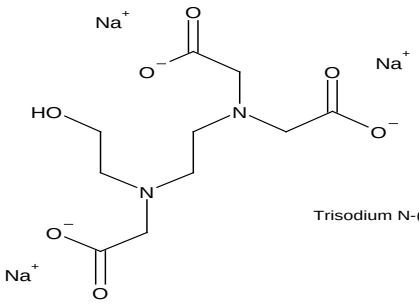
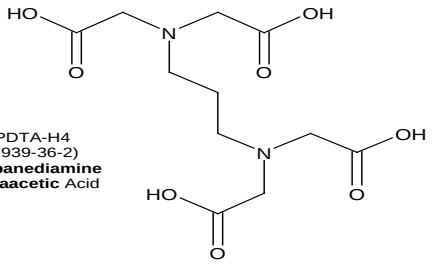
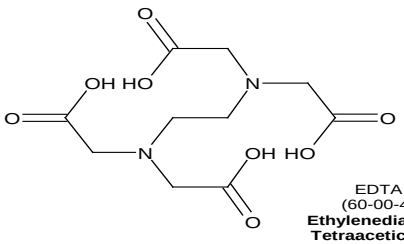
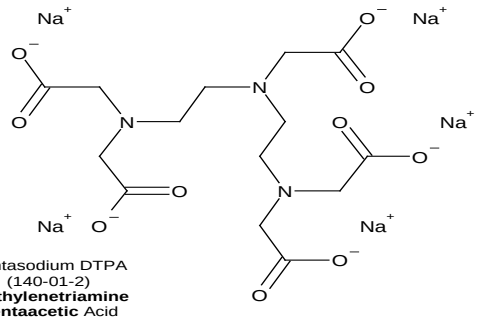
SIDS INITIAL ASSESSMENT PROFILE

Category Name	Amino Carboxylic Acid-Based Chelants Category		
CAS No(s). and Chemical Name(s)	139-33-3	Disodium EDTA; Na_2EDTA	Glycine, N,N'-1,2-ethanediylbis[N-(carboxymethyl)-, sodium salt (1:2)
	139-89-9	Trisodium HEDTA; Na_3HEDTA	Glycine,N-[2-(bis(carboxymethyl)amino)ethyl]-N-(2-hydroxyethyl)-, trisodium salt
	140-01-2	Pentasodium DTPA; Na_5DTPA	Glycine,N,N-bis[2-(bis(carboxymethyl)amino)ethyl]-, pentasodium salt
	1939-36-2	$PDTAH_4$	Glycine,N,N'-1,3-propanediylbis[N-(carboxymethyl)]-
	15708-41-5	Ferric monosodium EDTA; Fe(III)NaEDTA	Ferrate (1-), [[N,N'-1,2-ethanediylbis[N-(carboxymethyl)glycinato]](4-)-N,N',O,O',ON,ON']-, sodium, (OC-6-21)
	16485-47-5	Ferrous HEDTA; Fe(II)HEDTA	Ferrate(1-),[N-[2-[bis[(carboxy-.kappa.O)methyl]amino-.kappa.N]ethyl]-N-[2-(hydroxy-.kappa.O)ethyl]glycinato(3-)-.kappa.N,.kappa.O]-, sodium (1:1)
	17084-02-5	Ferric HEDTA; Fe(III)HEDTA	Iron, [N-[2-[bis[(carboxy-.kappa.O)methyl]amino-.kappa.N]ethyl]-N-[2-(hydroxy-.kappa.O)ethyl]glycinato(3-)-.kappa.N,.kappa.O]-
	18719-03-4	Tetrasodium PDTA; Na_4PDTA	Glycine,N,N'-1,3-propanediylbis[N-(carboxymethyl)-, tetrasodium salt
	20824-56-0	Diammonium EDTA; $(NH_4)_2EDTA$	Glycine,N,N'-1,2-ethanediylbis[N-(carboxymethyl)-, diammonium salt
	21265-50-9	Ferric ammonium EDTA; $Fe(III)(NH_4)EDTA$	Ferrate(1-), [[N,N'-1,2-ethanediylbis[N-[(carboxy-.kappa.O)methyl]glycinato-.kappa.N,.kappa.O]](4-)]-, ammonium (1:1), (OC-6-21)-
	22473-78-5	Tetraammonium EDTA; $(NH_4)_4EDTA$	Glycine,N,N'-1,2-ethanediylbis[N-(carboxymethyl)-, tetraammonium salt
	67859-51-2	**Zinc Diammonium EDTA; $Zn(NH_4)_2EDTA$**	**Zincate (2-), [N,N'-ethylenebis(N-(carboxymethyl)glycinato)](4-)-N,N',O,O',ON,ON'), diammonium (OC-6-21)-**

Structural Formula(s)	$(HOOCCH_2)_2NCH_2CH_2N(CH_2COOH)_2$, $(HOOCCH_2)_2NCH_2CH_2CH_2N\ (CH_2COOH)_2$, $(HOOCCH_2)_2NCH_2CH_2N(CH_2CH_2OH)(CH_2COOH)$, and $(HOOCCH_2)_2NCH_2CH_2\ N(CH_2COOH)CH_2CH_2N(CH_2COOH)_2$ Note: The above structural formulas may be either uncomplexed, or complexed with metal ions Na^+, K^+, NH_4^+, Zn^{2+}, Ca^{2+}, Fe^{2+}, and/or Fe^{3+}.  Trisodium HEDTA (139-89-9) Trisodium N-(2-Hydroxy**ethyl)ethylene diamine Triacetate**  PDTA-H4 (1939-36-2) **Propanediamine Tetraacetic** Acid  EDTA (60-00-4) **Ethylenediamine Tetraacetic** Acid  Pentasodium DTPA (140-01-2) **Diethylenetriamine Pentaacetic** Acid **Representative Structures of Ethylenediamine-, Propanediamine- and Diethylenetriamine-Based Chelants**

SUMMARY CONCLUSIONS OF THE SIAR

Category Analogue/Justification

Members of the aminocarboxylic acid-based chelant category possess similar molecular structures that contain common functional groups. All members have a molecular structure with an ethylenediamine, propanediamine or diethylenetriamine backbone, which has 3-5 acetic acid groups attached to the nitrogens. Therefore all category members in common possess amino acid groups. In addition for one member of the ethylenediamine backbone series (hydroxyethylethylenediamine or HEDTA), a 2-hydroxyethyl group appears in place of an acetic acid group, so there are only three acetic acid groups instead of four.

The ethylenediamine structure has either four acetic acid groups (EDTA), or three acetic acid groups and one hydroxyethyl group (HEDTA). The propanediamine structures contain four acetic acid groups. Finally, the diethylenetriamine structures contain five acetic acid groups. The carboxylic acid groups may be in the form of either the free carboxylic acid or the carboxylate anion, in which one or more hydrogens have been neutralized to an ammonium or a metal salt. When no hydrogens have been substituted (EDTA, **$PDTAH_4$**), the chelant exists as an inner salt or zwitterion. More commonly, the substance exists as an ammonium or metallic salt.

Therefore all category members have identical functional groups (except for HEDTA, where a hydroxyethyl group is also present). It is the presence of multiple carboxylic acid groups on the amine that provides chelants with their unique metal ion chelating or sequestering properties. This common property is the important feature to consider in assessing the aquatic and mammalian toxicity of chelants and in justifying their consideration as a category.

A common mechanism of action for the chelant category, based on structural and chemical similarity, is the fundamental basis for a category approach for these closely related chemicals. The ability of chelants to remove and add ions to solution is the mechanism whereby these chemicals produce toxicity. Environmental fate and ecological and mammalian toxicity profiles are consistent within the category. Category members have demonstrated high stability to hydrolysis, and most category members are commercially available primarily or solely in aqueous solution. Category members emitted to waterways will remain dissolved in this environmental compartment. If emitted to soil or sediment, category members will exhibit high water solubility and soil mobility. This behavior is based on the presence of multiple carboxylate anion groups in the molecular structure, and is supported by the demonstrated high water solubility and negligible vapor pressure of category members. With regard to environmental biodegradation, the majority of the members of the category have been tested in actual laboratory studies with similar and predictable results from standard laboratory tests, in general being found not to be readily biodegradable. However, results of recent studies indicate that EDTA, calcium EDTA and **Na_2EDTA** can biodegrade under certain conditions.

The substantial body of evidence that chelants are not directly toxic to aquatic and mammalian organisms but exert their influence by affecting mineral balance, together with the fact that the backbone structures of the chelants in the category have similar affinities for metals supports the inclusion of these chelants in a category. Subtle differences in toxicity due to the presence of ammonium, sodium, calcium, ferric or ferrous iron or potassium can be explained by their affinity towards these metals and their ability to supply metals to organisms. According to the chemical equilibrium and kinetic properties of metal-ligand complexes, a certain portion of a free metal ion is always present in solution. This is particularly important for aquatic systems. Uncomplexed chelants like EDTA and **$PDTAH_4$** would be expected to add H+ ions to media (which would lead to decreased pH), and would chelate metals present in their milieu. The ferric iron-containing chelants would not be expected to significantly affect mineral balance at low concentrations because the affinity for ferric ion is stronger than most other ions. The **$Zn(NH_4)_2EDTA$** would be expected to have less of an effect than **$(NH_4)_2EDTA$** on zinc balance. The sodium, potassium and calcium-containing chelants would be expected to be of intermediate toxicity (between EDTA and Fe or Zn-containing chelants), since they would not affect pH as much as the acids and would provide essential ions that are not toxic in amounts that would be supplied by the chelants, but also would chelate essential ions such as Zn^{2+} and Fe^{2+} or Fe^{3+}. Data show that the toxic profile of chelants in this category generally follows this pattern, and can be predicted by the type of ion that the chelant is complexed with and its affinity for the particular ion.

Log K values of metal chelates of DTPA, PDTA and HEDTA compared to EDTA (μ=0.1M, T=20°C)

Metal	EDTA	DTPA	PDTA	HEDTA
Fe^{3+}	25.1	28.6	21.6	19.8
Zn^{2+}	16.5	18.3	15.3	14.5
Fe_{2+}	14.3	16.5	13.4	11.6
Ca^{2+}	10.7	10.7	7.3	8.0
Na^{+}	1.66			

Using the category approach, read across has been performed (see below) from the appropriate tested members to those without available data. The toxicity of the counter-ion is considered for read-across but may not be the deciding factor in read-across. A conservative approach is used whereby read-across will always be from the most toxic substance to that without data.

Two analogue substances have previously been assessed in the OECD HPV Chemicals programme (SIAM 18): EDTA (CAS No. 60-00-4) and Na_4EDTA (CAS No. 64-02-8). The data can be viewed at http://www.oecd.org/env/hazard/data/. Data for counter ions can be viewed in the OECD HPV assessments for several calcium salts, ammonia category, zinc salts category and iron salts category found at: http://www.oecd.org/env/hazard/data/

Read-Across used for ecotoxicity endpoints for the Aminocarboxylic Acid-Based Chelants Category

Substance	CAS No.	Acute Toxicity to Fish	Acute Toxicity to Aquatic Invertebrates	Toxicity to Aquatic Plants
SPONSORED SUBSTANCES				
$(NH_4)_2$EDTA	**20824-56-0**	**X**	**O**	**O**
$(NH_4)_4$EDTA	**22473-78-5**	**X**	**O**	**O**
$Zn(NH_4)_2$EDTA	**67859-51-2**	**X**	**O**	**O**
Fe(III)NaEDTA	**15708-41-5**	**X**	**X**	**X**
Na_2EDTA	**139-33-3**	**O**	**X**	**X**
Na_3HEDTA	**139-89-9**	**X**	**X**	**X**
Fe(III)NH_4EDTA	**21265-50-9**	**X**	**X**	**X**
Fe(II) HEDTA	**16485-47-5**	**O**	**O**	**O**
Fe(III) HEDTA	**17084-02-5**	X	**O**	**O**
$PDTAH_4$	**1939-36-2**	X	**X**	**O**
Na_4PDTA	**18719-03-4**	**O**	**O**	**O**
Na_5DTPA	**140-01-2**	X	**X**	**X**
ANALOGUE SUBSTANCES				
EDTA	60-00-4	**X**	**X**	−
$CaNa_2$EDTA	62-33-9	**X**	**O**	−
Na_3EDTA	150-38-9	**X**	**X**	**X**
Na_4EDTA	64-02-8	**X**	**X**	**X**
K_5DTPA	7216-95-7	X	−	−

X = data available; O = read across; −Endpoint not addressed for this chemical

Read-Across used for human health endpoints for the Aminocarboxylic Acid-Based Chelants Category

Substance	CAS No.	S[1]	R[2]	Effects on Fertility	Developmental Toxicity	Genetic Toxicity		
						Gene Mutations (*in vitro*)	Chromosomal Aberrations (*in vitro*)	*In vivo*
SPONSORED SUBSTANCES								
$(NH_4)_2$EDTA	**20824-56-0**	WoE	Na_3EDTA	$CaNa_2$EDTA/ **Na_2EDTA**	EDTA/ Na_3EDTA	WoE	WoE	–
$(NH_4)_4$EDTA	**22473-78-5**	WoE	Na_3EDTA	$CaNa_2$EDTA **/Na_2EDTA**	EDTA/ Na_3EDTA	WoE	WoE	–
$Zn(NH_4)_2$ EDTA	**67859-51-2**	WoE	Na_3EDTA	$CaNa_2$EDTA **/Na_2EDTA**	EDTA/ Na_3EDTA	WoE	**X**	–
Fe(III)Na EDTA	**15708-41-5**	WoE	**X**	$CaNa_2$EDTA **/Na_2EDTA**	**X**	**X**	-	**X**
Na_2EDTA	**139-33-3**	**X**	**X**	**X**	**X**	**X**	–	**X**
Na_3HEDTA	**139-89-9**	WoE	Na_3EDTA	$CaNa_2$EDTA **/Na_2EDTA**	EDTA/ Na_3EDTA	**X**	WoE	–
Fe(III)NH_4 EDTA	**21265-50-9**	**X**	**Fe(III)Na EDTA**	$CaNa_2$EDTA **/Na_2EDTA**	EDTA/ Na_3EDTA	WoE	WoE	–
Fe(II) HEDTA	**16485-47-5**	WoE	**Fe(III)Na EDTA**	$CaNa_2$EDTA **/Na_2EDTA**	EDTA/ Na_3EDTA	WoE	WoE	–
Fe(III) HEDTA	**17084-02-5**	WoE	**Fe(III)Na EDTA**	$CaNa_2$EDTA **/Na_2EDTA**	EDTA/ Na_3EDTA	WoE	WoE	–
$PDTAH_4$	**1939-36-2**	**X**	**X**	**X**	**X**	**X**	WoE	–
Na_4PDTA	**18719-03-4**	WoE	**$PDTAH_4$**	**$PDTAH_4$**	**$PDTAH_4$**	WoE	WoE	–
Na_5DTPA	**140-01-2**	**X**	**X**	**$PDTAH_4$**	**X**	**X**	WoE	–
ANALOGUE SUBSTANCES								
Substance	**CAS No.**	**Repeated-dose toxicity**		**Effects on Fertility**	**Developmental Toxicity**	**Genetic Toxicity**		
						Gene Mutations (*in vitro*)	**Chromosomal Aberrations (*in vitro*)**	***In vivo***
EDTA	60-00-4	–		–	**X**	**X**	**X**	–
$CaNa_2$EDTA	62-33-9	**X**		**X**	**X**	**X**	–	–
Na_3EDTA	150-38-9	**X**		**X**	**X**	**X**	**X**	–
Na_4EDTA	64-02-8	–		–	**X**	–	–	–
K_5DTPA	7216-95-7	**X**		–	–	**X**	**X**	–

X = data available; O = read across; –**E**ndpoint not addressed for this chemical; WoE = weight of evidence

1 = Sensitisation

2 = Repeated-dose toxicity

Physical-Chemical Properties

The members of this category are all solid granular materials in the pure or neat state with molecular weights that range from 292 to 503 and possess similar physical/chemical properties. As metal-organic salts, or inner salts, all category members decompose before melting upon sufficient heating (generally at temperatures > 200 °C). Therefore true melting points are not applicable. Chelants that are metal salts do not exist as discrete neutral molecules, and therefore cannot volatilize, exert appreciable vapour pressure, or boil. Therefore, vapour pressure and boiling point data are not applicable for such chelants and are not determined. Henry's law constants are also expected to be negligible. Chelants that exist as neutral molecules (not metal salts) can exert vapour pressure, but in this case the vapour pressure is exceedingly low. All category members are highly soluble to miscible in water (generally > 10,000 mg/L) and insoluble in organic solvents, therefore also possessing negative partition coefficients (log Kows).

Human Health

Toxicokinetics, Metabolism and Distribution

Toxicokinetic data with category members and analogues are available. By the inhalation route, aerosolized DTPA and its salts are absorbed from the respiratory tract into systemic circulation but the degree of absorption is dependent on the site of deposition. Absorption via the oral and dermal routes is expected to be low. Dermal application of radiolabeled $CaNa_2$EDTA to human skin showed that 0.001% was found in the urine and none was found in the blood. Studies with CaEDTA, $CaNa_2$EDTA, **Na_2EDTA** and DTPA and its salts indicate that these complexes are poorly absorbed in mammals after oral administration. EDTA and its salts are eliminated from the body, 95% via the kidneys and 5% by the bile, along with the metals and free

ionic calcium which was bound in transit through the circulatory system. In whatever salt EDTA is administered, it is likely to chelate metal ions *in vivo*.

Acute Toxicity

Data are available on the sponsored and/or analogue substances for acute toxicity via the inhalation, oral and dermal routes of exposure. Limited acute inhalation toxicity data with atmospheres enriched in the dusts of certain of the chelants were generally without effect in rats. However, inhalation of respirable dust aerosols of **Na_2EDTA** in male rats exposed to 30, 300 or 1103 mg/m^3 6 hours/day for up to 5 days produced adverse effects at all concentration levels. Mortality was observed at 1103 mg/m^3 following a single 6-h exposure. These effects were fully reversed in surviving animals after a 14-day recovery. Acute dermal toxicity studies in rats with **Fe(III)NH_4EDTA**, **$PDTAH_4$**, **Na_4PDTA** and K_5DTPAshowed LD_{50} values ranging from >1800 to >2000 mg/kg bw. In rats, excepting **$(NH_4)_4$EDTA** (oral LD_{50} > 1870 mg/kg bw), **Fe(III)(NH_4)EDTA** (oral LD_{50} > 920 mg/kg bw) and Na_4EDTA (oral LD_{50} equal to 1658 mg/kg bw), oral LD_{50} values [EDTA, **$(NH_4)_2$EDTA, Zn$(NH_4)_2$EDTA**, $CaNa_2$EDTA**, Na_2EDTA**, Na_3EDTA, **Fe(III)NaEDTA**, **Na_3HEDTA**, **Fe(III)HEDTA, $PDTAH_4$**, **Na_4PDTA, Na_5PDTA** and K_5DTPA] were > 2000 mg/kg bw. At higher doses approaching the LD_{50} values, clinical signs consisting of dyspnea, diarrhea and spastic gait were observed.

Irritation and Sensitisation

The aminocarboxylic acid-based chelants are not irritating to moderately irritating to the intact skin, and slightly to moderately irritating to the eyes in rabbits. The irritancy potential is related to the pH of the individual salt. Thus, more acidic members of the category such as **diammonium** and **disodium EDTA**, and the more basic members such as **tetrasodium PDTA** and **pentasodium salt of PDTA**, have inherently greater irritancy potential. The aminocarboxylic acid-based chelants are not skin sensitisers based on studies in mice and guinea pigs.

Repeated-dose Toxicity. Reliable data are available for oral repeated-dose studies with **Na_2EDTA**, **$PDTAH_4$, Fe(III)NaEDTA,** Na_3EDTA, $CaNa_2$EDTA, K_5DTPA and **Na_5DTPA**. The toxicity observed has been attributed to nutrient metal deficiencies, resulting from chelation of critical metal species, most notably calcium and zinc. Under physiologically relevant conditions, the salts of various category members will ionize based on the dissociation constants of the parent chelate and thus all salts of a particular parent, such as EDTA or PDTA, are assumed to chelate metal ions *in vivo* based on the inherent chelating strength of the parent chelate molecule. As in the case of zinc, deficiency is presumed to exhibit a threshold effect, and both dose and duration of exposure become important factors in the overall toxicity observed with longer-term administration.

In a 13-week repeated-dose toxicity study, rats (both sexes) fed **Na_2EDTA** (0, 1, 5, 10%) showed mortality at the highest dose. In addition, there was decreased food consumption (emaciation at 10%) and diarrhea at doses of 5% (approximately 4206 mg/kg bw/day) and above. The NOAEL was 1% (approximately 692 mg/kg bw/day). Range finding studies with higher dose levels revealed diarrhea, emaciation, loss of body weight and sometimes parakeratosis in esophagus and forestomach as well as decreased hemoglobin and hematocrit levels. In a 2- year bioassay in rats and mice (both sexes) with Na_3EDTA (0, 3750 or 7500 ppm) a NOAEL of 7500 ppm (approximately 500 mg/kg bw/day in rats and 938 mg/kg bw/day in mice; highest dose tested) was determined. In a 2-year dietary study, rats fed $CaNa_2$EDTA at 0, 50, 125 or 250 mg/kg bw/day showed no effect on behaviour, appearance, growth, longevity or hematology up to one year. After 1 year, there was a downward trend in hematology parameters. There were no gross pathologic findings, changes in organ weights or treatment-related lesions any organ that was examined. The NOAEL was 250 mg/kg-bw/day (highest dose tested). In a 31-day dietary study, female rats fed $CaNa_2$EDTA (0, 0.3, 1.0, 3.0 or 5.0%) showed decreased body weight gain at 5.0% (approximately 3636 mg/kg bw/day). No effects on organ weight were observed. The NOAEL was 3.0 % (approximately 2216 mg/kg bw/day). In a 14-week repeated-dose toxicity oral gavage study in rats (both sexes) with **$PDTAH_4$** (0, 30, 100 or 300 mg/kg bw/day), urinary zinc concentrations increased with duration of treatment in males but not females. Increased urinary zinc concentrations did not appear to be associated with systemic toxicity as no other treatment-related findings were observed. The NOAEL was determined to be 300 mg/kg bw/day. In a 28-day study [OECD TG 407], rats treated by gavage with **$PDTAH_4$** (0, 100, 500 or 1000 mg/kg bw/day) showed mortality at 1000 mg/kg bw/day. In male rats, hyaline droplet formation resembling alpha 2µ globulin nephropathy was observed at 500 and 1000 mg/kg bw/day. No other effects were observed. The NOAEL was determined to be 500 mg/kg-bw/day. In another 28-day study, **$PDTAH_4$** (0, 100, 300 or 1000 mg/kg bw/day) showed mortality at 1000 mg/kg bw/day. At 300 mg/kg bw/day, histopathological findings were thymic atrophy and bone marrow atrophy and congestion in two females and serum zinc levels were significantly

decreased (50% of controls). At 100 and 1000 mg/kg bw/day, urinary zinc levels were higher than controls. No other adverse findings were observed. The NOAEL was determined to be 100 mg/kg bw/day. In 31-day and 61-day studies, male rats fed **Fe(III)NaEDTA** up to 86.15 mg/kg bw/day had decreased plasma sodium and calcium concentrations but did not exhibit any organ toxicity. The NOAEL was considered to be 86.15 mg/kg bw/day (highest concentration tested). Iron accumulated in the liver, spleen and kidneys in a dose-related manner but this did not result in excess iron in other tissue or in iron toxicity. In a 28-day repeated-dose oral gavage study with K_5DTPA, rats administered 0, 83, 333 or 1330 mg/kg bw/day, showed mortality at 1330 mg/kg bw/day. Other effects reported included increased serum potassium levels, decreased body weights, clinical signs and diarrhea. Less severe effects were observed at 333 mg/kg bw/day. The NOAEL was 83 mg/kg bw/day. In a 28-day drinking water study, rats received 0, 600, 3000 or 12,000 ppm **Na_5DTPA**. Body weight reductions and histopathological changes of the urinary tract were observed at 12,000 ppm and 3000 ppm. The NOAEL was 600 ppm (approximately 75 mg/kg bw/day).

Genetic Toxicity

Available data from *in vitro* [**Na_2EDTA, Na_3HEDTA**, **$PDTAH_4$**, Na_3EDTA, **Fe(III)NaEDTA** and **Na_5DTPA**] and *in vivo* [**Na_2EDTA,** Na_3EDTA and **Fe(III)NaEDTA**] testing of representative chelant category members indicate that these materials generally do not induce gene mutations or chromosomal aberrations *in vitro* or *in vivo*. Although there have been some positive findings reported *in vitro* and *in vivo* for some category members, these positive effects have been generally attributed to the threshold mechanisms of pH changes and the chelation of critical nutrient metals such as zinc. The weight of evidence leads to a conclusion that the members of the aminocarboxylic acid-based chelants category do not present a genotoxic hazard.

Carcinogenicity

An oral two-year study with Na_3EDTA trihydrate in mice and rats indicated no evidence of carcinogenicity. The amino carboxylic acid-based chelants category members are not expected to be carcinogens.

Toxicity to Reproduction (Fertility and Developmental Toxicity)

Reproductive toxicity data are available that evaluate the potential for reproductive effects from exposure to $CaNa_2$EDTA, **Na_2EDTA** and **$PDTAH_4$**. Chronic studies with Na_3EDTA that included histological examination of gonadal tissues for evidence of adverse effects also showed no adverse effects on reproductive organs. In a non-guideline chronic study, no adverse clinical, histological, hematological or reproductive effects were found over 4 generations in rats fed a diet of 0, 50, 125 or 250 mg/kg bw/day of $CaNa_2$EDTA. The NOAEL for reproductive toxicity was 250 mg/kg bw/day (highest dose tested). The weight of evidence from a two-generation reproductive toxicity study in rats shows that dietary ingestion of 1% **Na_2EDTA** (approx. 920 mg/kg bw/day) had no effect on reproduction; however, no litters were produced at 5% (approx. 4600 mg/kg bw/day); the NOAEL for reproductive toxicity was 920 mg/kg bw/day. In a one-generation reproductive toxicity study [OECD TG 415] in rats fed 0, 10, 60 or 300 mg/kg bw/day **$PDTAH_4$** decreased male and female fertility indices, and gestational and pup survival indices were noted at 300 mg/kg bw/day. In addition, testicular toxicity changes (degeneration and/or atrophy of seminiferous tubules, decreased or absent spermatids) and increased urinary zinc and decreased serum zinc levels were observed in this group. The NOAEL for reproductive toxicity was 60 mg/kg bw/day at which dose there was no severe zinc deficiency. Observed reproductive toxicity with **$PDTAH_4$** is indirect, and occurring subsequent to a severe zinc deficiency. Based on available data EDTA and HEDTA based category members do not show similar reproductive effects / and similar potency. In the absence of a deficiency of essential metals which is expected under normal nutrition, none of the category members would be considered reproductive toxicants.

Developmental toxicity data are available for EDTA, $CaNa_2$EDTA, **Na_2EDTA**, Na_3EDTA, and **Na_5DTPA**. Data from multigenerational and prenatal developmental toxicity studies suggest that developmental effects are observed in the presence of maternal toxicity and are related to plasma zinc concentrations. Studies on developmental toxicity showed a specific fetotoxic and teratogenic potential of EDTA, **Na_2EDTA** and $CaNa_2$EDTA; a LOAEL of 1000 mg/kg bw/day was determined. Increased proportions/litter and significantly lower fetal body weights are indicative for an impaired fetal development. The pattern of malformations comprised cleft palate, severe brain deformities, eye defects, micro- or agnathia, syndactyly, clubbed legs and tail anomalies. These effects were exhibited in studies using maternally toxic dose levels. The mechanism resulting in developmental effects is found to occur via zinc depletion resulting in zinc deficit. These effects are independent of whether the acid or sodium or calcium salts are applied. In a non-guideline prenatal developmental toxicity study, rats were administered a single dose of 1245 mg/kg bw/day

Na_3EDTA on gestation days 7-14. Clinical effects included diarrhea (35% of animals) and a reduction of body weight gain during the treatment period in dams; the NOAEL for maternal toxicity was not established. There was no effect of treatment on litter size, post-implantation loss, sex ratio, fetal body weight, or mortality. There was no effect of treatment on the incidence of fetal abnormalities; the NOAEL for developmental toxicity was 1245 mg/kg bw/day. In a prenatal developmental toxicity study [OECD TG 414], rats were administered (via gavage) 0, 100, 400 or 1000 mg/kg bw/day **Na_5DTPA**. At 400 mg/kg bw/day there was a statistically significant increase in the total number of fetuses with skeletal variations and retardations in fetuses (shortened or absent 13th rib, rudimentary cervical ribs, delays in ossification). At 1000 mg/kg bw/day, in addition to effects observed in the mid dose, there was a reduction in litter size and an increase in number of skeletal malformations (missing thoracic and lumbar vertebrae and bipartite sternebrae) but no visceral or external malformations were present. This dose also produced a reduction in maternal body weight gain (adjusted). The NOAEL for maternal toxicity was 400 mg/kg bw/day and for developmental toxicity, 100 mg/kg bw/day. Members of the aminocarboxylic acid-based chelants category would not be expected to exhibit reproductive and developmental effects in the absence of a metal deficiency which is not expected under normal nutrition.

The members of the amino carboxylic acid-based chelants category possess properties indicating a hazard for human health (skin and eye irritation, repeated-dose toxicity and reproductive/developmental toxicity). However, these effects are associated with the chelation of metals and the subsequent toxicological effects related to metal deficiency and therefore would only be considered relevant human hazards where there is significant exposure. Adequate screening-level data are available to characterize the human health hazard for the purposes of the OECD Cooperative Chemicals Assessment Programme.

Environment:

Photodegradation experimental data (EDTA, Na_4EDTA, and **Fe(III)NaEDTA**) indicate that these chelants are rapidly degraded by light when they are in the hydrosphere. 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 of Ferric monosodium EDTA. Splitting off of acetic acid residues appears to be an important conversion step. Formation of iron complexes by chelants is believed to be a major route of photodegradation in the aqueous environment. Because ferric salts are present in the environment, and the chelants in this category will readily displace their ions for ferric iron, it is suspected that these agents will photodegrade in the aqueous environment. Photodegradation rates of 1:1 ferric complexes of both EDTA and DTPA were calculated after irradiating aqueous solutions of these complexes with light which corresponded to the spectrum of the sun at 60° N. These rates corresponded to half-lives of 11.3 and 8.04 minutes respectively for the EDTA and DTPA complexes. Since the experimental conditions were ideal, actual conditions in natural waterways that take into consideration varying sunlight and cloudiness, varying opacity and depth of water would be expected to be associated with longer half-lives. The fate of EDTA and DTPA in aquatic environments receiving waste waters from Swedish pulp and paper mills was studied with results that indicated that the rate of disappearance of these chelants was dependent on sunlight intensity, and that light has a stronger influence on DTPA than on EDTA. All members of the amino carboxylic acid-based chelants category are stable in water, and most commercial chelants are sold as aqueous solutions. These substances are highly water-soluble salts, and possess no functional groups in their molecular structures subject to hydrolysis.

Hydroxyl radical induced atmospheric degradation cannot be estimated for members of the Chelants Category. Since the chelants are salts and therefore exert no significant vapor pressure, this endpoint is not applicable for category members.

Category members emitted to waterways are likely to remain dissolved in this environmental compartment. If emitted to soil or sediment, category members are likely to exhibit appreciable to high water solubility and soil mobility. This behavior is based on the presence of multiple carboxylate anion groups in the molecular structure, and is supported by the demonstrated high water solubility and negligible vapour pressure of most category members. The EPA EPIWIN Fugacity Level III modeling has been run for category members (see SIAR), with results consistent with negligible partitioning to the atmosphere, and predominant partitioning to the hydrosphere. These results must be viewed with caution, because the Level III fugacity model has not been well validated for ionised organic salts.

Available biodegradation experimental data indicate that category members are not readily biodegradable in

soil or water in standard laboratory tests. Studies with adapted microorganisms have indicated that EDTA, calcium disodium EDTA, disodium EDTA, DTPA, **Fe(III)NH_4EDTA**, and **Fe(III)NaEDTA** can be biodegraded under certain conditions (e.g. slightly alkaline pH and long retention times). One study showed that >99% of EDTA is biodegraded in an industrial wastewater treatment plant, suggesting that laboratory methods may underestimate the potential for biodegradation in the environment. It is evident that these conditions are **not** present in municipal wastewater treatment plants (WWTP). Therefore, it is assumed that no biodegradation occurs in municipal waste water treatment plants. This is supported by monitoring studies, where no degradation was observed. As neither adsorption onto sludge nor volatilisation is expected, 100% of the widely dispersed EDTA is expected to be released into the hydrosphere." However, EDTA used for instance by the food or pulp & paper industry is, or can be, treated biologically. Industrial WWTPs are often operated at slightly alkaline conditions and high sludge retention times. Counter-ions exert effects on the biodegradation of chelating agents. A particular strain has been identified that degrades metal-EDTA complexes with a thermodynamic stability constant below 1012, like Ca, Mg and Mn complexes, but not those with constants > 1012, such as Cu and Fe. Another has been shown to degrade EDTA when it was complexed with Mg, Zn, Mn, Co or Cu, but not when uncomplexed or complexed to Ca, Ni or Fe(III) ions. Conditions that favour EDTA biodegradation are also expected to lead to biodegradation of the other members of the category. The ferric-iron-containing chelants are expected to be the most resistant to biodegradation, but the most susceptible to photodegradation.

The pH of the test medium may affect aquatic toxicity of certain of the chelate salts, in particular the ammonium salts, which are generally of less toxicity in typical waters of pH range 5 to 8, but which increase in toxicity at higher pH values due to free ammonia. Aquatic toxicity testing with salts of EDTA has shown a relationship between water hardness and toxicity, with toxicities generally higher in soft water and decreasing in harder waters, due to chelation of calcium.

It could be shown in short-term tests on fish, that EDTA and Na-EDTA are more toxic in an uncomplexed form. This can only occur if they are available in over-stoichiometric amounts to the chelants. Under these conditions the complexing agents can cause nutrient deficiency by reducing the essential concentration of different ions. The higher the water hardness the higher is the concentration of EDTA necessary to cause a toxic effect expressed as mortality.

According to the results from different ecotoxicological studies, EDTA mainly influences the pathway of metal ions. For EDTA long-term studies with fish, daphnids and algae are available. The following results were found: *Danio rerio*: 35 d-NOEC > 26.8 mg/L ($CaNa_2EDTA$); *Daphnia magna*: 21d-NOEC = 22 mg/L; *Scenedesmus subspicatus*: 72h-EC10 = > 100 mg/L. For **Na_2EDTA**, *Daphnia magna*: 21d-NOEC = 25 mg/L. For aquatic plants, the low EC_{50} values are related to interference of some category members with essential metal nutrients in the test medium of the standard algae test resulting in nutrient deficiency in the laboratory test. These effects can be overcome by supplementing the algae medium with growth limiting metal nutrients as seen in studies where iron complexes of EDTA are tested. In the environment, there is always a vast molar surplus of the essential nutrients in comparison with actual chelant concentrations. In general, chelants are not considered to be hazardous to plants.

Test Chemical	CAS No.	Acute Toxicity to Fish			
		Species	Time (h)	LC_{50} (mg/L)	NOEC (mg/L)
EDTA	60-00-4	bluegill	96	159	100
		channel catfish	96	129	
$(NH_4)_2$EDTA	**20824-56-0**	bluegill	96	936	540
$(NH_4)_4$EDTA	**22473-78-5**	bluegill	96	275	94
$Zn(NH_4)_2$EDTA	**67859-51-2**	bluegill	96	363	170
$CaNa_2$ EDTA	**62-33-9**	bluegill	96	2340	1000
Na_2EDTA	**139-33-3**	guppy	96	320	
		Oncorhynchus mykiss	24	860 LC_{100}	
Na_3EDTA	150-38-9	fathead minnow	96	> 300 (trihydrate)	
Na_4EDTA	64-02-8	bluegill	96	486	456
		Leuciscus idus	48	1590	
Fe(III)NH_4 EDTA	**21265-50-9**	fathead minnow	96	190	
Fe(III)NaEDTA	**15708-41-5**	bluegill	96	2592	1792
		rainbow trout (ferric potassium EDTA)	96	> 116	116
Na_3HEDTA	**139-89-9**	bluegill	96	331	230
		golden orfe	96	1856 (LC_{100})	860
Fe(III)HEDTA	**17084-02-5**	bluegill	96	2155	1490
Na_5DTPA	**140-01-2**	bluegill	96	424	285
K_5DTPA	7216-95-7	rainbow trout	96	>1000	1000

Test Chemical	CAS No.	Acute Toxicity to Aquatic Invertebrates			
		Species	Time (hr)	LC_{50} (mg/L)	EC_{50} (mg/L)
EDTA	60-00-4	*Daphnia magna*	48		113
		D. magna	48	~230	
		Artemia salina	24	280 (LC_{100})	
Na_2EDTA	**139-33-3**	*Artemia salina*	24		660 (EC100)
Na_3EDTA	150-38-9	Daphnid (trihydrate)	96		> 100
Na_4 EDTA	64-02-8	*D. magna*	24		610
		D. magna	24	625	
		D. magna	24		1033
Fe(III)NaEDTA	**15708-41-5**	Daphnid	24		110
		D. magna	96	13-32	
		Daphnid (ferric potassium EDTA)	48		> 114
Na_3HEDTA	**139-89-9**	*D. magna*	48	> 500	
$PDTAH_4$	**1939-36-2**	*D. magna*		>88	
Na_5DTPA	**140-01-2**	*D. magna*	48		>500
K_5DTPA	7216-95-7	*D. magna*	48		890

Test Chemical	CAS No.	Toxicity to Algae		
		Species	Time (h)	EC_{50} (mg/L)
Na_2EDTA	**139-33-3**	*S. quadricauda*	24 day	200 (NOEC)
Na_3EDTA	150-38-9	*S. capricornutum*	7 day	> 1 <10
Na_4EDTA	64-02-8	*S. subspicatus*	72	1.01
Fe(III)NH_4EDTA	**21265-50-9**	*S. capricornutum*	168	>100
Fe(III)NaEDTA	**15708-41-5**	*S. capricornutum* (Na_2-EDTA + Fe^{3+})	72	>72.7
Na_3HEDTA	**139-89-9**	*S. subspicatus*	96	10.4
Na_5DTPA	**140-01-2**	*S. subspicatus*	72	2.62

The amino carboxylic acid-based chelants category members possess properties indicating a hazard to the environment (acute toxicity to aquatic organisms between 1-100 mg/L). However, the toxicity is associated with the chelation of essential nutrients by the category members which may not be seen in nutrient rich environments. The category members are not readily biodegradable and have low potential for bioaccumulation. Adequate screening-level data are available to characterize the hazard for the environment for the purposes of the OECD Cooperative Chemicals Programme.

Exposure

Environmental release of chelants during manufacture is incidental. Manufacture takes place in closed systems with incidental release to waste streams. The same incidental release is associated with the formulation of chelants into aqueous commercial mixtures or preparations. Chelants enter the environment primarily as a result of their multiple uses, which can be characterized as dispersive. The actual amount released depends on the type of use, however, most uses result in eventual environmental release to waterways, via aqueous wastes. Some aqueous waste streams undergo waste treatments, but most chelants have limited biodegradability; therefore the chelant may pass through a waste treatment system to a waterway. The predominant environmental compartmental destination is the hydrosphere. Chelants as salts have negligible volatility, and therefore cannot enter the atmosphere in significant amounts. Chelants released to soil or biota will have substantial soil mobility based on their high water solubilities, and therefore will tend to partition to water.

Aggregate Production and/or Import Volume in the United States in 2005

Substance	CAS No.	Production Volume (metric tons)
$(NH_4)_2$EDTA	**20824-56-0**	**454 - < 4540**
$(NH_4)_4$EDTA	**22473-78-5**	**454 - < 4540**
Zn$(NH_4)_2$EDTA	**67859-51-2**	**454 - < 4540**
Fe(III)NaEDTA	**15708-41-5**	**454 - < 4540**
NaEDTA	**139-33-3**	**454 - < 4540**
Na_3HEDTA	**139-89-9**	**4540 - < 22,680**
Fe(III)NH_4EDTA	**21265-50-9**	**NA**
Fe(II) HEDTA	**16485-47-5**	**NA**
Fe(III) HEDTA	**17084-02-5**	**4540 - < 22,680**
$PDTAH_4$	**1939-36-2**	**227 - < 454**
Na_4PDTA	**18719-03-4**	**NA**
Na_5DTPA	**140-01-2**	**45,400 - < 226,800**

NA = Not available

Based on the expected widespread application of engineering controls (closed systems) and the lack of volatility of chelants, occupational exposure during manufacture or processing into formulations or preparations is expected to be low via the inhalation route. The most likely route of occupational exposure is through the dermal route. Dermal exposure is minimized by closed systems and personal protective equipment (e.g. gloves) when used. Industries with a higher exposure potential include the use of chelants in

the pulp and paper industry, and the textile industry where the predominant route of potential exposure will still be dermal.

Chelants are present in preparations used by consumers. A typical concentration of chelants in various consumer products is 10%. Based on negligible volatility of chelant salts and very low volatility of neutral chelants, the potential for inhalation exposure is expected to be low. However, inhalation exposure can occur when using chelant containing surface cleaners which are aerosolised. Most consumer exposure will occur by dermal contact with chelant formulations, or by the oral route. Chelants are used as approved direct and indirect food additives. In these applications the chelants function as food preservatives, or as fortifications (e.g., to improve iron status in populations). Chelant formulations are also administered clinically in treating heavy metal poisoning (e.g. lead).