDTA and Na_3EDTA will be considered.

Oral application in rats for one month revealed a NOAEL of 1,125 mg/kg/day=2.25% in diet. This was calculated from a feeding study with Na_2EDTA where the test compound was incorporated at levels of 1, 2.25 and 5% in the diet (15 rats per sex and dose level over a period of one month). At the upper dose level body weight decrease, some mortalities and a reduction of total leucocytes and lymphocytes as well as an increase of bound urine nitrogen (BUN) and a decrease Ca serum levels were found. Pathological investigation at this dose level revealed a decrease of liver, spleen and thymus weight. Some parakeratosis was detected in the oesophagus and forestomac by histopathology (Kawamata, 1980).

Groups of 10 male Holtzman rats were placed on 1, 5 and 10% (respectively 500 mg/kg bw; 2,500 mg/kg bw and 5,000 mg/kg bw) Na_2EDTA in the diet for 90 days. The mid and high dose animals expressed significant decreased body weights and food consumption. Dose dependent mortality was evident by 20% in the 5% and 60% in the 10% group. In these groups animals exhibited diarrhea and were emaciated. Water consumption was increased. In the upper dose there was an intermittent decrease of hematocrit and hemoglobin levels and livers appeared to be pale. Histological investigation failed to reveal any pathological alteration. From this investigation, a NOAEL of 500 mg/kg/day equivalent to 1% in diet can be deduced for male rats (Wynn, 1970). It should be noted that in this study no complete biochemical investigations have been performed.

Investigations with Na_3EDTA over a period of two years in rats and mice (50 animals per dose-group and sex) revealed a NOAEL of 500 mg/kg/day (corresponding to 7,500 ppm in the diet). In this feeding study with two dose levels (3,750 ppm and 7,500 ppm) no substance related toxic effects could be observed for both species. In this study a range finding study with 5 males and 5 females being fed with 4,640, 6,800, 10,000, 14,700 and 21,600 ppm Na_3EDTA in the diet for seven weeks is reported; which revealed soft stool in males at 10,000 ppm and above and in females at 14,700 ppm and above (NTIS, 1977).

Other information

There is quite a number of information on pharmacological actions of various EDTA-compounds mainly under the aspect of complex formation. These informations contain aspects of neuro and nephrotoxicity of EDTA, but are considered not to be relevant because EDTA has been administered by the i.p., s.c. or i.v. routes. These applications do not represent normal exposure conditions and are therefore not taken into consideration for risk assessment (Doolan et al., 1967; Duhr et al., 1993; Engström et al., 1980).

Conclusion on repeated dose toxicity

The 90-day study as well as the two years investigations provide reliable toxicological information to consider a NOAEL of about 500 mg/kg/day for rats and mice (corresponding to

435 mg/kg bw EDTA). 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.

Range finding studies with higher dose levels revealed diarrhea, emaciation, loss of body weight and sometimes parakeratosis in oesophagus and forestomac as well as decreased hemoglobin and hematocrit levels.

4.1.2.7 Mutagenicity

Concerning the free acid EDTA only a few data from genotoxicity assays in vitro and in vivo are available, so that data from structurally related EDTA sodium salts (in vitro, Na_3EDTA and in vivo, Na_2EDTA) have also been considered.

4.1.2.7.1 *In vitro* genotoxicity tests

Bacterial mutation tests

The bacterial mutation tests are available for Na_3EDTA.

Na_3EDTA was negative in bacterial mutation tests employing Salmonella typhimurium strains TA 97, TA 98, TA 100, TA 1535, TA 1537, TA 1538 and E. coli WP2uvrA with rat, mouse and hamster liver S-9 mix as well as without S-9 mix up to 10,000 µg/plate (Dunkel et al., 1985; Zeiger et al., 1988). Toxic effects were observed with and without S-9 mix at doses of 3,333 µg/plate and higher.

Mammalian cell culture tests

Mammalian cell culture tests were performed with EDTA (free acid).

In a mouse lymphoma assay which was done only without metabolic activation, 2-fold to 6-fold increases of mutant frequencies were induced by EDTA at very high concentrations of 25 and 30 mmol/l and a treatment time of 4 hours; relative total growths at these concentrations were 57% and 16% respectively. The pH, measured in a parallel experiment where EDTA was dissolved in culture medium (pH of 7.2), was reduced to 5.8 at 30 mmol/l and to 6.1 at 20 mmol/l, when measured directly after preparation of the solution. Whether the mutagenic activity was due to pH effects or due to the high tested concentrations seems to be unclear (Wangenheim and Bolcsfoldi, 1988).

In an alkaline elution assay with mouse lymphoma cells EDTA induced DNA single strand breaks in very high concentrations from 40 mmol/l upwards. Data on toxicity were not given; the assay was conducted without a metabolic activation system only (Garberg et al., 1988). In concentrations up to 30 mmol/l EDTA induced no effects with and without S-9 mix in alkaline elution assays with V79 cells (Swenberg et al., 1976; Swenberg, 1981).

Regarding Na_3EDTA, negative findings were reported by NTP (2003) in an *in vitro* chromosomal aberration test, in an in vitro SCE test and also in a mouse lymphoma test. Detailed data for these tests are not available up to now.

Table 4.6 Summary of *in vitro* genotoxicity results

Test system	Concentration range		Result	Toxicity	Remarks	Test substance	Reference
	with S-9 mix	without S-9 mix					
Gene mutations, Salm. typh. TA 98, TA 100, TA 1535, TA 1537, TA 1538, E. coli WP2 uvrA	10-10'000 μg/plate	10-10'000 μg/plate	negative	with and without S-9 mix at doses of 3,333 μg/plate and higher		Na_3EDTA	Dunkel et al. (1985)
Gene mutations, Salm. typh. TA 97, TA 98, TA 100, TA1535	100-10'000 μg/plate	100-10'000 μg/plate	negative	with and without S-9 mix at doses of 6,666 μg/plate and higher		Na_3EDTA	Zeiger et al. (1988)
Mouse lymphoma assay	not done	10-30 mmol/l	positive	at doses of 25 mmol/l and higher	4 h treatment; effect only at very high concentrations; possibly the result was due to pH effects	EDTA	Wangenheim and Bolcsfoldi (1988)
DNA damage; alkaline elution; V79 cells	1.0-10 mmol/l	1.0-10 mmol/l	negative	no data		EDTA	Swenberg et al., (1976)
DNA damage; alkaline elution; V79 cells	3.0-30 mmol/l	3.0-30 mmol/l	negative	no data		EDTA	Swenberg et al. (1981)
DNA damage; alkaline elution; L 5178Y cells	10-50 mmol/l	10-50 mmol/l	positive	none	single strand breaks at extremely high concentrations from 40 mmol/l upwards	EDTA	Garberg et al., (1988)

4.1.2.7.2 *In vivo* tests

Rodent bone marrow micronucleus tests

In an *in vivo* micronucleus test on polychromatic erythrocytes with mice (strain: NMRI) Na_2EDTA led to a negative result after repeated oral administration (twice with a 24-hour interval between administrations) of 500, 1,000 and 2,000 mg/kg bodyweight (BASF, 2000b). This study was well conducted according to the guideline and GLP. Sampling time was 24 hours after second administration. As clinical sign only piloerection was observed after second administration of 2,000 mg/kg. No lethal effects or cytotoxicity (PCE/NCE ratio) were induced. Only males (5 per group) were used because no distinct symptomatic differences between males and females were noticed in a pre-test.

In another well-conducted in vivo micronucleus assay Na_2EDTA was negative in bone marrow cells of mice (strain: BALB/c) for a single intraperitoneal dose of 186 mg/kg bodyweight; the sampling times were 24 hours and 48 hours after treatment (Russo and Levis, 1992). The tested

dose is near to the LD50 value. No cytotoxic effects (PCE/NCE) were induced; informations about clinical signs or lethal effects were not given. Only males (3 per 24-hour group; 4 per 48-hour group) were used.

Muralidhara and Narasimhamurthy (1991) reported on a positive micronucleus assay in mice (strain: CFT) after oral administration of Na_2EDTA (from Sigma Chemicals) in a dose range from 5.0 up to 20 mg/kg bodyweight; the study was not conducted according to GLP. Doses of 15 and 20 mg/kg bodyweight induced a dose-dependent increase in the incidence of micronucleated polychromatic erythrocytes at the only sampling time of 24 hours. The highest micronucleus frequency was 1.43% (20 mg/kg) as compared to 0.35% in the vehicle control. Neither clinical signs nor lethal effects were described. The PCE/NCE ratio was not affected by EDTA treatment. Only males (4 per group) were used. Preliminary studies showed that oral administration of Na_2EDTA at doses of 5.0, 10 and 15 mg/kg bodyweight per day on 5 consecutive days did not induce any obvious sign of toxicity. The acute oral LD50 dose computed by probit regression was indicated with 30 mg/kg bodyweight in the mouse strain used.

Altogether, compared with the negative results of the micronucleus tests after oral (BASF, 2000) and intraperitonael administration (Russo and Levis, 1992), the positive result reported by Muralidhara and Narasimhamurthy (1991) seems to be of low reliability. The positive effect after oral administration of low doses, such as 15 and 20 mg/kg bodyweight, is not plausible. Therefore, it is concluded that EDTA does not induce micronuclei in bone marrow cells.

Tests for aneuploidy and sister chromatid exchange in bone marrow cells

Zordan et al. (1990) investigated aneugenic properties of Na_2EDTA in the bone marrow cells of male mice (strain: BALB/c). After single i.p. administration of 93 and 186 mg/kg bodyweight (higher dosages resulted in lethality) no increases in aneuploid bone marrow cells were observed. A parallel conducted SCE test in bone marrow cells yielded also negative results.

Table 4.7 Summary of *in vivo* genotoxicity results in rodent bone marrow cells

Test system	Doses	Expos. regimen	Sampl. times	Result	Local cytotox.	General toxicity	Remarks	Test substance	Reference
Micronucleus test	500-2000 mg/kg	2 x p.o.	24 hours after second applica-tion	negative	no effect	clinical signs at the highest tested dose	applica-tion: each dose twice at an interval of 24 hours	Na_2EDTA	BASF (2000)
Micronucleus test	186 mg/kg	1 x i.p.	24, 48 hours	negative	no effect	no data		Na_2EDTA	Russo and Lewvis (1992)
Micronucleus test	5.0-20 mg/kg	1 x p.o.	24 hours	positive	no effect	no data	dose-dependent positive effect at 15 and 20 mg/kg	Na_2EDTA	Muralidhara and Narasimha-murty (1991)
Aneuploidy	93–186 mg/kg	1 x i.p.	20 hours	negative			higher doses resulted in lethality	Na_2EDTA	Zordan et al. (1990)
Sister chromatid exchange (SCE)	93–186 mg/kg	1 x i.p.	20 hours	negative			higher doses resulted in lethality	Na_2EDTA	Zordan et al., (1990)

Rodent germ cell tests

Na_2EDTA was reported to induce micronuclei in germ cells at the late stages of spermacytogenesis after intraperitonal administration of mice (strain: BALB/c) with a very high dose of 186 mg/kg bodyweight in order of the LD50 value (Russo and Levis, 1992). The frequency of micronuclei was analysed in Golgi phase and Cap phase, representing the two earliest phases of spermatid development. The sampling times were 24 hours and 48 hours after administration. Na_2EDTA induced micronuclei in Golgi phase spermatids (0.30% and 0.38% micronucleated spermatids at 24 hours and 48 hours sampling as compared to 0.08% in controls); in Cap phase spermatids negative results were obtained. Toxicity data were not given. Aneuploidy is discussed as most probable origin of micronuclei produced by NA_2EDTA in secondary spermatocytes because the substance generally induced micronuclei of larger size in comparison with other substances. In addition, Na_2EDTA does not induce chromosomal aberrations in the spermatogonial phase, the most suitable germ cell population to detect chromosomal aberrations.

Zordan et al. (1990) investigated aneugenic properties of Na_2EDTA in primary and secondary spermatocytes of mouse (strain: BALB/c). After single i.p. administration of 93 and 186 mg/kg bodyweight no increases in aneuploid spermatocytes were observed. The sampling was 6 hours and 5 days after administration; higher doses resulted in lethality.

An *in vivo* chromosomal aberration assay with mouse spermatogonia (strain: BALB/c) led to a negative result after a single i.p. administration of 186 mg/kg bw Na_2EDTA. The sampling time was 24 hours sampling time after administration (Russo and Levis, 1992).

In a dominant lethal assay Na_2EDTA did not induce dominant lethal mutations when mice (strain: CFT) were administered orally 10 mg/kg bodyweight per day for 5 consecutive days (Muralidhara and Narasimhamurthy, 1991).

Table 4.8 Summary of *in vivo* rodent germ cell tests

Test system	Doses	Exposure regimen	Exposure period	Result	General toxicity	Test substance	Remarks	Reference
Micronucleus test in spermatids	186 g/kg	1 x i.p.	24, 48 hours	positive	no data	Na_2EDTA	positive in sperma-tids of the Golgi phase	Russo and Levis (1992)
Aneuploidy in secondary and primary spermatocytes	93– 186 mg/kg	1 x i.p.	6 hours and 5 days	negative	no data	Na_2EDTA	higher doses resulted in lethality	Zordan et al. (1990)
Chromosomal aberrations in spermatogonia	186 g/kg	1 x i.p.	24 hours	negative	no data	Na_2EDTA		Russo and Levis (1992)
Dominant lethal test	10 mg/kg	drinking water	5 days	negative	no data	Na_2EDTA	dose on 5 days con-secutive	Muralidhara and Narasimhamurty (1991)

Altogether, in germ cell tests Na2EDTA was negative 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). On the basis of different susceptibilities of the various stages of spermatogenesis it cannot be ruled out completely that Na_2EDTA has the potential for induction of aneuploidy in germ line cells. However, the positive effect was bound to the use of an extremely high dose in the LD50 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.

Drosophila melanogaster

In vivo tests with Drosophila melanogaster were performed with EDTA (free acid) and Na_2EDTA.

Table 4.9 Summary of *in vivo* tests with Drosophila melanogaster

Test system	Doses	Exposure period	Result	General toxicity	Test substance	Remarks	Reference
Drosophila; aneuploidy in germ line cells	700 ppm (oral feed)	unclear	positive	no data	EDTA	positive for chromoso-mal loss	Ramel and Magnusson (1979)
Drosophila; aneuploidy in germ line cells	7.5–25 mmol/l (oral feed)	3 days	positive	no data	Na_2EDTA	FIX test for aneuploidy; positive at doses of 7.5 mmol and higher	Zordan et al. (1990)
Drosophila; somatic cell genotoxicity	7.5–25 mmol/l (oral feed)	24 hours	negative	no data	Na_2EDTA	somatic mutation and recom-bination test (SMART)	Zordan et al. (1990)

In two tests for chemically induced aneuploidy in germ cells of Drosophila melanogaster positive results were described. An assay for nondisjunction and loss of the sex chromosomes EDTA (700 ppm in substrate) was positive with respect to the endpoint chromosome loss (Ramel and Magnusson, 1979). Zordan et al. (1990) investigated the genetic effect of Na_2EDTA by using the FIX test for heritable aneuploidy after treatment of adult female Drosophila melanogaster. Na2EDTA was assayed at 7.5 mmol/l and 25 mmol/l. Genetic effects were observed for both exposure levels.

In a somatic mutation and recombination test (SMART) Na2EDTA was negative after treatment of larvae with 7.5 mmol/l and 25 mmol/l (Zordan et al., 1990).

4.1.2.7.3 Conclusion on 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 spermacytoge-nesis). The effect was bound to the use of an extremely high dose in the LD50 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. Furthermore, the effects may be indirect, resulting from the lower bioavailability of essential elements.

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 its sodium salts are not mutagenic for humans.

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

Carcinogenicity studies of EDTA are not available. However, the carcinogenicity of Na_3EDTA has been investigated in rats and mice. A justification for using data from $Na_3EDTA \cdot 3H_2O$ is given in Section 4.1.2 "Introductory remarks". In a standard carcinogenicity study in rats, 50 male and 50 female Fischer 344 rats were administered with 3,750 and 7,500 ppm (equivalent to about 248 and 495 mg/kg bw/day) daily in the feed for 103 weeks. In a similar study in mice, 50 male and 50 female B6C3F1 mice were administered with the same dose concentrations (3,750 and 7,500 ppm, equivalent to about 469 and 938 mg/kg bw/day) daily in the feed for 103 weeks. Matched control groups were composed of 20 males and 20 females of each species (NTIS: Bioassay of Trisodium Ethylendiaminetetraacetate Trihydrate (EDTA) for possible Carcinogenicity, CAS No. 150-38-9; NCI-CG-TR-11 (1977) [PB 270 938], 1977).

In rats, average body weights of treated males and females were comparable to those of the matched controls throughout the study. In male mice only the high-dose group showed throughout most of the study period a decrease in average body weight compared to the controls. In female mice average body weights of the treatment groups were depressed in a dose-related manner during the study period, although the effect was small.

No treatment-related clinical signs were observed in animals of both species and sexes.

In rats and mice no statistically significant differences in survival were noted between dose groups and control groups and sexes, respectively.

Inflammatory and degenerative changes were observed in about the same frequency in all groups. The lesions appeared to be related to age and not to the administration of the test substance.

Overall, results of this study did not demonstrate that Na_3EDTA is carcinogenic in experimental animals (rats and mice) after treatment with dosages up to 495 mg/kg bw/day in rats and 938 mg/kg bw/day in mice. However, the substance has not been tested at the maximum tolerated dose.

Histopathology findings on neoplasms in rats

A high incidence of tumors has been observed in the reproductive and endocrine systems and low incidences occurred in the hematopoietic, respiratory, integumentary, and digestive systems. No neoplasms were observed in the nervous, musculoskeletal, or urinary systems.

No tumor appeared in a statistically significant positive trend in either dose groups or sexes. A variety of endocrine tumors were found, some types occurring only in treated animals. However, these tumors occurred in low numbers and have frequently been seen in untreated animals in other studies. Therefore, they are probably unrelated to treatment.

Males: Interstitial-cell tumors of the testes were observed in nearly all male rats in each feeding group. This high incidence of interstitial-cell tumors in both treated and control animals reflects this commonly occurring age-related lesion in the male Fischer 344 rat (see **Table 4.10**).

Females: The distribution of neoplasms in the reproductive system among control and treated rats was random, the tumors occurred mainly in the uterus. The majority of these were endometrial stromal polyps. However, one adenocarcinoma and one leiomyosarcoma occurred at 7,500 ppm. An ovarian cystadenoma was detected in a single 3,750 ppm-dose rat (see **Table 4.11**).

A number of tumors occurred in other organ systems of both sexes (hematopoietic system, liver and lungs) with comparable rates in control groups and treated groups. In some instances the incidence of tumors in the controls exceeded that of the treated animals.

In conclusion, the non-significantly increased incidence of some tumor types observed in the study provides no clear evidence of carcinogenic effects in the rat.

Table 4.10 Incidence of primary tumors at specific sites in male rats fed Na_3EDTA in the diet

Topography: Morphology	Matched control	3,750 ppm	7,500 ppm
Hematopoietic system: leukemia, malignant lymphoma, and lymphocytic leukaemia	3/20	4/50	4/50
Weeks to first observed tumor:	76	104	102
Adrenal: phenochromacytoma	2/20	5/49	4/50
Weeks to first observed tumor:	104	104	67
Thyroid: C-cell adenoma	0/17	6/35	3/38
Weeks to first observed tumor:	-	104	67
Pituitary: chromophobe adenoma	0/18	3/47	5/44
Weeks to first observed tumor:	-	88	104
Lung: alveolar/bronchiolar adenoma and carcinoma	1/18	2/50	3/49
Weeks to first observed tumor:	104	95	67
Liver: hepatocellular adenoma and neoplastic nodule	0/20	1/48	1/50
Weeks to first observed tumor:	-	104	104
Testis: interstitial-cell tumor	19/20	43/50	44/50
Weeks to first observed tumor:	88	85	95

Table 4.11 Incidence of primary tumors at specific sites in female rats fed Na_3EDTA the diet

Topography: Morphology	Matched control	3,750 ppm	7,500 ppm
Hematopoietic system: malignant lymphoma,leukemia, and lymphocytic leukaemia Weeks to first observed tumor:	1/20 104	8/50 80	0/50 -
Adrenal: phenochromacytoma Weeks to first observed tumor:	1/20 98	1/49 104	3/48 104
Thyroid: C-cell adenoma Weeks to first observed tumor:	0/11 -	0/36 -	1/37 104
Pituitary: chromophobe adenoma Weeks to first observed tumor:	6/19 95	10/48 104	11/50 104
Lung: alveolar/bronchiolar adenoma Weeks to first observed tumor:	0/20 -	3/48 104	2/48 104
Liver: neoplastic nodule Weeks to first observed tumor:	0/20 -	1/48 104	0/48 -
Uterus: endometrial stromal polyp Weeks to first observed tumor:	5/20 104	6/50 96	7/50 85
Mammary gland: fibroadenoma Weeks to first observed tumor:	4/20 85	3/50 96	3/50 97

Histopathology findings on neoplasms in mice

A variety of neoplasms were found in both treated and control animals that were well known from historical controls of the same strain. There was a high incidence of tumors in the hematopoietic, endocrine, digestive, and respiratory systems. The incidence of neoplasms in other systems was variable. For all tumor types observed no statistical significance were seen between incidences in dose groups and control groups.

With the exception of a splenic hemangioma in a control female and a 3,750 ppm-male, all of the tumors of the hematopoietic system were malignant lymphomas or leukemias.

The distribution of endocrine tumors varied little between treated and control mice.

For all groups, the incidences of hepatic neoplasms were considerably higher in males than in females. Liver tumors occurred in the 3,750 ppm-dose (10/44, 22%) and 7,500 ppm-dose (10/47, 21%) male groups. Percentage was approximately the same as in the male controls (3/19, 16%).

Primary neoplasms of the respiratory system were observed in both treated and control groups. The highest incidence of pulmonary neoplasms was found in the 7,500 ppm-dose male mice (control: 2/18, 11%; 3,750 ppm: 8/44, 18%; 7,500 ppm: 12/45, 26%). This may suggest a treatment related effect. Lung tumors were frequently seen in mice of this strain and age, and therefore, the increase of incidence in this mouse study is probably not related to treatment.

In conclusion, the non-significantly increased incidence of some tumor types observed in the study provides no clear evidence of carcinogenic effects in the mice (see Tables 4.12 and 4.13).

Table 4.12 Incidence of primary tumors at specific sites in male mice fed Na_3EDTA in the diet

Topography: Morphology	Matched control	3,750 ppm	7,500 ppm
Hematopoietic system: malignant lymphoma	2/20	7/46	7/48
Weeks to first observed tumor:	91	73	87
Lung: alveolar/bronchiolar adenoma and carcinoma	2/18	8/44	12/45
Weeks to first observed tumor:	105	99	96
Pituitary: chromophobe adenoma	1/13	0/19	1/26
Weeks to first observed tumor:	105	-	105
Liver: hepatocellular adenoma and carcinoma	3/19	10/44	10/47
Weeks to first observed tumor:	103	84	105
Thyroid: follicular-cell adenoma and carcinoma	0/10	1/29	1/33
Weeks to first observed tumor:	-	104	105

Table 4.13 Incidence of primary tumors at specific sites in female mice fed Na_3EDTA in the diet

Topography: Morphology	Matched control	3,750 ppm	7,500 ppm
Hematopoietic system: malignant lymphoma	5/19	11/49	12/47
Weeks to first observed tumor:	85	99	93
Lung: alveolar/bronchiolar adenoma	0/19	3/47	4/45
Weeks to first observed tumor:	-	105	102
Pituitary: chromophobe adenoma	2/12	6/34	4/29
Weeks to first observed tumor:	105	105	105
Liver: hepatocellular adenoma and carcinoma	0/19	1/46	1/47
Weeks to first observed tumor:	-	105	105
Thyroid: follicular-cell adenoma and carcinoma	1/12	3/33	1/34
Weeks to first observed tumor:	105	99	105

4.1.2.8.2 Studies in humans

Epidemiological studies are not available for evaluation of the carcinogenic potential.

In vitro tests: Cell transformation tests

No data concerning edetic acid are available. However, data from different sodium salts of EDTA (Na_3EDTA and Na_2EDTA) have to be considered.

In vitro cell transformation tests with both sodium salts of EDTA gave negative results. Na_3EDTA induced no increased cell transformations both in BALB/c-3T3 cells (Matthews et al., 1993) and in SHE cells (Fukuda, 1987; see also: Isfort et al., 1996) up to toxic concentrations. LeBoeuf et al. (1996) reported on a negative result of Na_2EDTA in SHE cells also up to toxic concentrations.

Table 4.14 *In vitro* tests: Cell transformation

Test system	Concentration range		Result	Toxicity	Remarks	Reference
	with S-9 mix	without S-9 mix				
BALB/c-3T3 cells	not done	1.89 mM (677.0 µg/ml)	negative	'lethal dose' for 50% of the cells at 1.89 mM	Na_3EDTA; 48-hour exposure	Matthews et al. (1993)
SHE cells	not done	0.03-0.3 mM (10.7-107.4 µg/ml)	negative	dose-dependent decrease of cell survival up to 63% at 0.3 mM	Na_3EDTA	Fukuda (1987) (cited in: Isfort et al., 1996)
SHE cells	not done	50–150 µg/ml	negative	dose-dependent decrease of relative plating efficiency up to 14% at 150 µg/ml	Na_2EDTA; 7-day exposure	LeBoeuf et al. (1996)
	not done	25-100 µg/ml	negative	dose-dependent decrease of relative plating efficiency up to 49% at 100 µg/ml	Na_2EDTA; 24-day exposure	

4.1.2.8.3 Conclusion on carcinogenicity

Epidemiological studies are not available for evaluation of the carcinogenic potential of EDTA. 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 tumors occurred among test and control animals of both species, no tumors were related to treatment.

Taking together the negative results of the carcinogenicity study and of the cell transformation assays as well as the low mutagenic potential only expressed at extremely high dose levels it can be concluded that there is no concern on a carcinogenic potential of EDTA.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Studies in animals

Effects on fertility

Generation studies, in particular fertility studies with EDTA are not available.

In a 2 year feeding study on Wistar rats including reproductive and lactation experiments in four successive generations groups of 25 male and 25 female animals were exposed to $CaNa_2EDTA$ at dietary levels providing daily doses of approximately 50, 125, and 250 mg/kg bw (Oser et al., 1963). No significant differences in behaviour or appearance nor adverse effects on the growth or on the longevity of the rats in any of the generations or among the various dose levels were reported. Evaluations of various tissues and organs (weight, histopathologic examinations) including gonads (testes) gave negative results even in the high dose group. Criteria for reproductive and lactational effects were evaluated as proportion of matings resulting in pregnancy (fertility index), proportion of pregnancies resulting in live litters (gestation index),

proportion of rats born that survive 4 days or longer (viability index), and proportion of rats alive at 4 days that survive to weaning. Poor responses with respect to some of the criteria of reproductive performance occurred occasionally but were not correlated with dosage or with the number of generations through which dosage continued. The overall data for two matings in the four successive generations did not give evidence for significant treatment related differences in either of these indexes. The authors concluded that no adverse effect of $CaNa_2EDTA$ was observed as measured by any of the usual indexes of reproduction or lactation efficiency even under the stresses of repeated pregnancies and lactation.

In a poorly documented summary of a reproduction study which had been performed already in 1952 preliminary data on the effects of exposure of Wistar albino rats to diets containing 0.5, 1.0, and 5.0% Na_2EDTA (according to about 300, 600, and 3,000 mg/kg bw/day) were presented (Yang and Chan, 1964). It was reported, that the parent generations of the two lower exposure groups gave birth to normal first and second litters, while those animals of the highest dose level failed to produce any litters, even though they had been mated for 2 months. No more details were given. Also data on the second generation were not available.

Additional information related to fertility can be obtained from a further study (Muralidhara and Narasimhamurthy, 1991). Oral administration of 5, 10, and 15 mg Na_2EDTA/kg bw to male adult Swiss albino mice for five consecutive days did not affect neither absolute or relative weights of epididymides and testes nor histoarchitecture of these two organs assayed at 1, 3, 5, and 7 weeks after treatment. Likewise, no effects were detected on caudal sperm counts, and there were no changes in the incidence of sperm head abnormalities or in the percentage of abnormal sperms. Furthermore treatment of male mice with 10 mg Na_2EDTA/kg bw for 5 consecutive days induced no increase in the incidence of post implantation embryonic deaths over a mating period of 8 weeks, except for a statistically insignificant about twofold increase during week 2 and 3 of mating.

Developmental toxicity

Developmental effects of EDTA, sodium salts and calcium and zinc chelates were investigated in various in vivo animal studies with various routes of administration in different rat species. Most of these studies were single dose studies. Guideline according studies with EDTA for developmental toxicity are not available.

The toxic and teratogenic effects of EDTA were studied in female CD rats following different routes of administration during g.d. 7-14 (Kimmel, 1977). Dietary exposure to 3% EDTA (as disodium salt) amounting to an average dose of 954 mg EDTA/kg bw/day resulted in reduced food intake, severe diarrhea and severe weight loss in the dams during treatment and produced a significant proportion of fetal deaths (about 33% resorptions/litter), significantly lower average fetal weight and gross external, internal and skeletal malformations in about 71% of the survivors. Treatment with 1,500 or 1,250 mg EDTA (dissolved in phosphate buffer) per kg body weight per day administered by gavage (respectively 625 mg/kg and 750 mg/kg twice daily) resulted in severe toxicity to the dams (7 out of 8 animals died in the 1,500 mg dose group), in particular 36% maternal deaths, significantly reduced weight gain, and diarrhea in the 1,250 mg dose group and a significantly higher proportion of (about 21%) malformed survivors. Treatment with 375 mg EDTA (dissolved in phosphate buffer) and administered subcutaneously produced signs of severe pain (vocalisations and shock) to the dams and resulted in 24% maternal deaths, significantly reduced food intake and maternal weight loss during the period of treatment. Fetal toxicity (about 32% resorptions/litter, significantly reduced fetal weight) and a rate of about 4% malformed survivors/litter were reported for this route of application.

In a further study (Swenerton and Hurley, 1971) pregnant Sprague-Dawley rats were exposed during various periods of gestation to purified diets adjusted to either 100 or 1,000 ppm zinc (provided as zinc carbonate) and containing 2 or 3% Na_2EDTA. The groups of 8 to 16 females had been set on the control ration at least 5 days before breeding and mated to normal stock-fed males. The evaluation of treatment related effects to the dams was not indicated in this study, except for the report on moderate to severe diarrhea in all females that were fed diets containing EDTA. While obviously complete reproductive failure occurred with the 3% Na_2EDTA/100 ppm zinc diet fed during g.d. 0-21, with the 2% Na_2EDTA/100 ppm zinc diet reproductive outcome was essentially comparable to that of controls, however with lower mean body weight of the pups and with 7% malformed of the fullterm fetuses. Exposure to the 3% Na_2EDTA/100 ppm zinc diet during the period of g.d. 6-14, and 6-21 resulted in respectively 40% and 54% dead or absorbed fetuses, reduced number of dams with live pubs, clearly reduced mean fetal body weight and ratios of respectively 87% and 100% malformed living offspring. Gross malformations comprised cleft palate, severe brain deformities, eye defects, micro- or agnathia, syndactyly, clubbed legs and tail anomalies. The reported fetotoxic and teratogenic effects were similar to those from earlier experiments (Hurley and Swenerton, 1966; Hurley et al., 1971) with zinc deficient diets administered to pregnant rats for various periods of during gestation. In contrast, the live offspring of dams fed 3% Na_2EDTA supplemented with 1,000 ppm zinc from g.d. 6-21 did not exhibit any malformations, and the mean number of live pups/litter and the mean fetal body weight were comparable to those of controls. The authors concluded from this study that Na_2EDTA ingested during pregnancy was teratogenic, whereas supplemantation with zinc prevented the detrimental effects of EDTA. It was suggested that the congenital anomalies caused by EDTA were due specifically to zinc deficiency. This was also supported by zinc analyses of fetuses (Hurley and Swenerton, 1966), where clearly lower zinc contents were found in fetuses from deficient mothers in comparison to those from zinc supplemented dams, indicating that the reported effects rather occur because of a direct lack of zinc in fetal tissues than from indirect effects of maternal metabolism on fetal development.

EDTA and four of its salts were evaluated for their teratogenic potential in CD albino rats (Schardein et al., 1981). Groups of 20 females were treated by gavage during g.d. 7 to 14 with 1,000 mg EDTA/kg bw/day as well as with equimolar doses of disodium, trisodium, calcium disodium and tetrasodium edetate (dissolved and suspended in phosphate buffer with final pH values ranging from 3.9 to 9.2). The dose level had been selected from preliminary studies with edetic acid in which there had been some evidence of both maternal and fetotoxicity under the same experimental conditions. For the dams significant drug-related reactions including diarrhea and depression of activity were reported. The former occurred in all drug groups with highest incidences for tetrasodium edetate (90%) and edetic acid (80%) and lowest incidence for calcium disodium edetate (10%). Three dams died during treatment with disodium edetate. Besides slightly decreased food intake in all test groups, treatment with all of the test compounds caused reduced weight gain in the dams during the treatment period. The mortality index of offspring in all treated groups as measured by postimplantation loss was comparable to that of the vehicle and untreated control group. None of the test compounds significantly affected litter size at term or mean fetal body weight when compared to either control. Fetuses were examined for external, visceral and skeletal anomalies. Incidental findings of skeletal anomalies did not reveal a definitive pattern regarding treatment with a particular compound. The authors stated that under these experimental conditions no teratogenic effects were evidenced even at maternally toxic doses.

In a further study the calcium chelate and the zinc chelate of EDTA as well as a mix of both ZnEDTA and CaEDTA were investigated in pregnant Long Evan rats (Brownie et al., 1986). Groups of 20 dams were treated subcutaneously (total doses given as twice daily injections)

during g.d. 11 to 15 with 2, 4, 6 and 8 mmol CaEDTA/m^2/day and with ZnEDTA and ZnEDTA/CaEDTA mix at doses of respectively 8 and 20 mmol/m^2/day. Additional animals per group were treated for zinc analyses in maternal plasma and liver on g.d. 16 and 21 and for fetal zinc determinations on g.d. 16. The administration of CaEDTA produced signs of maternal toxicity at all dose groups (diarrhea, decreased water intake and urine production, anorexia, lethargy, reduced feed intake, significantly less weight gain, respectively weight loss and maternal deaths) increasing with the dose. A LOAEL for maternal toxicity of 2 mmol CaEDTA/m^2/day (corresponding to about 90 mg/kg/day) can be assumed from the data. A dose related increase in fetotoxicity (significantly lower mean fetal body weight and fetal crown-rump length) and in prenatal death (significantly increased resorptions and significantly fewer live births/dam) was observed. Treatment with CaEDTA also resulted in a dose related increase in the number of abnormal fetuses and affected litters. The pattern of malformations comprised cleft palate, adactyly-syndactyly, brachygnathia, curly tail and abnormal rib and vertebrae. A LOAEL for fetotoxicity/teratogenicity of 4 mmol CaEDTA/m^2/day (corresponding to about 180 mg/kg/day) can be assumed from these data. Since developmental toxicity was observed in the presence of maternal toxicity like significant body weight loss, pairfeeding studies to the highest dose level of 8 mmol CaEDTA/m^2/day were performed to rule out whether the abnormalities were due directly to CaEDTA or mediated indirectly through maternally toxic effects. The pairfed dams also revealed significant weight loss, however, for their pups, there was neither an indication of increased prenatal death nor of malformations in comparison to those of normal fed controls. Administration of ZnEDTA was maternally toxic (reduced feed intake, significant weight loss) at the highest dose level of 20 mmol/m^2/day only. Fetal parameters were not different from controls at 8 and at 20 mmol/m^2/day. Treatment with ZnEDTA was without teratogenic effects at either dose level. Zinc analyses in CaEDTA treated dams revealed dose related transitory increased daily urinary zinc excretion and significantly reduced hepatic and plasma zinc concentrations. Also in their fetuses total zinc per pup decreased as the CaEDTA dose increased. On the other hand, appreciable elevations in maternal plasma zinc concentrations occurred after ZnEDTA treatment.

Other information

EDTA was revealed to be teratogenic also by means of repeated i.m. applications (Tuchmann-Duplessis and Mercier-Parot, 1956).

With in vivo screening tests (Chernoff Kavlock) on rats (Wickmaratne, 1987) and mice (Chernoff and Kavlock, 1983; Gray and Kavlock, 1984) and with in vitro screening with whole embryo culture with rats (Schmid et al., 1983; Schmid, 1985) EDTA was not classified as a fetotoxic/teratogenic agent, whereas short-term in vitro screening test systems using cells of different origin (Flint et al., 1984; Flint and Orton, 1984; Bournias-Vardiabasis et al., 1983; Mummery et al., 1984) gave inconsistent results.

4.1.2.9.2 Studies in humans

Two case reports are available of women treated for lead intoxication with $CaNa_2EDTA$ and which delivered normal infants (Angle and McIntire, 1964; Abendroth, 1971). Since this measure was carried out in late pregnancy (4, respectively 12 weeks before delivery) these data are considered to be less relevant for risk assessment.

4.1.2.9.3 Summary of toxicity to reproduction

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.

From a less valid study with disodium edetate conducted on rats complete reproductive failure was reported to have occurred 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 on 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). Gross malformations comprised cleft palate, severe brain deformities, eye defects, micro- or agnathia, syndactyly, clubbed legs and tail anomalies. These effects were almost exclusively exhibited in studies using maternally toxic dosage levels.

From studies with oral application it appeared that developmental effects were more marked when test compounds were provided via the diet than via gavage. Since single dosages in these studies had been administered mainly, no oral NOAEL for either developmental toxicity or maternal toxicity could be established.

However, from the investigations of Swenerton and Hurley, 1971, which represent the only feeding study that had applied two different dosages of 2% and 3% Na_2EDTA in the diet (calculated to a mean daily intake of 1,000 and 1,500 mg Na_2EDTA/kg bw/day) a dose-effect relationship can be derived. In this study, at dietary exposure levels corresponding to 1,500 mg/kg bw/day clearcut developmental impairment in terms of an increased ratio of dead or resorbed fetuses (40-54%), an increased percentage of implantation sites having dead, resorbed or malformed fetuses (97-100%), an increased incidence in malformed live pups (87-100%), a decreased mean number of pups/litter and a decreased mean fetal body weight was evidenced. Effects were also revealed at dietary exposure levels corresponding to 1,000 mg/kg bw/day to a lower extent (increased percentage (11%) of implantation sites having dead, resorbed or malformed fetuses, increased incidence in malformed live pups (7%) and a decreased mean fetal body weight). Hence, we conclude that a rather steep slope for the dose response for developmental effects can be assumed.

Although maternal toxicity was concomitant to the observed teratogenic effects at both levels of dietary exposure, it appears that the specific outcome of malformations in offspring was not secondary to the substance induced impairment of the dams, as evidenced for instance by reduced food intake, reduced maternal weight (gain) and by diarrhea, but rather results from compound specific interference with endogenous Zn homeostasis. This is supported by the following observations:

- Food restricted dams pairfed to rats of the CaEDTA group during the studies with the calcium and zinc chelates of EDTA (Brownie et al., 1986) also revealed significant maternal weight loss and reduced fetal body weight, but did not reveal any significant teratogenic effect in their offspring. Likewise, the administration of ZnEDTA at maternally toxic dose levels (reduced feed intake, significant weight loss) did not reveal any fetotoxic or teratogenic effects.

- Food restricted dams pairfed to rats of a zinc depleted diet that per se had led to significant maternal weight loss (Hurley et al., 1971) also revealed significant maternal weight loss and reduced fetal body weight, but did not reveal any teratogenic effect in their offspring.
- On the other hand it was demonstrated from the study of Swenerton and Hurley, 1971, that with sufficient dietary zinc supplementation the (fetotoxic and) teratogenic effects of 3% Na_2EDTA could be prevented although all dams fed diets containing EDTA salts had moderate to severe diarrhea.

In addition, it has been repeatedly reported that the pattern of malformations observed after exposure of pregnant female rats to edetic salts or calcium chelates of 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.

However, the relationship between zinc depletion in dams and in pups and effects has been investigated in a single study where calcium or zinc chelates of EDTA had been administered by the s.c. route (Brownie et al., 1986) at different dose levels. Reduction of plasma zinc concentrations of 30–40% in dams caused by 4 mmol/m^2/day calcium EDTA appeared to be of critical significance for the induction of toxic effects (reduced food intake and body weight gain). In the same study fetal zinc tissue concentrations of about 12 µg/g, fetal zinc contents of about 4 µg/pup appeared to be of critical significance for the induction of malformations and developmental impairment in offspring which occurred at the same level as toxicity in dams. However, any significant correlation between averages of maternal plasma zinc and the amount of zinc per pup were not demonstrated.

The extent of endogenous zinc depletion during administration of EDTA salts which has to be assumed to be higher compared with the effect of the calcium EDTA chelate, however, has not been investigated sofar.

Since it has been demonstrated that zinc deficient diets per se lead to developmental and teratogenic effects in offspring (Hurley and Swenerton, 1966; Hurley et al., 1971), the depletion of zinc in the diet and/or the depletion of endogenous zinc tissue concentrations caused by EDTA 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 or minimised. The zinc chelate of EDTA obviously lacks a specific teratogenic potential.

4.1.2.9.4 Conclusion on toxicity for reproduction

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.

With incorporation of 2% and 3% Na_2EDTA (about 1,000 and 1,500 mg/kg bw/day) and normal zinc content (100 ppm $ZnCO_3$) in the diet (molar ratio $Na_2EDTA/ZnCO_3$=74 and 112) prenatal toxicity is seen with a steep dose-response-curve. No signs of prenatal toxicity were seen with incorporation of 3% Na_2EDTA in the diet (about 1,500 mg/kg bw/day) when excess Zn (1,000 ppm $ZnCO_3$) had been supplemented to the diet (molar ratio $Na_2EDTA/ZnCO_3$=11.2). The teratogenic effect of EDTA 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: 1) reduction of available zinc by complexation in the upper intestine, 2) enhanced urinary excretion, and 3) enhanced zinc excretion into the gut lumen by diarrhea. With the exception of one oral (single-dose/gavage) study, during which no teratogenic effects were induced, the fetotoxic and teratogenic effects are occurring at exposure levels of approximately 1,000 mg/kg bw/day and above.

Hence, we do not recommend classifying Na_4EDTA/EDTA as being a reproductive toxicant due to the following reasons. The malformations have been demonstrated at relatively high oral dose levels (i.e. 1,000 mg/kg bw/day and above) and a steep dose response relationship can be assumed. No oral NOAEL for either developmental toxicity or maternal toxicity could be established.

The study of Brownie et al. (1986) which is reported for completeness of the database with regard to contributions on developmental effects produced by different EDTA compounds (see Section 4.1.2) used s.c. application of CaEDTA to study the effects of zinc complexation. A LOAEL for fetotoxicity/teratogenicity of 4 mmol CaEDTA/m^2/day (corresponding to about 180 mg/kg bw/day) was derived from these data whereas the NOAEL for these effects was 2 mmol CaEDTA/m^2/day (corresponding to about 90 mg/kg bw/day). However, this dose represents already the LOAEL for maternal toxicity. The subcutaneous application route represents an application route irrelevant for normal exposure considerations and therefore is considered to be not suitable for decisions upon classification of EDTA/Na_4EDTA as a developmental toxicant.

4.1.3 Risk characterisation

4.1.3.1 General aspects

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 $CaNa_2$EDTA. It is poorly absorbed from the gastrointestinal tract (a maximum of 5% was detected in the urine). Only 0.001% of $CaNa_2$EDTA is absorbed after dermal application. 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 > 2,000 mg/kg were reported. The data on acute inhalation toxicity are not valid for risk characterisation. No data are available for acute dermal toxicity. 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.

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. Range finding studies with higher dose levels revealed diarrhea, emaciation, loss of body weight and sometimes parakeratosis in oesophagus and forestomac as well as decreased hemoglobin and hematocrit levels.

EDTA and its sodium salts have shown 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 its 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 concluded 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. From studies on developmental toxicity a specific fetotoxic and teratogenic potential of EDTA, Na_2EDTA and $CaNa_2EDTA$ was evidenced, a LOAEL of 1,000 mg/kg bw was determined. The mechanism resulting in developmental effects is found to occur via zinc depletion resulting in zinc deficit. These effects are independent of whether the edetic acid or alkali- and/or calcium salts are applied.

4.1.3.2 Workers

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.

In principle inhalation and dermal contact are the exposure routes of occupational risk assessment, but in case of H_4EDTA and Na_4EDTA the dermal exposure is not of importance because of no relevant skin irritation and negligible skin absorption. A worst-case calculation of dermal systemic MOS is described under “Repeated dose toxicity” (MOS >36,000). 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. Due to the lack of quantitative human data the risk assessment is mainly based on animal data. The following default values of body weights and physiological parameters are used in the risk assessment.

Body weight, rat	250 g
Body weight, worker	70 kg
Respiratory volume of worker during 8 hours of light activity	10 m^3

Considerations on oral, dermal and inhalation absorption

Oral studies represent the central database for the quantitative assessment of acute toxicity, repeated dose toxicity and reproductive toxicity. Performing a risk assessment of the dermal contact and inhalation exposure systemic availability via all routes has to be considered. Human data on absorption after oral intake and dermal contact are described in Section 4.1.2.1 and processed in the risk assessment. The maximum systemic availability after oral application is 5%, while for the dermal route a maximum value of 0.001% is given.

As to the inhalation route no experimental data of the free acid or salts of EDTA are available. Estimating the systemic availability of aerosols parameters like deposition and absorption plays a central role. The deposition area in the respiratory tract and the deposited fraction of the airborne substance depend on the particle size, which is available for the production and further processing of powdery EDTA (H_4EDTA: 15% <63 µm, Na_4EDTA: 30% <63 µm). However information is only available from one producer, thus the deposited fraction and respective areas in the respiratory tract cannot be identified with sufficient certainty. The maximum value of 100% deposition is taken as worst-case assumption. The absorption of the deposited part is not known and should be influenced by the barrier function of different epithelia in the respiratory tract. The charged EDTA-anion with a molecular weight of 298 g/mol or partly charged complexes of EDTA with metal cations are not supposed to cross membrane barriers quickly, especially in the nasopharyngeal region. The non-absorbed fraction will be translocated by mucociliary transport, partly expelled if deposited in the nose and partly swallowed. The latter part is available for the reduced gastrointestinal absorption. The overall absorption should be higher than that after ingestion alone; a precise value cannot be estimated. Due to these uncertainties a 100% absorption of the deposited part is chosen as a worst-case estimation for risk assessment. It may be lower in practice. Overall the combination of 100% deposition with 100% absorption results in the worst-case estimate of 100% systemic availability, which is supposed to err on the side of caution. In this approach the systemic availability via inhalation is 20-fold higher than that after ingestion.

The assumption of a 100% systemic availability by inhalation is used for calculating internal body burdens and corresponding MOS values; decisions on concern for borderline situations should be aware of this rather cautious approach.

Systemic availability after ingestion:	max. 5% (human data)
Systemic availability after dermal contact:	max. 0.001% (human data)
Systemic availability after inhalation:	100% (worst-case assumption)

Occupational exposure and internal body burden

The production and further processing in the large-scale chemical industry is assumed to be mainly performed in closed systems with high levels of protection. Most of the substance is produced in a liquid form. For this case exposure is assessed as negligible, thus this scenario is not listed in **Table 4.1** and **Table 4.15**. If powders are produced, exposure of dusts occurs if the closed systems are breached for certain activities (Scenario 1). If the substances are mixed on site, possibilities of inhalation exposure occur during the weighing and filling of the powdery substance (Scenario 2). Inhalation exposure has to be considered if droplet aerosols are formed during the application of aqueous preparations. Among the different fields of applications high-pressure cleaning is considered to be the most important exposure scenario (Scenario 3). Exposure is negligible if aerosols are not formed. In **Table 4.15** the external exposure levels via inhalation and the assumed internal body burdens are listed.

Table 4.15 Occupational exposure levels and internal body burden

Area of production and use		Inhalation	
		Shift average in mg/m³	Internal body burden in mg/kg/day[1)]
1	Production and further processing of powdery EDTA	5	0.71
2a)	Preparation of formulations, handling of the powdery substance (with LEV)	0.3	0.043
2b)	Preparation of formulations, handling of the powdery substance (dilution ventilation)	0.6	0.086
3	High pressure cleaning, droplet aerosols (diluted solutions, < 2%)	0.3	0.043

1) systemic availability of 100% via inhalation (worst-case assumption)

Calculation of MOS values

Acute toxicity, repeated dose toxicity and developmental toxicity are assessed on the basis of MOS values. The internal body burden was selected for MOS calculation, because of the differences in exposure routes and systemic availabilities. Thus the oral toxicity data are converted into values of internal body burden as "starting points" for MOS calculation, taking the 5% systemic availability into account. Due to the negligible contribution of dermal exposure to the inner body burden the calculation of dermal MOS values is restricted to a worst-case example under "Repeated dose toxicity". Consequently the quantitative assessment of combined exposure is not considered to be necessary.

Evaluation of MOS values

According to TGD (Chapter 4) several aspects have to be considered in deciding on the acceptability of MOS values.

Differences in exposure route have been considered estimating the internal body burden. A duration adjustment (e. g. for the assessment of repeated dose toxicity) is not necessary, since chronic studies are available. However interspecies differences have to be addressed, because the central toxicity studies are oral rat studies. Substance specific informations allowing a quantitative assessment are not available. As default method, interspecies extrapolation relies upon the concept of metabolic rate scaling, that is based on empirical data and considerations on time depending physiological parameters. For interspecies extrapolation of oral or dermal data metabolic rate scaling results in 4-times lower effective dose levels in humans (in mg/kg/day) compared to rats.

Further relevant parameters of MOS evaluation are not covered by scientifically based adjustment factors. Because of the limited degree of confidence in many experimental data generally an additional uncertainty factor is deemed necessary to account for parameters e.g. intraspecies variability, nature and severity of effects, dose-response relationship, variability in the experimental data and overall confidence in the database. A standard uncertainty factor of about 5 is proposed when risk assessment is based on oral animal data and a NOAEL is available. The uncertainty factor may be lower in case of additional relevant data (human data available, route-to-route extrapolation not necessary) or in case of adverse effects that are not considered severe. The uncertainty factor usually is higher than 5 in case of e. g. specific reproductive toxicity or lack of NOAEL.

The minimal acceptable MOS is derived by multiplication of the specific factors.

4.1.3.3 Occupational risk assessment

Acute toxicity

Inhalation

There are no valid data on acute inhalation toxicity (H_4EDTA and Na_4EDTA). In a modified inhalation hazard test the exposure of rats for 8 hours to an unknown concentration resulted in no lethality, but mild irritation of mucous membranes (H_4EDTA and Na_4EDTA).

For the assessment of acute systemic toxicity additional information can be gathered from data on oral acute toxicity. As to H_4EDTA an oral LD50 of >2,000 mg/kg was determined. At higher doses clinical signs and autopsy findings were observed, but up to 2,000 mg/kg no lethality or other effects were observed. Thus 2,000 mg/kg can be considered as a NOAEL.

As to Na_4EDTA the lowest oral LD50 of various studies was 1,700 mg/kg. A dose without effect cannot be described, since the clinical signs and autopsy findings listed from all studies cannot be associated to specific doses. Furthermore route specific local effects in the stomach like bloody ulceration occurred questioning the adequacy of the data to assess acute inhalation. Having in mind that the NOAEL for repeated dose toxicity of Na_4EDTA is set to be 565 mg/kg/day in Section 4.1.2.6 it can be assumed that at this dose acute effects should not be expected, too. In lack of better data the NOAELs of 2,000 mg/kg (H_4EDTA) and 565 mg/kg/day (Na_4EDTA) are taken for risk assessment for acute toxicity.

To perform a MOS calculation on the basis of internal body burden the oral NOAEL is converted into an internal NAEL considering the 5% oral absorption. An internal NAEL of 100 mg/kg is calculated for H_4EDTA (28 mg/kg for Na_4EDTA). Based on these values and the body burden from inhalation exposure the MOS values are calculated and listed in **Table 4.16** and **4.17**.

For the selection of a minimal acceptable MOS the following subfactors are applied (see above):

- interspecies adjustment factor: 4
- uncertainty factor: 5

A minimal acceptable MOS of 20 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 corresponding acceptable exposure concentration assuming a 100% absorption via inhalation is 35 mg/m^3 for H_4EDTA (9.9 mg/m^3 for Na_4EDTA). Concern is not derived.

Conclusion (ii).

Dermal

There are no dermal studies available (H_4EDTA and Na_4EDTA). Regarding the oral LD50 and the marginal dermal absorption (0.001%) compared to the oral one (5%) an acute systemic toxicity is not expected.

Conclusion (ii).

Table 4.16 H_4EDTA: MOS values of systemic inhalation toxicity

			Acute toxicity		**Repeated dose toxicity**		**Developmental toxicity**	
Starting point (internal body burden)			100 mg/kg/day		22 mg/kg/day		50 mg/kg/day	
Minimal acceptable MOS			20		20		60	
Acceptable internal body burden			5 mg/kg/day		1.1 mg/kg/day		0.83 mg/kg/day	
Acceptable inhalation exposure			35 mg/m³		7.4 mg/m³		5.8 mg/m³	
Area of production and use		Internal body burden in mg/kg/day	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion
1	Production and further processing of powdery EDTA	0.71	140	ii	31	ii	70	ii
2a)	Preparation of formulations, handling of the powdery substance (with LEV)	0.043	2,300		510		1,200	
2b)	Preparation of formulations, handling of the powdery substance (dilution ventilation)	0.086	1,200		260		580	
3	High pressure cleaning (diluted solutions, < 2%)	0.043	2,300		510		1,200	

Table 4.17 Na_4EDTA: MOS values of systemic inhalation toxicity

			Acute toxicity		**Repeated dose toxicity**		**Developmental toxicity**	
Starting point (internal body burden)			28 mg/kg/day		28 mg/kg/day		50 mg/kg/day	
Minimal acceptable MOS			20		20		60	
Acceptable internal body burden			1.4 mg/kg/day		1.4 mg/kg/day		0.83 mg/kg/day	
Acceptable inhalation exposure			9.9 mg/m³		9.9 mg/m³		5.8 mg/m³	
Area of production and use		Internal body burden in mg/kg/day	MOS	Conclusion	MOS	Conclusion	MOS	Conclusion
1	Production and further processing of powdery EDTA	0.71	39	ii	39	ii	70	ii
2a)	Preparation of formulations, handling of the powdery substance (with LEV)	0.043	650		650		1,200	
2b)	Preparation of formulations, handling of the powdery substance (dilution ventilation)	0.086	330		330		580	
3	High pressure cleaning (diluted solutions, < 2%)	0.043	650		650		1,200	

Irritation/Corrosivity

Dermal

Weak effects have been observed in skin irritation studies of H_4EDTA and Na_4EDTA. This was not sufficient for classification; no concern for workers is derived.

Conclusion (ii).

Eyes

H_4EDTA is considered to be irritating to the eyes. Na_4EDTA may result in serious damage to the eye.

Eye contact can be largely excluded during production and further processing (Scenario 1), a risk of eye irritation is not expected. For the preparation and the use of formulations (Scenario 2 and 3) it cannot be excluded, that EDTA is handled without using suitable eye protection and a risk of eye irritation is assumed.

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.

Inhalation

See under "Repeated dose toxicity/Inhalation (local effects)", no further information available.

Conclusion (ii).

Sensitisation

Dermal

In a Magnusson Kligman Test with Na_2EDTA according to OECD 406 3/10 (30%) of the guinea pigs showed a positive response after a first challenge and 1/10 (10%) after a second challenge. There are only two reports on humans. 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 is too low to derive concern as to skin sensitisation.

Conclusion (ii).

Inhalation

It was reported (Beasley et al., 1987) that inhalation of nebulised EDTA solution might have caused bronchoconstriction in asthmatics (non-asthmatics were not experimentally exposed to EDTA). However, the validity of these data is very limited due to unclear experimental details with regard to the dissolved amount of EDTA. In letters from industry it was reported, that no acute or chronic respiratory health effects from exposure to EDTA have been observed in workers. Thus, 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. Furthermore the substance is mainly handled in the chemical industry as an aqueous solution with a negligible inhalation exposure. The handling of the powdery form is supposed to be of secondary importance as to the production volume, but exposure is estimated to be 5 mg/m^3. Additionally the shift average concentrations for the preparation and use of formulations of 0.3 and 0.6 mg/m^3 are not as high that a need of further investigations could be clearly derived.

Conclusion (ii).

Inhalation (systemic effects)

Inhalation studies with repeated administration are not available. For the assessment of systemic effects after repeated inhalation the repeated oral studies can be taken into account. Oral chronic toxicity studies with EDTA (as Na_3HEDTA) resulted in a NOAEL of about 500 mg/kg/day for rats and mice. In a 90-day rat study adverse effects (e. g. diarrhea and emaciation) were observed at higher dose levels. The corresponding NOAEL of 435 mg/kg/day for H_4EDTA (565 mg/kg/day for Na_4EDTA) is used for risk assessment.

To perform a MOS calculation on the basis of internal body burden the oral NOAEL is converted into an internal NAEL considering the 5% oral absorption. An internal NAEL of 21.8 mg/kg/day is calculated for H_4EDTA (28.2 mg/kg/day for Na_4EDTA). Based on these values and the body burden from inhalation exposure the MOS values are calculated and listed in **Table 4.16** and **4.17**.

For the selection of a minimal acceptable MOS the following subfactors are applied (see above):

- interspecies adjustment factor: 4
- uncertainty factor: 5

A minimal acceptable MOS of 20 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 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). Concern is not derived.

Conclusion (ii).

Dermal (local effects)

See under “Irritation/Corrosivity/Dermal”, no further information available.

Conclusion (ii).

Dermal (systemic effects)

Dermal studies with repeated administration are not available. The marginal dermal absorption of 0.001% indicates a negligible importance of this exposure route. As a theoretical worst-case example dermal EASE estimates of 5 mg/cm^2/day and an exposed area of 840 cm^2 (both hands) would lead to an internal body burden of 0.6 µg/kg/day (5 · 840 · 0.001% / 70). Comparing this

value with the internal NAEL of 21.8 mg/kg/day for H_4EDTA (28.2 mg/kg/day for Na_4EDTA) the MOS values of > 36,000 are clearly beyond concern.

Conclusion (ii).

Combined dermal and inhalation exposure

Since the dermal absorption is very low the dermal exposure will not contribute to the body burden in a significant way. A particular risk based on combined exposure is not expected.

Conclusion (ii).

Mutagenicity

With reference to Section 4.1.2.7 H_4EDTA and Na_4EDTA are not considered to be mutagens in humans.

Conclusion (ii).

Carcinogenicity

Based on the results of oral longtime studies in rats and mice, H_4EDTA and Na_4EDTA are not considered to be carcinogenic.

Conclusion (ii).

4.1.3.3.1 Toxicity for reproduction

Fertility impairment

Inhalation/Dermal

In Section 4.1.2.9 a rat multigeneration study conducted with $CaNa_2$EDTA is described. Up to the highest tested dose of 250 mg/kg/day there was no evidence for adverse effects on fertility. This dose is equivalent to 196 mg/kg/day H_4ETDA and 255 mg/kg/day Na_4ETDA. It is not clear whether this data can be quantitatively used for an assessment of fertility impairment, since calcium might mitigate a possible toxicity that is discussed to be based on the chelating property. Effects on the reproductive organs are not reported in the subchronic and chronic studies described in Section 4.1.2.6. Based on these data H_4EDTA and Na_4EDTA are not considered to impair fertility. Corresponding risks at workplaces are not anticipated to occur.

Conclusion (ii).

Developmental toxicity

Inhalation

The central study(ies) relevant for MOS-calculation are identified in Section 4.1.2.9. It is assumed that the developmental toxicity of EDTA is based on its metal chelating capacity and especially on endogenous zinc depletion. High oral doses of EDTA (as Na_2H_2EDTA) led to fetotoxicity and teratogenicity, accompanied by maternal toxicity. The maternal and fetal LOAEL in rats was approx. 1,000 mg/kg/day (application with the diet). The application with the

diet seems to be more efficient than by gavage, that led to a fetal NOAEL (gavage) of 1,000 mg/kg. Developmental toxicity data also exist for subcutaneous injection of CaEDTA showing a NOAEL of around 80 mg/kg/day. However subcutaneous application is usually not considered as an appropriate route of application, in addition there are some uncertainties as to the use of Ca-studies for the assessment of EDTA and Na_4EDTA. Thus the subcutaneous study is considered as a qualitative information for the MOS evaluation, but the MOS calculation is based on the above mentioned oral data. Comparing diet and gavage application the diet is considered to be more similar to continuous inhalation exposure, so the oral LOAEL of approx. 1,000 mg/kg/day is used for the acid and the tetrasodium salt as a starting point.

To perform a MOS calculation on the basis of internal body burden the oral LOAEL is converted into an internal LAEL considering the 5% oral absorption. An internal LAEL of 50 mg/kg/day is calculated for EDTA. Based on this value and the body burden from inhalation exposure the MOS values are calculated and listed in **Table 4.16** and **4.17**.

For the selection of a minimal acceptable MOS the following subfactors are applied:

- interspecies adjustment factor: 4 (see introductory remarks)
- uncertainty factor: 15

An uncertainty factor of 15 was selected because a specific mechanism of teratogenicity was detected, a steep dose-response relationship was observed and a LOAEL was the starting point of MOS calculation. On the other hand it was considered that further oral data provided a NOAEL at 1,000 mg/kg/day and that the subcutaneous data indicate a higher internal NAEL (about 80 mg/kg/day).

A minimal acceptable MOS of 60 is calculated which results in an acceptable internal body burden of 0.83 mg/kg/day. 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) 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, a conclusion (ii) is recommended for all scenarios.

Conclusion (ii).

Dermal

Due to the very poor dermal absorption developmental toxicity by skin contact is not anticipated to occur even at very high dermal exposure (for a model calculation see under “Repeated dose toxicity/dermal”). A risk of developmental toxicity due to dermal exposure is not expected.

Conclusion (ii).

4.1.3.3.2 Summary of conclusions for the occupational risk assessment

The occupational risk assessment assessed dermal and inhalation exposure and 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)**).

4.1.3.4 Consumers

Consumer exposure

EDTA is used as a component of cosmetics and of cleansing and dish washing agents**.** Oral exposure may result from the use of cleansers of tooth brackets if they are not properly cleaned after use.

Based on the knowledge and identified uses of EDTA in products, the main route of potential consumer exposure is via dermal contact/absorption through the skin.

The calculation of dermal exposure of consumers results in a value of ~0.72 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. The internal exposure from dermal contact may result in a maximum amount of 0.0000072 mg/kg bw/day.

The calculation of oral exposure (only for tooth brackets wearing children) is 0.1 mg/kg bw/day.

Acute Toxicity

In rats, the substance exhibited only low acute toxicity with oral LD_{50} > 2,000 mg/kg bw.

No data is available on acute dermal toxicity. Taking into account the poor dermal absorption, there is reason to assume that the result of an acute dermal toxicity test would not reveal toxic properties warranting a classification and labelling for acute dermal toxicity.

There are no valid data on acute inhalation toxicity. 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.

Following the exposure assessment, the consumer may be exposed to EDTA via dermal and oral routes. Consumers are not expected to be exposed to EDTA in the range of hazardous doses, which can be derived from acute oral figures based on animal LD50 values. Therefore, the substance is of no concern in relation to acute oral or dermal toxicity.

Conclusion (ii).

Irritation

No data are available on humans.

The substance has weak irritant properties on rabbit skin but has irritant properties to the rabbit eye.

In practice, however, the risk for consumers related to ocular exposure is low, given the low levels of EDTA contained in consumer products. According to the dermal exposure scenarios for cosmetics and household cleansers or dish washing agents (reasonable worst-case) it can be assumed that irritant concentrations of the substance will not occur. It is concluded therefore that EDTA is of no concern for consumers in relation to possible eye irritating effects.

Conclusion (ii).

Corrosivity

No data on humans are available.

The substance is not corrosive to the skin of rabbits.

Conclusion (ii).

Sensitisation

In a Magnusson Kligman Test with Na_2EDTA according to OECD Guideline 406 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, the substance EDTA is considered as non-sensitising to humans.

Conclusion (ii).

Repeated dose toxicity

There are no repeated dose studies with EDTA itself or its tetrasodium salt available. Under the assumption of a comparable biomechanism, investigations on Na_2EDTA and Na_3EDTA will be considered.

Oral application in rats for 1 month revealed a NOAEL of 1125 mg/kg/day=2.25% in diet. From 90 days investigation in rats (Na_2EDTA), a NOAEL of 500 mg/kg/day equivalent to 1% in diet can be deduced for male rats. This corresponds to 435 mg/kg bw/day edetic acid. The effects were increased in mortality, reduced body weight, reduced food consumption and diarrhea.

Investigations with Na_3EDTA over a period of two years in rats and mice (50 animals per dose-group and sex) revealed an NOAEL of 500 mg/kg/day hence supporting the NOAEL of 435 mg/kg/day seen in the 90 days study which was taken for further consideration of MOS.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account:

- Overall confidence in the database

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to Section 3.2 of the TGD. There is no study which is performed in accordance with internationally recognised guidelines and to GLP. However, the findings of all studies are not contradictory so that the judgment can be based on the database.

Some of the effects have not been investigated in more detail and lack of data has to be stated (biochemical data are lacking).

- Uncertainty arising from the variability in the experimental data

The studies cited above allow concluding on the NOAEL of the substances' toxicity. The NOAEL of 435 mg/kg bw/day from the rat studies is considered to be the most appropriate value for risk assessment. The main findings from all studies showed identical main toxic effects. No species differences have been observed.

There are no reasons to assume a special extent of uncertainty which has to be taken into account.

– Intra- and interspecies variation

Data on kinetics of the substance do not allow calculating the intraspecies and interspecies variability by applying modern approaches. From the excretion mechanism by the renal route it is concluded that no species differences have to be taken into consideration as the mechanism of excretion concerns.

– Nature and severity of the effect

There is no target organ for toxicity but the administration of EDTA is causing diarrhea, loss of weight and less food consumption. It is assumed that the toxic effect is mediated by zinc depletion. The effects are considered to be severe health effects and data are lacking to support a statement on reversibility. According to the data there seem**s** to be a steep relationship between dose and effect.

There are no reasons to assume that the effects shown in the animal experiments are limited to the species tested, hence they are of relevance for humans. Because of the seriousness of the effects there is concern, which has to be expressed in the magnitude of the MOS.

– Differences in exposure (route, duration, frequency and pattern)

The estimated total daily intake can be compared with an oral NOAEL from a 90-day study because the internal intake has been corrected for different absorption by different routes of exposure.

– Human population to which the quantitative and/or qualitative information on exposure applies

Considering the route of excretion there is reason to assume a special risk for the elderly and for patients with impaired renal function. Theoretically, a population depleted for zinc or in a zinc deficient state would be at higher risk. However, it is not known whether a zinc depleted population exists in Europe. Following the exposure scenarios for consumers there is no special risk for patients with hyperreactive airways**.**

– Other factors

There are no other factors known requiring a peculiar margin of safety.

MOS for the dermal exposure scenario

The internal exposure has been calculated to be 0.0000072 mg/kg bw/day. The margin of safety between the assumed internal exposure level of 0.0000072 mg/kg bw/day and the oral NOAEL (EDTA) of 21.8 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 435 mg/kg bw/day has been converted into an internal value of 21.8 mg/kg bw/day considering the maximum oral absorption of 5%.

Conclusion (ii).

MOS for the oral exposure scenario

The oral exposure of children (via 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 (EDTA) of 435 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.

Conclusion (ii).

Mutagenicity

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.

Conclusion (ii).

Carcinogenicity

There are no data available on carcinogenic properties of EDTA. There is no evidence on carcinogenic properties of Na_3EDTA from studies in experimental animals.

Conclusion (ii).

Reproductive toxicity

Fertility

There are no repeated dose studies with EDTA itself or its tetrasodium salt available. Under the assumption of a comparable biomechanism, investigations on $CaNa_2EDTA$ will be considered.

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.

For estimating a NOAEL other studies were not taken into consideration because of methodological flaws. Hence the NOAEL is 250 mg/kg bw/day corresponding to 196 mg/kg bw edetic acid.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account:

– Overall confidence in the database

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to Section 3.2 of the TGD. No studies were according to internationally acknowledged guidelines were presented.

However, despite some limitations and weaknesses in the performance and reporting of the one single study it is justified to take its results for further considerations.

– Uncertainty arising from the variability in the experimental data

The study cited above allows concluding on the NOAEL of fertility impairment of EDTA/Na_4-EDTA. The oral NOAEL for fertility of 196 mg/kg bw/day from the rat study is considered to be an appropriate value for risk assessment.

There are no reasons to assume a special extent of uncertainty which has to be taken into account.

– Intra- and interspecies variation

Data on kinetics of the substance do not allow calculating the intraspecies and interspecies variability by applying modern approaches. From the excretion mechanism by the renal route it is concluded that no species differences have to be taken into consideration as the mechanism of excretion concerns.

– The nature and severity of the effect

The effects are considered to be severe health effects per se. It is assumed that the toxic effect is mediated by zinc depletion.

There are no reasons to assume that the effects shown in the animal experiments are limited to the species tested, thus being not of relevance for humans.

– Differences in exposure (route, duration, frequency and pattern)

The internal intake can be compared with the oral NOAEL from the only study because the internal intake has been corrected for different absorption by different routes of exposure.

– Human population to which the quantitative and/or qualitative information on exposure applies

Considering the route of excretion there is reason to assume a special risk for patients with impaired renal function. Theoretically, a population depleted for zinc or in a zinc deficient state would be at higher risk. However, it is not known whether a zinc depleted population exists in Europe. Not applicable for this endpoint.

– Other factors

There are no other factors known requiring a peculiar margin of safety.

MOS for the dermal exposure scenario

The internal exposure has been calculated to 0.0000072 mg/kg bw/day. The margin of safety between the assumed internal exposure level of 0.0000072 mg/kg bw/day and the oral NOAEL (EDTA) of 9.8 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 196 mg/kg bw/day has been converted into an internal value of 9.8 mg/kg bw/day considering the maximum oral absorption of 5%.

Conclusion (ii).

Developmental toxicity

There are several studies on developmental toxicity which have been performed with EDTA, sodium salts of EDTA and calcium and zinc chelates. Because of several methodological aspects the studies with Na_2EDTA form the basis for the estimation of NOAEL, first the studies are independent and the studies have been performed with oral application of the sodium salt of EDTA by different techniques which is preferred to the s.c. application in the studies with chelates which has been judged to be not appropriate for considerations of MOS taking into account the routes of exposure scenarios in humans.

For the decision on the appropriateness of MOS, the following aspects have been considered and taken into account:

– Overall confidence in the database

The data taken into account for performing the risk characterisation have been evaluated with regard to their reliability, relevance and completeness according to Section 3.2 of the TGD.

No studies were presented, according to internationally acknowledged guidelines.

However, despite some limitations and weaknesses in the performance and reporting of the studies it is justified to take their results for further considerations.

– Uncertainty arising from the variability in the experimental data

The studies cited above allow concluding only on the LOAEL of developmental toxicity of EDTA/Na_4EDTA. For developmental toxicity an oral LOAEL of about 1,000 mg/kg bw/day was established.

Because of consistency between the different studies with the exception of the Schardein-study there are no reasons to assume a special extent of uncertainty for the LOAEL which has to be taken into account.

– Intra- and interspecies variation

Data on kinetics of the substance do not allow calculating the intraspecies and interspecies variability by applying modern approaches. From the excretion mechanism by the renal route it is concluded that no species differences have to be taken into consideration as the mechanism of excretion concerns.

– Nature and severity of the effect

The effects are considered to be severe health effects per se. It is assumed that the toxic effect is mediated by zinc depletion. According to the data there seems to be a steep relationship between dose and effect.

There are no reasons to assume that the effects shown in the animal experiments are limited to the species tested, thus being not of relevance for humans.

– Differences in exposure (route, duration, frequency and pattern)

The estimated internal intake can be compared with the oral LOAEL from the studies because the internal intake has been corrected for different absorption by different routes of exposure.

– Human population to which the quantitative and/or qualitative information on exposure applies

Considering the route of excretion there is reason to assume a special risk for patients with impaired renal function. Theoretically, a population depleted for zinc or in a zinc deficient state would be at higher risk. However, it is not known whether a zinc depleted population exists in Europe.

– Other factors

There are no other factors known requiring a peculiar margin of safety.

MOS for the dermal exposure scenario

The internal exposure has been calculated to be 0.0000072 mg/kg bw/day. The margin of safety between the assumed internal exposure level of 0.0000072 mg/kg bw/day and the oral LOAEL (EDTA) of 50 mg/kg bw/day is judged to be sufficient, even if special considerations i.e. no established NOAEL, the nature and severity of the effects are taken into account. The oral LOAEL of 1,000 mg/kg bw/day has been converted into an internal value of 50 mg/kg bw/day considering the maximum oral absorption of 5%.

Conclusion (ii).

4.1.3.5 Humans exposed via the environment

Exposure

As EDTA does not accumulate in biota, a significant intake via fish, plants or meat is not expected. The only significant indirect exposure for human occurs via drinking water.

Model calculations for the local scenario performed for the different producers resulted in a total daily dose in the range from 0.003 to 0.38 mg/kg bw/day (see Section 4.1.1.4). 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 value of 0.38 mg/kg bw/day has been used.

Repeated dose toxicity

From different repeated dose toxicity studies (2 years; 90 days-studies) with mice and rats with Na_3EDTA a NOAEL of 500 mg/kg bw/day was derived (respectively 435 mg/kg bw/day EDTA).

Comparison indirect exposure–NOAEL

$$\frac{\text{Indirect exposure}}{\text{NOAEL}} = \frac{0.38\ \text{mg/kg bw/d}}{435\ \text{mg/kg bw}}$$

The margin of safety between the calculated exposure for the only significant indirect exposure source drinking water and the NOAEL is judged to be sufficient. Thus, regarding of repeated dose effects the substance is of no concern in relation to indirect exposure via the environment.

Conclusion (ii).

Reproductive toxicity

Fertility

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 (respectively 196 mg/kg bw EDTA).

Comparison indirect exposure–NOAEL

$$\frac{\text{Indirect exposure}}{\text{NOAEL}} = \frac{0.38 \text{ mg/kg bw/d}}{196 \text{ mg/kg bw}}$$

The margin of safety between the calculated exposure for the only significant indirect exposure source drinking water and the NOAEL is judged to be sufficient. Thus, regarding of adverse effects on reproductive performance the substance is of no concern in relation to indirect exposure via the environment.

Conclusion (ii).

Developmental toxicity

Fetotoxic and teratogenic effects in rats occur at EDTA exposure levels of approximately 1,000 mg/kg bw/day (LOAEL) and above.

Comparison indirect exposure-LOAEL

$$\frac{\text{Indirect exposure}}{\text{LOAEL}} = \frac{0.38 \text{ mg/kg bw/d}}{1000 \text{ mg/kg bw}}$$

The margin of safety between the calculated exposure for the only significant indirect exposure source drinking water and the LOAEL is judged to be sufficient. Thus, the substance is, regarding of fetotoxic and teratogenic effects, of no concern in relation to indirect exposure via the environment.

Conclusion (ii).

4.1.3.6 Combined exposure

It is possible for an individual to receive exposure to EDTA at work, from consumer products and indirectly via the environment. Occupational exposure may occur via different inhalation scenarios to estimated concentrations of 0.3 to 0.6 mg/m^3, resulting in internal body burdens of 43 to 86 µg/kg bw/day (see **Tables 4.16** and **4.17**). The dermal exposure can be neglected due to the poor absorption of EDTA. The exposure levels to EDTA in consumer products (up to 0.72 mg/kg bw/day) and the levels that would be received indirectly from environmental sources via drinking water (range 0.003 to 0.38 mg/kg bw/day) are also so low that there is no concern.

Taken together, the conclusions (ii) reached for workers, consumers, and humans exposed via the environment apply also to combined exposure.

Conclusion (ii).

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Exposure assessment

n.a.

4.2.2 Effects assessment: Hazard identification

Explosivity

EDTA is not explosive.

Flammability

EDTA is not highly flammable.

Oxidising potential

Due to its chemical structure, EDTA is not expected to possess any oxidising properties.

4.2.3 Risk characterisation

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, the exposure model for the recovery of photochemical based on default values was used for the risk characterisation which lead to a risk for aquatic organisms.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

5.2.1.1 Workers

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

5.2.1.2 Consumers

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

5.2.1.3 Humans exposed indirectly via the environment

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

5.2.2 Human health (risks from physico-chemical properties)

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

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ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
BOD	Biochemical Oxygen Demand
bw	body weight / *Bw*, *bw*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CEPE	European Committee for Paints and Inks
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 90 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]

EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests
EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
foc	Organic carbon factor (compartment depending)
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 tonnes/annum)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues

Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient
Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidising (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
OC	Organic Carbon content
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling

PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$
pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst-Case
S phrases	Safety phrases according to Annex IV of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
ThOD	Theoritical Oxygen Demand
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme

US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative
VOC	Volatile Organic Compound
vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organisation
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex II of Directive 67/548/EEC)

European Commission

EUR 21314 EN **European Union Risk Assessment Report**
Edetic acid (EDTA), **Volume 49**

Editors: S.J. Munn, R. Allanou, K. Aschberger, F. Berthault, O. Cosgrove, J. de Bruijn, C. Musset, S. O'Connor, S. Pakalin, A. Paya-Perez, G. Pellegrini, S. Scheer, B. Schwarz-Schulz

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Environment and quality of life series

The report provides the comprehensive risk assessment of human health part of the substance edetic acid (EDTA). It has been prepared by Germany in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to humans and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined. For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.

The human health risk assessment for edetic acid (EDTA) concludes that there is no concern for workers, consumers and humans exposed via the environment.

The environmental risk assessment for edetic acid (EDTA) concludes that there is at present risk the aquatic ecosystem.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commissions committee on risk reduction strategies set up in support of Council Regulation (EEC) N. 793/93.

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European Commission – Joint Research Centre
Institute for Health and Consumer Protection
European Chemicals Bureau (ECB)

European Union Risk Assessment Report

edetic acid (EDTA)

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