ANALYSIS OF THE MOST APPROPRIATE RISK MANAGEMENT OPTION(S) FOR "DTPA" SALTS

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CONTENT

1 BACKGROUND

1.1 General context

Method

The French National mandated institute ANSES[1] has defined a method that aims to conduct an *a priori* analysis to identify candidates for management measures in the context of the REACH and CLP Regulations (i.e. harmonised classification, authorisation and/or restriction), based on the screening of the thousands of chemicals placed on the European market
This work completes the actions being coordinated by ECHA (e.g. the manual screening mainly for the selection of substances for the CoRAP) and the possibility of formal requests from different Ministries at national level.

The tool used for this exercise was the SIRIS method (System of Integration of Risk with Interaction of Scores), a mathematical multi-criteria decision support tool developed in the 1980s and used primarily for environmental risk assessments. This method has mainly been used to establish priority lists of substances to be screened for in water, and to classify plant protection substances based on the environmental risk they pose to surface waters.
The criterion adopted in the first approach for the hazard level was the CMR classification (harmonized and self-classification), while those selected for potential exposure were tonnage, consumer use, dispersive use and potentially significant exposure of workers.

The starting list was the list of substances registered under REACH in July 2011. This concerns 4938 substances, corresponding to substances produced or imported in quantities over 1000 tonnes per year, substances classified as CMR Category 1A or 1B (more than 1 tonne per year) and substances classified as very toxic to aquatic organisms (more than 100 tonnes per year). Substances already being managed or having undergone preliminary work by a Member State or ECHA were removed from the list.

Most of the first substances appearing on this list belong to the family of petroleum derivatives (hydrocarbons), regarded as UVCB in the context of REACH. Assessing the risks associated with these types of compounds is considered difficult and will be endorsed by the "PetCo Group" under SVHC Implementation Roadmap.
Other priority substances identified were nickel and lead compounds already intended to be analysed or managed in a near future according to the ACT[2] Table.

Na5DTPA (pentasodium (carboxylatomethyl)iminobis(ethylenenitrilo)tetraacetate) is part of next priority substances identified in this exercise (high production volume, wide-dispersive use, consumer use and self-classified reprotoxic category 2): this substance is therefore chosen for a RMOA.

This work has been published on Anses website (Opinion on the development of a method for identifying substances of interest for ANSES's REACH-CLP work programme. March 2013. www.anses.fr).

[1] French Agency for Food, Environmental and Occupational Health & Safety.

[2] Authorities Coordination Tool.

2 IDENTITY OF THE SUBSTANCES

2.1 Main identifiers of the substance

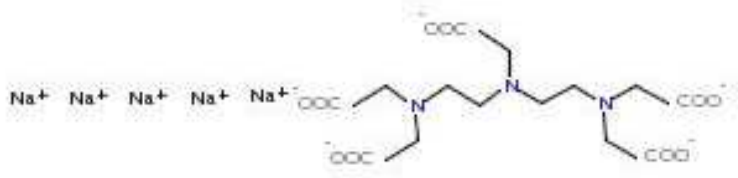
The designation "DTPA" refers to the uncomplexed chelant. Many additional aminocarboxylic acid-based chelants and their metal complexes are in commercial use.

Table 1: Substance identity of Na5DTPA

EC Number:	205-391-3
CAS Number:	140-01-2
EC name:	pentasodium (carboxylatomethyl)iminobis(ethylenenitrilo)tetraacetate
IUPAC name:	pentasodium 2,2',2'',2''',2''''-(ethane-1,2-diylnitrilo)pentaacetate
Molecular formula:	C14H23N3O10.5Na
Molecular weight or molecular weight range:	508.3
Synonyms/Trade names:	*Glycine, N,N-bis[2-[bis(carboxymethyl)amino]ethyl]-, sodium salt (1:5)* *Na5DTPA*

Type of substance: ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



Purity: > 89%

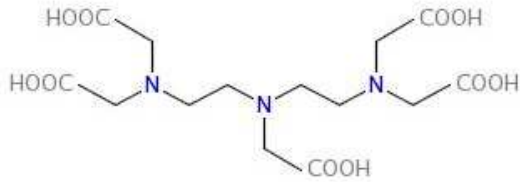
Total tonnage*:* 10,000 - 100,000 tonnes per annum

Table 2: Substance identity of DTPA Acid

EC Number:	200-652-8
CAS Number:	67-43-6
EC name:	N-carboxymethyliminobis(ethylenenitrilo)tetra(acetic acid)
IUPAC name:	2-[bis[2-(bis(carboxymethyl)amino)ethyl]amino]acetic acid
Molecular formula:	C14H23N3O10
Molecular weight or molecular weight range:	393.35
Synonyms/Trade names:	*Glycine, N,N-bis[2-[bis(carboxymethyl)amino]ethyl]-* *DTPA Acid*

Type of substance: ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



Total tonnage*:* 1,000 - 10,000 tonnes per annum

***Other DTPA complexes* in ECHA database**
Pré-registered : : Pentapotassium DTPA (EC No 615-726-9, CAS No 7216-95-7)

Other DTPA complexes registered only for a use in agriculture as fertilisers:

DTPA-FeHNa (EC No 235-627-0, CAS No 12389-75-2)
100 – 1,000 tonnes per annum
Agricultural use: Fertilisers

FeDTPA (EC No 243-136-8, CAS No 19529-38-5)
1,000 - 10,000 tonnes per annum
Agricultural use: Fertilisers

DTPA-Fe(NH4)2 (EC No 289-064-0, CAS No 85959-68-8)
100 – 1,000 tonnes per annum

Agricultural use: Fertilisers

Na_5DTPA and DTPA Acid are potentially used in a wide number of industries including pulp and paper industries (main use), laundry detergents, cleaners, soaps, and textiles.
The 3 others iron chelate DTPA have only agricultural use as components of fertilizers. Considering this very specific use, these substances are not included in this RMOA.
This RMOA covers Na5DTPA and DTPA Acid.

2.2 Similar substances/grouping possibilities

EDTA stands for Ethylenediaminetetraacetate (CAS No 60-00-4, EINECS No 200-449-4).
As DTPA, EDTA is used as a complexing agent in many industrial branches (pulp and paper industry, textiles, metal plating, etc.).

EDTA and DTPA are included in the aminocarboxylic acid-based chelants category. Chelant category members have indeed similar molecular structures, similar physical and environmental fate properties, similar functionality and chelate metal ions.

EDTA has a harmonized classification and a risk assessment report (RAR) has been performed by Germany in the framework of former Directive 93/67/EEC.

<u>The harmonized classification of EDTA is (according to CLP):</u>

- H319: Eye Irrit. 2

There are also several additional C&L notifications (in parenthesis, no joint entries):

- H332: Acute Tox. 4
- STOT RE 2 H373 (Respiratory tract; inhalation)
- (H412: Aquatic Chronic 3)
- (H335: STOT SE 3)

<u>RAR of EDTA (European Union Risk Assessment Report, Final Report 2004, Germany)</u>
The conclusions of the RAR for EDTA are the following:
Human health
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.

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.

<u>Strategy for limiting risks (Official Journal of the European Union, 13.4.2006)</u>
For the Environment, it is recommended:

- To facilitate permitting and monitoring under Council Directive 96/61/EC (IPPC)[3], EDTA should be included in the "Best Available Techniques" (BAT).
- To take persistent complexing agents into account in the European eco-labelling for cleaners to industrial cleaners under Regulation 1980/2000/EC. The objective of the Community eco-label award scheme is to promote

[3] Transposed in Directive 2010/75/EU of the European Parliament and of the Council of 24 November 2010 on industrial emissions.

products which have the potential to reduce negative environmental impacts, as compared with the other products in the same product group, thus contributing to the efficient use of resources and a high level of environmental protection.
EDTA and its salts shall not be included in the product, either as part of the formulation or as part of any mixture included in the formulation, according to criterion 3 of EU Ecolabel described in Commission Decision of 28 June 2011 on establishing the ecological criteria for the award of the EU Ecolabel to all-purpose cleaners and sanitary cleaners).

2.3 Regulatory context

Directive 2010/75/EU of 24 November 2010 on industrial emissions (integrated pollution prevention and control)
The Directive 2010/75/EU of 24 November 2010 on industrial emissions (integrated pollution prevention and control) strengthens the application of Best Available Techniques (BAT), making BAT conclusions the reference point in the permitting process.

In order to determine best available techniques and to limit imbalances in the Union as regards the level of emissions from industrial activities, reference documents for best available techniques (BREF) are drawn up, reviewed and, where necessary, updated through an exchange of information with stakeholders.
The following BREF referencing DTPA have been identified:

BREF Production of Pulp, Paper and Board, Final Draft July 2013

Emissions from the use of chelating agents in peroxide-based bleaching technologies:
The presence of heavy metal ions promotes the decomposition of peroxide resulting in lower brightness and higher peroxide consumption. Therefore, sodium silicate (waterglass, Na_2SiO_3) and chelating agents (e.g. EDTA, DTPA) are added both during bleaching and before bleaching to form complexes with heavy metals (Fe, Mn, Cu, Cr), which prevents the pulp from discolouring and the peroxide from decomposing.

Once in the environment, EDTA/DTPA have the ability to remobilise heavy metals (lead, mercury, cadmium) from natural water sediments, may accumulate in water bodies or reach the drinking water supply via waste water input.

2.2.2 Emission data production in pulp and paper mills
2.2.2.1 Monitoring of waste water discharges
Examples of DTPA monitoring are cited in the BREF: "EDTA/DTPA are analysed on weekly composite samples in some chemical or mechanical pulp mills, e.g. in Sweden and Germany. EDTA is not a routine parameter and is only determined when it is used as a chelating agent and also not in all cases. Recent permits, e.g. in Germany include target values for daily loads of EDTA released to water bodies that have to be monitored."

2.9.9 Reduction of emissions from the use of chelating agents in peroxide-based bleaching technologies
"DTPA and EDTA are powerful chelants, but are poorly biodegradable and are emitted to receiving water bodies at the end of the process. Even though EDTA and DTPA are considered stable molecules, some studies suggest that they are degraded substantially in the harsh conditions of bleaching. [...]
DTPA is more degradable than EDTA in aquatic environment, but it is probable that DTPA decomposes to EDTA during the bleaching process or in the waste water treatment.
[...]
Some national regulations and regional competent authorities ask pulp mills within the area of their responsibility to reduce emissions of EDTA or DTPA to the receiving waters (e.g. in Austria or Germany), assessing the availability of substitutes case by case. If recipient rivers

or lakes are used to provide drinking water, environmental officials set increasingly strict limits on permissible EDTA and DTPA concentrations."

4.2.2.4 Waste water flow and emissions to water
Most of the chelating agents used in the acid chelating stage are washed out of the pulp and are discharged to waste water treatment plants. Because the currently used chelating agents are heavily biodegradable, a high percentage of these chemicals will end up in the recipient. In most mills the acid Q-stages are led to waste water treatment. The use of EDTA or DTPA is in the range of 0 – 3 kg chelating agent/ADt[4]. Complexing agents are normally not measured in the effluents of sulphite pulp mills in Europe. Therefore, no measured emission data are given here. However, at least one mill in Germany (SCA Mannheim) has recently got a permit limit value for DTPA emissions (60 kg DTPA/day) to be met.

BAT is to carry out the monitoring and measurement of emissions to water, on a regular basis according to EN standards. If EN standards are not available, BAT is to use ISO, national or other international standards that ensure the provision of data of an equivalent scientific quality:
If EDTA / DTPA used in the process: monitoring once a month.

BREF for the Textiles Industry, European Commission, July 2003
Considerable amounts of surfactants are used in pretreatment as detergents, wetting agents, etc. Pollutants of concern may be found in water effluent from pretreatment activities, such as poorly bio-eliminable complexing agents used as hydrogen peroxide stabilisers (e.g. EDTA, DTPA, phosphonates), etc.

When complexing agents need to be used, some compounds that are readily biodegradable or at least bioeliminable and that do not contain N or P in their molecule (e.g. polycarbonates, polyacrylates, gluconates, citrates and some sugar-acrylic acid copolymers) are available as alternatives to conventional sequestering agents. Costs are comparable, although higher quantities may be necessary in some cases.

PARCOM Recommendation 94/5 concerning Best Available Techniques and Best Environmental Practice for Wet Processes in the Textile Processing Industry
OSPAR Convention for the protection of the marine environment of the North-East Atlantic
Meeting of the Hazardous Substances Committee (HSC) - WISMAR: 19 - 23 April 2004

This commission recommends the substitution of such chemicals, giving preference in the selection of auxiliaries and chemicals to products with a high degree of biodegradability, low human and ecological toxicology, low volatility and low smell intensity. The avoidance of EDTA, DTPA and NTA is cited.

Overview assessment of implementation of PARCOM Recommendations 94/5 on textile industry:
As an example, in Germany, legislative measures with regard to discharge limit values and good housekeeping are stipulated in Annex 38 of the Ordinance on Requirements for the Discharge of Waste Water into Waters in accordance with the German Federal Water Act (§ 7a Wasserhaushaltsgesetz). In this Annex, there is no direct ban of certain substances for textile processing, but it sets some general requirements concerning the chemicals used and limits, or excludes, the use of harmful substances by banning them in the discharges ("Discharges must not contain: ...").
In particular, the waste water at the site of occurrence must not contain EDTA, DTPA and phosphonates.

Regulation 2003/2003 EC of 13 October 2003 relating to fertilisers

[4] "ADt" means an air dry tonne of pulp product where the weight of the pulp product is corrected to reflect the weight that the pulp product would be if the pulp were composed of 10% water and 90% fibre.

DTPA is part of the List of authorised organic chelating and complexing agents for micro-nutrients. The chelating agents are to be identified and quantified by European Standard EN 13368 part 1 and part 2.
Fertilisers must display certain technical characteristics laid down by mandatory provisions. These provisions concern more particularly the composition. This regulation states that it is "necessary to authorise tolerances on the declared nutrient contents. In the interest of the agricultural user, it is advisable to keep these tolerances within narrow limits." For instance, for iron chelate the minimum content of nutrients (percentage by weight) is 5 % of water soluble iron, of which the chelated fraction is at least 80 %.

No limit concentration of chelatants present in the fertilizers has been identified.

3 HAZARD INFORMATION

Hazards properties presented in this section are mainly based on available data from the CSR of DTPA Acid and the CSR of Na5DTPA, as well as on previous European evaluations on chelants: the Risk Assessment Report on EDTA (RAR, 2004) and the SIDS Initial Assessment Report on amino carboxylic acid-based chelants category (SIAR, 2012).

3.1 Key hazard information

3.1.1 Health hazards related to DTPA

As it is discussed in the SIDS Initial Assessment Profile (COCAM 3, 16-18 October 2012) for aminocarboxylic acid-Based chelants, this category of chelants are not directly toxic to aquatic and mammalian organisms. The chelants exert their influence by affecting mineral (metal ion) balance in aqueous or biological systems. These effects vary, sometimes in subtle ways, depending on whether or not the chelant is complexed with metal ions, and because chelating strength depends also on how many ligands are available on the chelant for forming. The variation in properties and environmental and mammalian toxicology are explained primarily in terms of metal complexing and chelating power. Variations in pH with different chelant formulations can also influence toxicity.

3.1.1.1 Toxicokinetics

Oral:
The oral absorption of DTPA and DTPA salts appears to be low, with an average intestinal absorption of 3 to 5% across all species.

Dermal:
There are no data available on the dermal absorption potential of DTPA, however in a risk assessment by the European Chemicals Bureau (2004), a structurally related chelating agent, EDTA was reported as having very low dermal penetration potential, with approximately 0.001% absorption through the skin. Considering the larger molecular weight of DTPA compared to EDTA it is believed that the dermal penetration of DTPA will be equally low, i.e. approximately 0.001%.

Inhalation:
In humans, DTPA absorption following the administration of a nebulised spray containing DTPA was estimated to be 20% of the administered dose.
Exposure to DTPA is also possible via inhalation of the powdered form of the chelating agent.

Distribution / excretion:
Following exposure, the portion of the dose that is absorbed and thus available systemically is excreted via the urine very quickly. Following an oral dose, the unabsorbed material remains in the gastrointestinal tract and is excreted via the faeces.

There are many studies where the effects of administering DTPA to animals and man on the excretion of essential metals such as calcium, zinc, iron, manganese, magnesium etc. have been studied. Systemic administration of DTPA (intravenous, intraperitoneal, subcutaneous) causes an increased urinary excretion of zinc, calcium and to a lesser extent iron and manganese. The reason for the increase in the urinary excretion of certain metals following systemic exposure to DTPA is due to its formation of complexes with 'free' metals in the blood and lymph.

3.1.1.2 Acute toxicity

In a subacute inhalation study conducted with disodium EDTA there were local irritation effects noted at the dose level of 30 mg/m^3 (6 hours of exposure). The mechanism of action

appears to be the chelation of calcium ions from the epithelial cells, causing the tight junctions between cells to fail. This leads to epithelial cells sloughing away.
The acute oral and dermal toxicity of DTPA is low.

Lead registrant of Na5DTPA considered appropriate to classify this substance as Acute Inhalation Category 4 according to the CLP Regulation; R20, Harmful via inhalation, according to the DSD.

3.1.1.3 Irritation

The irritancy potential of the Sodium salt of DTPA is linked to the presence of residual hydroxide. The 'pure' Pentasodium DTPA, containing no residual hydroxide would not be irritating to the skin or eyes.

3.1.1.4 Sensitisation

Due to the lack of skin sensitising potential it is unlikely that DTPA or the potassium/sodium salts are respiratory sensitisers (according to Lead registrant). But the lack of results for skin does not necessarily indicate a low potential for respiratory sensitization.

3.1.1.5 Repeated dose toxicity

There are two standard guideline repeated dose toxicity studies available for DTPA. The studies were conducted using either the potassium or sodium salt:
Repeated-dose studies in rats are available for Na5DTPA and K5DTPA (study reports 1987; 2002). Administration of Na5DTPA for 28 days in the drinking water at 12,000 ppm (approx. 1775 mg/kg bw/day) resulted most significantly in body weight reductions and changes in the urinary tract. These effects were minimal at 3000 ppm (approx. 420 mg/kg bw/day). A NOAEL of 600 ppm (approx. 75 mg/kg bw/day) was assigned in this study. Administration of K5DTPA by gavage to rats for 28 days caused mortality at 1330 mg/kg bw/day with other effects reported including 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.

The toxicity observed in repeated-dose oral studies has been attributed to nutrient metal deficiencies, resulting from chelation of critical metal species, most notably calcium and zinc.

Rather than leading to a significantly lower no effect level, lead registrant stated that a longer term study would probably just lead to a greater degree of zinc deficiency thus it would show an increased severity of the effects observed in the shorter study. This assumption is however not confirmed.

The starting point for the calculation of the DNELs (long-term, systemic effect) in the registration dossier from the lead registrant is taken from drinking water study conducted using pentasodium DTPA. In this study the NOEL was 75 mg/kg bw/day.

3.1.1.6 Mutagenicity

Lead registrant suggests that if DTPA is capable of binding zinc, and under some circumstances *in vitro*, this chelation of zinc can limit its availability to dividing cells where it is used as a co-factor for enzymes involved in DNA synthesis. However in the available *in vitro* genotoxicity studies on DTPA acid and the potassium salt there was no evidence of mutagenicity or clastogenicity.
In the EU risk assessment of the similar chelating agent EDTA, EDTA and its sodium salts were considered to have a low mutagenic potential only at extremely high doses and this was related to the pH and the ability to chelate metals rather direct DNA reactivity. However on the basis of the various negative findings and the assumption of a threshold mode-of action

for aneugens, it was concluded that EDTA and its sodium salts are not mutagenic for humans. As such it is argued that DTPA is also not mutagenic for humans based on the structural similarity of these substances.

3.1.1.7 Carcinogenicity

No studies in the REACH registration report for Na5DTPA.
A bioassay performed with Na3EDTA trihydrate in rats and mice and a two year study of CaNa2EDTA in rats, indicated no evidence of carcinogenicity.

3.1.1.8 Toxicity for reproduction

Effects on Fertility
In a developmental toxicity study DTPA caused developmental toxicity via an induced zinc deficiency. Such a mode of action is also known to produce effects on male fertility (testicular toxicity) but only in the presence of other signs of systemic toxicity related to a zinc deficiency. According to the Lead registrant, a multigeneration study performed using DTPA in the diet would likely result in a zinc deficiency in the animals due to chelation of the dietary zinc by DTPA. As such, this type of study would only demonstrate the toxicity associated with a zinc deficiency rather than that of DTPA. Therefore a reproductive toxicity study is considered unjustified by Lead registrant since it would not produce data that cannot already be predicted (data waiving): it is argued that reproductive toxicity secondary to a zinc deficiency would not be relevant for classification.

In a one-generation reproductive study in rats with dose levels (in the diet) of up to 300 mg/kg bw/day, the analogue PDTAH4 produced no apparent effects on mating performance, decreased male and female fertility indices, and gestational and pup survival indices were noted in high dose animals. 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. There were no adverse effects at a lower dose (60 mg/kg bw/day) that did not produce severe zinc deficiency.

Developmental Toxicity
Studies with the calcium and zinc complexes of DTPA are reported. In studies conducted by Fukuda et al. (1982), pregnant females rats were injected subcutaneously daily on gestation days 9-13 with 30, 180, 360, 720 and 1080 µmol/kg body weight of CaDTPA or ZnDTPA, respectively. In the dams, no toxic effects were observed. In the fetuses, the decrease of the survival rate was observed in only the group injected daily with 1080 µmol/kg body weight (CaDTPA). Some cases of gross defects of fetuses: the exencephaly, microphthalmia, anophthalmia and fusion of ribs were observed in the groups injected daily with 360, 720 and 1080 µmol/kg body weight (Ca-DTPA). In studies conducted by Brummett et al. (1977), pregnant rats that were injected on gestation days 2-6 with 5760 µmole ZnDTPA/kg bw/day were similar to controls in terms of embryo and fetal loss, but those receiving 11520 µmole/kg/day had a 6-fold greater percentage of abortions and more than twice the percentage of resorbed fetuses than did controls. Hypersaline-injected animals had about a 6-fold greater percentage of abortions than controls, but neither of the two animals carrying to term had uterine resorption sites. Animals injected on gestation days 7-11 with 5760 µmole ZnDTPA/kg/day were not greatly different from the controls. With the 11520 µmole/kg/day dosage, however, the percentage of aborted litters was almost 3 times that of controls and all of the 25 fetuses (5 litters) were resorbed. The hypersaline group had about twice the percentage of abortions and twice the percentage of resorbed fetuses compared to controls. The group receiving 1440 µmole Ca-DTPA/kg/day had nearly 4 times the percentage of aborted litters and 3 times the percentage of resorption sites than did the control animals. In these same studies, nine females were given 8 daily injections of 5760 µmole ZnDTPA/kg on days 5-12. Five were not pregnant at autopsy and 3 others that were checked early in gestation had evidence of abortion. One gave birth early and ate her pups. None of the fetuses exhibited any gross deformities, externally or skeletally, except for one

fetus from a dam given 1440 µmole CaDTPA/kg/day, which had exencephaly (extrusion of the brain from the skull).

In a guideline study [OECD 414] prenatal developmental toxicity study, treatment of rats (via gavage) with 400 mg/kg Na5DTPA (the maternal NOAEL) during gestation was associated with 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 the high dose of 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). A dose of 100 mg/kg Na5DTPA had no effect on parents or fetuses (study report, 1994). Another study has been conducted with ZnDTPA (6 mice at 360 µmol/kg bw and 6 mice at 2900 µmol/kg bw), CaDTPA (6 mice at 360 µmol/kg bw and 12 mice at 2900 µmol/kg bw) or saline solution (12 mice) to female mice (strain C57BL/Do) via daily subcutaneous injections. These doses are equivalent to 199 or 1600mg ZnDTPA/kg bw and 179 or 1441 mg CaDTPA/kg bw. The dosing period started 4 days after the mating period began and continued throughout pregnancy until the pups reached an age of 13 days. In the group of mice dosed with 2900 µmol/kg bw CaDTPA there were no viable offspring observed. Only one stillborn pup was observed but it appeared grossly normal. In the 360 µmol/kg bw CaDTPA group there were no adverse effects on reproduction or developmental parameters. Both dose levels of ZnDTPA were reported to be 'completely harmless' to the mothers and the pups. Brummett et al. (1977) investigated the teratogenicity of the zinc salt of DTPA in the mouse. Pregnant mice were subcutaneously dosed with ZnDTPA daily either from days 2-6 or 7-11 during gestation. The doses of ZnDTPA used were either 0, 5720 or 11520 µmoles/kg bw; these doses are equivalent to 0, 3163 and 6371 mg/kg bw. Due to the hypertonic nature of the test material an additional group of mice were treated with a solution of sodium chloride (1380 µmole NaCl/ml) at the same ion concentration, osmolality, pH and volume as the high dose ZnDTPA treatment. A CaDTPA dose group (1440 µmole/kg bw = 715 mg/kg bw) dosed daily on days 7-11 was also included in this study. The pregnant mice were euthanized on day 18 of gestation and the fetuses removed and examined for gross malformations, visceral malformations and skeletal malformations. Dosing with ZnDTPA in this study did not result in any malformations of the fetuses although 6371 mg/kg (days 2-6 and 7-11) and 3163 mg/kg (days 7-11) caused an increase in embryo toxicity relative to controls (aborted litters or resorptions). However administration of the hypertonic saline solution also caused an increase in aborted litters and resorbed fetuses relative to control. The only malformed fetus observed was in the CaDTPA group which had exencephaly. Considering the previous studies on CaDTPA it seems likely that had it been dosed in this study from days 2-6 then the malformations observed would have been far more extensive. This seems to suggest that it could take a few days for DTPA to induce a zinc deficiency and that it might last for a few days after dosing has ceased since organogenesis peaks in the mouse between days 7 and 11 of gestation, thus the sensitivity to zinc induced malformations should be greatest during this time period. The above studies appear to demonstrate that CaDTPA is capable of causing fetotoxicity and malformations consistent with zinc deficiency and that the frequency and type of these malformations is dependent on the dosage and dosing period during pregnancy. Conversely ZnDTPA dosed at significantly higher dose levels for equivalent dosing periods does not appear to cause malformations. It does however result in increased fetotoxicity albeit at extremely high dose levels. The explanation given by the investigators as to why there is a difference in teratogenicity between the calcium and zinc salts of DTPA is that the toxicity is due to the chelation of essential metals such as zinc and manganese (consider the data on increased excretion of zinc following DTPA administration) and that the zinc salt of DTPA cannot chelate any additional zinc.

Robust study summary of the key study (study report 1994)
Test group 3 (1,000 mg/kg body weight/day): statistically significantly reduced food consumption during the first half of the treatment period; if calculated for the whole

treatment period (days 6- 15 p .c .) about 7% less food intake than the controls / statistically significantly lower body weights than the controls on days 17 and 20 p.c / statistically significant impairment in body weight gain; if calculated for the total treatment period about 21% less weight gain than the controls / about 12% lower corrected body weight gain than the controls / dark-yellow discoloration of the feces in all females during most days of the treatment period and the first days of the posttreatment phase / statistically significantly lower mean gravid uterus weight (about 21% lower than in the control group) / statistically significant reduction of the mean number of live fetuses/litter (11.9 vs. 14.3 in the control group); slightly increased number of resorptions and insignificantly increased postimplantation loss value / about 8% lower mean fetal body weights in comparison to the control group / statistically significantly increased malformation rate (15.4% affected fetuses/litter vs. 3.5% affected fetuses/litter in the control group), predominantly caused by an increased occurrence of skeletal malformations / statistically significantly increased rate of fetuses with skeletal variations (78.4% affected fetuses/litter vs. 49.6% affected fetuses/litter in the control group) and retardations (78.0% affected fetuses/litter vs. 47.4% affected fetuses/litter in the control group).
Test qroup 2 (400 mg/kg body weight/day): statistically significantly increased rate of fetuses with skeletal retardations (63.8% affected fetuses/litter vs. 47.4% affected fetuses/litter in the control group).
Test group 1 (100 mg/kg body weight/day): no substance-related effects on dams, gestational parameters or fetuses.

Interpretation and conclusion:

At the highest dose:
- The maternal weight loss is partly explained by developmental effects (resorptions). Maternal effects are moderate: decrease of body weight gain corrected 12% (corresponding to a probably minor corrected drop body weight). The decreased food consumption in early stage of administration is consistent with the irritant effects observed by gavage in other studies, indicating a low maternal toxicity.
- Clear effects on induction of malformations and fetal mortality. Effect on fetal weight (- 8%) in possible association with decreased maternal food consumption is less clear.
- This is consistent with results of a rat feeding study 28d (study report 1987 cited in the CLH report from Industry): only reduced food consumption for few males at 333 mg/kg (mortality at the highest dose of 1330 mg/kg).
- Developmental effects cannot be considered secondary to non-specific maternal toxicity. The increased sensitivity of the fetus compared to the adult may be explained by an increased need for the development.

At the median dose:
- No maternal toxicity is observed.
- Effects on delayed ossification (skeletal retardation) without effect on fetal weight: specific effect on skeletal development.
- This confirms that developmental effects are not secondary to a non-specific maternal toxicity.

The NOAEL of 100 mg/kg seems adequate according to the key study (study report 1994).

Maternal toxicity is low and cannot explain the developmental effects of non-specific effects. Concerning the mode of action, developmental effects are likely secondary to Zinc deficiency (and / or Calcium salts, or other minerals). DTPA complexes with essential metals such as Zinc in the gut: these essential metals become not bio-available. This deprivation of essential nutrients may lead to toxic effects such as developmental toxicity due to the importance of zinc in the healthy development of a growing fetus. There is no clear evidence that the developmental effects are secondary to Zinc deficiency (or Calcium), but this hypothesis is plausible considering that ZnDTPA has no effect and fractionated exposures have less effect.

Industry argues in its CLH Proposal (see section 4.3.2) that such effects due to essential nutrients deprivation are observed only at high doses in unrealistic exposure situations. That's why the classification Repr. 2 according to CLP Regulation is considered appropriate by Industry. However exposure-based arguments should not be considered for CLH purposes. Furthermore dietary intakes vary depending on the diet (vegetarian or not) and needs are more important for pregnant women. Zn-deficiency may also be exacerbated in conjunction with absorption defects in many diseases (e.g. celiac disease, diabetes).

Considering these different elements, a classification Repr. 1B (Presumed human reproductive toxicant) may be supported, according to CLP Regulation, even if affinity of each salt of DTPA for different minerals can vary (for instance, results are less clear with ZnDTPA that already chelate zinc).

3.1.2 DNELs derivation

The Tables below summarize the DNELs derived by the Lead Registrant for Na5DTPA (more details in **annex 1**):

Table 3: DNELs developed by Lead registrant of Na5DTPA for workers

DNELs workers	Value	Key effect
Acute - local effects (inhalation)	2.5 mg/m³	irritation (respiratory tract)
Long-term - systemic effects (dermal)	11718 mg/kg bw/day	repeated dose toxicity
Long-term - systemic effects (inhalation, aerosol - nebulized)	4.1 mg/m³	repeated dose toxicity
Long-term - systemic effects (inhalation, aerosol - dust)	5.7 mg/m³	repeated dose toxicity

Table 4: DNELs developed by Lead registrant of Na5DTPA for the general population

DNELs for the general population	Value	Key effect
Acute - local effects (inhalation)	2.5 mg/m³	irritation (respiratory tract)
Long-term - systemic effects (dermal)	5859 mg/kg bw/day	repeated dose toxicity
Long-term - systemic effects (inhalation)	1 mg/m³	repeated dose toxicity
Long-term - systemic effects (oral)	1.2 mg/kg bw/day	repeated dose toxicity

3.2 E-fate and ecotoxicity

Both pentasodium or the free acid form of Diethylenetriaminepentaacetic acid (DTPA or H_5DTPA) have low octanol-water partition coefficient (LogKow < 3) and are water soluble (solubility > 3500 mg/L). They have a low potential for adsorption to soil or sediments and a low potential of bioaccumulation. H_5DTPA and Na_5DTPA are hydrolytically stable in water. They have negligible volatility and therefore cannot enter the atmosphere in significant

amounts. H_5DTPA and Na_5DTPA are **not readily biodegradable** in the environment. Considering the environmental properties and uses of H_5DTPA and Na_5DTPA, the main receiving compartment is the hydrosphere. When released to water, they will tend to remain in the water compartment.

Several acute and chronic aquatic toxicity studies with either the pentasodium salt or the free acid form of DTPA were conducted with fish, invertebrates, and algal species. According to the results from these acute and long-term studies, the lowest aquatic toxicity values for Na_5DTPA and H_5DTPA are the NOEC of 64 mg/L and 50 mg/L respectively, based on *Daphnia carinata* reproduction. Based on the available data, an AF of 10 could be applied to derive the respective $PNEC_{surface\ water}$ of 6.4 mg/L and 5 mg/L which were used for the aquatic risk assessment in the CSR. No data on sediment and terrestrial organisms are available and the risks for these two compartments were based in the CSR on the aquatic data. However as the log Kow value is well below 3, the derivation of the $PNEC_{sed}$ and the $PNEC_{soil}$ was not possible. Na_5DTPA and H_5DTPA are not toxic to microorganisms ($PNEC_{stp}$ = 50 mg/L). These values are in the same range of those observed for EDTA, a structurally and chemically similar chelant (RAR, 2004).

A general important feature of complexing agents is that the toxic effects on aquatic organisms are **not directly due to the inherent toxicity of the chelant molecule**, but are most often related to metal deficiencies caused by complexation of essential metals in the test media. For instance, studies revealed that the observed reproductive toxicity in *Daphnia carinata* was mainly caused by complexation of manganese, zinc, and iron (van Dam et al., 1998; van Dam et al., 1999). Also, iron deficiency can lead to toxicity in algae. Thus, in toxicity studies with algae, fish and invertebrates, the observed toxicity of Na_5DTPA will likely reflect the limitation of essential metals in the test media. The OECD 23 guidance (Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures) recommends that, when testing chelants, compensatory adjustment to water quality parameters or the testing of an appropriate salt of the test substance help achieve a valid test result (OECD, 2000). However, the deficit compensation in the concentration of essential ions is rarely mentioned in the available assessment reports for EDTA and DTPA (CSR, RAR 2004, SIAR 2012). Nevertheless, it was demonstrated that it is not the absolute EDTA concentration, but rather the ratio of the EDTA concentration to the metal cations which 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. 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 thus there is no uncomplexed EDTA (RAR, 2004). This conclusion could be applied for Na_5DTPA and H_5DTPA based on their structural and chemical similarities (RAR 2004, SIAR 2012).

The extent of complexation depends on some environmental conditions (RAR, 2004). The studies performed with various chelating agents shown that **water hardness** can greatly affect their level of toxicity. The toxicity of sodium salts and the free acid form of DTPA decreases as water hardness increases: most of the chelators were converted to the Ca-complex, thus less uncomplexed chelants are available to exert a toxic effect through complexation (Schmidt and Brauch, 2004). The form under which the complexing agent is present has a significant impact on the level of toxicity which depends on the type of cations presents and not on the type of chelants. For example, ferric-chelants complexes are very strong and they will affect cation balance only at high concentrations, higher than Na_5DTPA. In addition to the **chelant stability**, **the amounts of chelant-complexes relative to free metals** will influence the metal ion exchange reactions occurring in the aquatic media, and indirectly the level of toxicity to organisms. In un-buffered systems, the addition of the free acid form of DTPA can make the **pH** more acidic, while the addition of the pentasodium salt of DTPA can make the pH more alkaline. The extreme pH variations affect the aquatic biota and can also modify the interactions between chelants and free ions, their speciations and indirectly their toxicity. For the interpretation of toxicity tests, the **complex formation properties** of chelants have to be taken into account (Nowack, 2005).

Even though chelants, in particular Na_5DTPA and H_5DTPA, are not expected to cause direct ecotoxicological effects at the levels typically found in natural waters, their widespread use has raised concern about their ultimate fate in the environment (Sillanpää, 2009). Their complex formation capacity may affect the **distribution and mobilization of heavy metals**. Additionally the nitrogen contained in the molecule may contribute to the **eutrophication** of natural water bodies (Schmidt and Brauch, 2004).

3.3 Classification and labelling

3.3.1 Harmonised Classification in Annex VI of the CLP

There is no harmonized classification for these substances.

3.3.2 Self classification

The classification and labelling inventory presents the following self-classification (> 400 notifiers for Na5DTPA, > 200 notifiers for DTPA Acid):

Repr.2 - H361: Suspected of damaging fertility or the unborn child; Acute Tox.4 - H332: Harmful if inhaled; Eye Irrit.2 - H319: Causes serious eye irritation.

Some notifiers add the following classifications:
Skin irritation – H315;
Aquatic Chronic 2 – H411.

An annex VI proposal for harmonized Classification and Labelling has been prepared by Industry as an annex of the Chemical Safety Report (CSR)[5]. This Proposal covers DTPA Acid, Na5DTPA and K5DTPA. Pentapotassium DTPA (K5DTPA) is not registered (but pre-registered). Reprotoxicity is the only endpoint covered in this Proposal.

In 2010, this CLH proposal for DTPA was presented to and reviewed by the German "Committee on Hazardous Substances (Working group III: Hazard risk assessment) (AGS, UA III)", an expert panel with members from authorities, stakeholders and industry. The panel's decisions rather have recommendation value for the actual German CA for CLH processes. As CLP article 37(2) foresees the possibility for industry to submit CLH proposals on their own, it was decided that this would be the preferable course of action for an industry dossier. However, according to the Registry of Intention, industry has not submitted this proposal for a harmonized classification to ECHA.

3.4 PBT Assessment

Na5DTPA and DTPA Acid are not biodegradable. In standard biodegradation screening tests, including several ready biodegradation tests, no detectable biodegradation of DTPA was observed (Douglas, 1987a; Hinck et al., 1997; Pitter et al., 2001; Pitter et al., 2001; Kettunen-Knuutila et al., 2004; Metsarinne et al., 2004; Allard et al., 1996; Sykora et al., 2001a). In several studies, increasing the sludge age or increasing the pH of the test system resulted in some degradation of the DTPA. Since it does not readily biodegrade, Na5DTPA and DTPA Acid are assumed to meet the criteria for persistence (P).

[5] Annex VI Proposal for Harmonized Classification and Labelling for DTPA Acid (CAS No 67-43-6), Pentasodium DTPA (CAS No 140-01-2) and Pentapotassium DTPA (CAS 7216-95-7). Annexed to Na5DTPA Chemical Safety report. 18 September 2009.

Na5DTPA and DTPA Acid have a low potential to bioaccumulate because of their low log Pow and are relatively high water soluble. REACH guidance states that test substances with log Pow values ≤ 4.5 are not B and not vB. Therefore, DTPA Acid is not expected to be bioaccumulative (B).

Based on a 28-day exposure with the crimson spotted rainbow fish, the NOEC for DTPA (free acid) was 100 mg/L based on a lack of effects on reproduction (van Dam et al., 1999). In an 18-day exposure with D. carinata, the NOEC (reproduction) for DTPA (free acid) was determined to be 50 mg/L via stoichiometric conversion from Fe(III)-DTPA (van Dam et al., 1996). Due to the similarity in chemical structure, mechanism of action, and the reported aquatic toxicity of H4EDTA and DTPA, it is assumed that both the NOEC and LC50 for algal toxicity would be in the range of 310 mg/L Na5DTPA and H5DTPA, similar to that of H4EDTA (Dufkova, 1984). Overall, the chronic values for aquatic organisms were ≥50 mg/L for Na5DTPA and DTPA Acid, indicating that the classification criteria (T) is not met with regard to aquatic organisms.

4 INFORMATION ON USES

4.1 Registration status

Table 5: Registrations for Na5DTPA

	Registrations	
Type	Full Art. 10	Intermediate Art. 17 or 18
Total number	6	1
Tonnage band	10,000 - 100,000 tonnes per annum	

Table 6: Registrations for DTPA Acid

	Registrations	
Type	Full Art. 10	Intermediate Art. 17 or 18
Total number	3	1
Tonnage band	1,000 - 10,000 tonnes per annum	

4.2 Overview of uses

Aminocarboxylic chelating agents are used as components or process chemicals in a wide variety of applications, but five uses (pulp & paper, cleaning, chemical processing, agriculture and water treatment) account for about 80% of worldwide consumption:

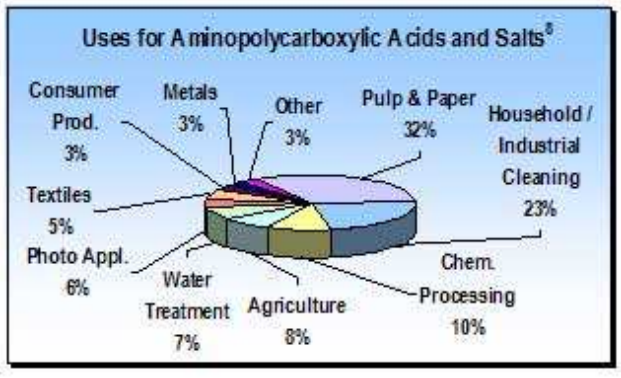


Figure 1: Uses for aminocarboxylic acids and salts[6]

Na5DTPA is widely used as a chelating agent in pulp and paper, cleaning detergents industrial and professional applications. Minor industrial applications cover use as process chemical (polymerization), intermediate (micronutrient production) and oil field applications. Consumer uses comprise a wide spectrum of applications, e.g. in washing and cleaning products, personal care products, food and beverage, water treatment-hardness control, textiles and pharmaceuticals, in which small amount of Na5DTPA is used to control the undesired metal ions. According to the registrant, DTPA concentration in consumer products is low (< 2% consumer cleaning products and <0.1% in personal care products).

[6] Source: Chemical Economics Handbook Product Review Chelating Agents, SRI International, October 2003, pages 5-6, and 16-17.

The following different uses are listed by the registrants of Na5DTPA:

Industrial / professional uses:

- Industrial use in pulp bleaching and washing (in a mixture)
- Industrial use in cleaning products (in a mixture)
- Professional use in cleaning products (substance itself and in a mixture)
- Industrial use in production gypsum board (in a mixture)
- Use as a process chemical
- Use as an intermediate
- Industrial use in oil/gas field drilling and production operations

Consumer uses:

- Consumer adhesives and sealants
- Consumer air care products
- Consumer artists supply and hobby preparations (sub category of painting)
- Consumer biocidal products
- Consumer coatings and paints, fillers, putties, thinners
- Consumer building and construction preparations not covered elsewhere
- Consumer metal treatment products, including galvanic and electroplating products
- Consumer non metal surface treatment products
- Consumer product such as pH regulators, flocculants, precipitations, neutralization agents, other unspecifics
- Consumer leather tanning, dye, finishing, impregnation and care products
- Consumer polishes and wax blends
- Consumer textile dyes, finishing and impregnating products
- Consumer washing and cleaning products

4.3 Exposure information

The most likely route of human exposure (workers and consumers) to Na5DTPA is through inhalation or dermal contact.
According to the registrant, exposures of DTPA to the general public are low. The product is only used in "trace" amounts in final products (< 2% consumer cleaning products and <0.1% in personal care products), is poorly absorbed dermally, and does not volatilize. Thus consumer exposure, whilst it occurs, would be expected to be significantly lower than workers involved in manufacturing and formulating DTPA.

Worker exposure can occur in manufacturing facilities or the industrial facilities where the substance is used as a process chemical and in formulation activities. Since these types of activities are mainly undertaken in closed systems and since Na5DTPA is mainly produced and used in liquid solutions, exposure is fairly low.
Somewhat higher worker exposures are likely in industrial or professional applications of end products, where the product is used in powder form or where there is some likelihood of aerosol generation (e.g. formulation of products, cleaning applications).

The most likely route of emission of Na5DTPA in the environment is to the water compartment, e.g. in the paper and pulp applications. The use of onsite technologies allows reducing the release to water from industrial sites. Na5DTPA emitted to the environment to water and soil will partition predominately to the water.

More information on exposure estimation of Na5DTPA is given in **annex 2**.

4.4 Risks presented for human health

Risk characterization ratios (RCR) calculated in the CSR of the lead registrant of Na5DTPA are below 1 (long term and acute exposure), for all exposure scenarios. The Table in Annex 3 summarizes main calculated RCR for DTPA (occupational exposure):

For a similar substance with similar uses, EDTA, Germany concluded in its RAR that there is at present (in 2004) no need for further information and/or testing and for risk reduction measures beyond those which are being applied already. This conclusion is consistent with the CSA of the Lead registrant of Na5DTPA.
Consequently, based on the CSR review for Na5DTPA and the comparison with EDTA RAR conclusions, **the risks for workers appear to be adequately controlled**.

Using a conservative approach, the RCR values for consumers exposed by all routes (dermal, oral and inhalation) are estimated less than 0.1 by the Lead registrant of Na5DTPA. As for workers, Germany concluded in its RAR for EDTA that there is at present (in 2004) no need for further information and/or testing and for risk reduction measures beyond those which are being applied already.

DTPA are regularly detected in drinking water along the Ruhr in Germany. During 2007 and 2008, about 50 % of the values measured were below the limit of detection. During the monitoring period 2001-2008, the maximum value measured in the Rhine at the German-Dutch border (Lobith) amounted to 18 µg/L. In the R. Main at Bischofsheim, DTPA was measured in all samples, the maximum value during 2007 to 2008 amounted to 13 µg/L, in the R. Ruhr the maximum concentration amounted to 21.6 µg/L (ICPR 2012).
Values are however much less than the DNEL derived for general population (1.2 mg/kg bw/day[7]).

4.5 Risks for the Environment

The environmental risk assessments presented in both CSR (Na_5DTPA and DTPA Acid) lead to risk characterization ratios (RCR) relatively high, in particular the RCR values for the manufacture of Na_5DTPA, its formulation, its industrial uses in pulp bleaching and washing (paper industry), and its use as a process chemical and as an intermediate, where RCR are close to 1 for the aquatic compartment (STP, surface water and sediment). These high ratios could be due to the relative high tonnage applied to estimate emissions. The registrants indicate, without any explanation, that the use of onsite technologies allows reducing the release to water from industrial sites to acceptable level. For example, recycled water and high biodegradation rates have been considered in the exposure scenario for industrial use and pulp bleaching/washing, but none of these risk mitigation measures (RMM) have been clearly justified in the CSR.

The risk characterization of EDTA in the RAR (2004) led to a risk for the aquatic organisms when high releases were foreseen (uses in industrial detergents, in paper mills, in circuit board production and during recovery of EDTA containing wastes). Based on tests and monitoring data showing that EDTA can be biologically degraded, those risks have been considered in the RAR as acceptable if a number of specific conditions were present such as specific conditions of wastewater treatment in the STP (relatively high hydraulic and sludge retention time, an alkaline pH value of the wastewater, a relatively high EDTA concentration, and EDTA is not complexed with heavy metal ions). The assessment report concluded that: ”there is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account”.

[7] For an adult of 60 kg drinking 2 L/day of water, it corresponds to 36 mg/L.

DTPA has been measured in the aquatic compartment. Some monitoring data in Germany reveals that due to the wide field of their application, their high polarity and low degradability, aminopolycarboxylic acids such DTPA reached the aquatic environment at considerable concentrations and have also been detected in drinking water (Schmidt et al, 2004). DTPA concentrations found in sewage effluents of paper and pulp mills are between 2 and 2880 µg/L, while maximum concentrations reported for rivers are up to 72 µg/L (Knepper, 2003).
In the review on chelating agents and compounds exhibiting complexing properties in the aquatic environment (Knepper, 2003), It is recommended that the entry of chelating and metal-binding agents into the water phase should be minimized by applying various measures. All industrial processes and productions dealing with poorly degradable chelating agents and compounds that bind metal ions should be used as little as possible, and their emission into the aquatic environment should be as low as possible. Wherever possible, substitution with compounds exhibiting better degradability should also be sought (Kneeper 2003). The replacement of these persistent compounds by biodegradable alternatives has been the object of study in the last three decades (Sillanpää, 2009; Pinto in press).
The occurrence of complexing agents in the Swedish environment has been studied in a screening investigation by Swedish EPA (Sternbeck and Österas, 2012). DTPA was mainly detected in lake Vättern, where six samples were taken close to a paper mill and shown concentrations of DTPA in the range of 0.6 – 3.9 µg/L. this report also mentions that background concentration in Vättern was in the range 0,43-0,66 µg/l. In 1998, the average DTPA concentration in lake Vättern was ca 0,2 µg/l, with a maximum of 0,6 µg/l close to the paper mill (Remberger, 2001).

5 ALTERNATIVES

"Traditional chelating agents"
Two groups of chelating agents are commonly used:

- Aminopolycarboxylates: Nitrilotriacetic acid (NTA), EDTA, DTPA.
- Polyphosphonates: besides DTPPH (diethylenetriaminepenta(methylenephosphonic acid)) and NTMP (nitrilotris(methylenephosphonic acid)), HEDP (1-hydroxyethane-1,1-diphosphonic acid) is the most important in this group. HEDP is widely used in a broad variety of applications, among others, as ingredients of detergents. Bonding Ca(II) ions, which deactivate the surfactants improves their cleaning process. Its ability to prevent precipitation of calcium salts (called the threshold effect) finds also wide application in water treatment for scale inhibition in circulating cool water system, oil field and low-pressure boilers in such fields as electric power, chemical industry, metallurgy, fertilizer production, etc.

Chelating agents of a new generation[8]
New developed ligands to be used in practice should form strong complexes with the minimal content of nitrogen. The following biodegradable ligands of a new generation contain a basic nitrogen atom or two atoms (in the case of EDDS) with an electron pair capable of interacting with metal ions and acidic carboxylic groups capable of coordinating metal ions through the oxygen:

- IDS (N-(1,2-dicarboxyethyl)-D,L-aspartic acid also known as *iminodisuccinic acid*) [CAS No 131669-35-7],
- DS (polyaspartic acid) [CAS No 181828-06-8],
- EDDS (ethylenediamine-N,N'-disuccinic acid) [CAS No 20846-91-7],
- GLDA (N,Nbis(carboxymethyl)glutamic acid) [CAS No 51981-21-6] and
- MGDA (methylglycinediacetic acid) [CAS No 164462-16-2].

[8] Sources: Chelators for Heavy Metal Ions Removal from Different Waste Waters (Kołodyńska D. 2014). And BREF Production of Pulp, Paper and Board, Final Draft July 2013. Industrial use in pulp bleaching and washing.

According to the author, all of these "new" chelating agents are readily biodegradable, although in the case of IDS or EDDS, the biodegradability depends significantly on the isomeric form of the compound.

Some new complexing agents reach biodegradation levels above 70 or 80% according to the biodegradation test standard EN ISO 7827. Some chemical suppliers report that biodegradable chelant systems have been developed that match the performance of the 'classical' chelants in the chemical pulping processes. For example, IDS is a readily biodegradable chelating agent. The biodegradability of N-bis-dicarboxyethoxy-ethyl aspartic acid (AES) is reported to be 20 – 70%, depending on the used sludge: this novel complexing agent is therefore considered not readily biodegradable but showing slight biodegradation (Metsärinne S. 2007).
The following substances were positively tested, i.e. meet 80% biodegradability, by Holzforschung Austria: EDDS, IDS, AES (not consistent with the conclusions of Metsärinne S. 2007) and sodium gluconate.

With regard to functionality (chelatant), these substances nearly meet the performance of EDTA/DTPA, but in some cases not completely:

Table 7: summary of alternatives identified in the literature

Substance identification	Registration status	Other information
EDDS (N,N'-ethylene-diamin-disuccinic acid, CAS No 20846-91-7)	registered substance (individual submission, 100-1,000 t/y)	no self-classified, readily biodegradable according to the registrant (read-across)
IDS (Iminodi-succinic acid, CAS No 131669-35-7):	not registered in REACH	/
AES (N-bis-dicarboxyethoxyethyl N-hydroxyethyl aspartic acid, CAS No 205699-22-5)	not registered in REACH	/
Sodium gluconate (CAS No 527-07-1)	pre-registered in REACH	no self-classified; large amounts are needed; cannot be used exclusively
GLDA (N,Nbis(carboxymethyl)glutamic acid, CAS No 51981-21-6)	registered substance (1,000-10,000 t/y)	no self-classified (few notifiers: skin & eye irrit. 2), readily biodegradable in an OECD 301D study according to the registrant
MGDA (methylglycinediacetic acid, CAS No 164462-16-2)	registered substance (Na3MGDA, individual submission, 1,000-10,000 t/y)	no self-classified, readily biodegradable according to the registrant
DS (polyaspartic acid, CAS No 181828-06-8)	not registered in REACH	/

Little/no information is available regarding these alternatives, to assess their toxicity and ecotoxicity. However, for 3 substances registered, the registrants state that the substances are readily biodegradable in water (source: ECHA dissemination website).

Distinguishing between the major pulp grades, some operational experience regarding reduced emissions of aminopolycarboxylates chelating agents are summarized below[9]:

Sulphite pulping

[9] Source: BREF Production of Pulp, Paper and Board, Final Draft July 2013. Industrial use in pulp bleaching and washing

The effectiveness of the substitutes for EDTA or DTPA seems to depend on a number of factors such as the type of pulping and bleaching, the wood species used and their metal content, the alkaline earth and heavy metal content (impurities) of the bleaching base (e.g. make-up MgO for sulphite pulp mills) and the final objectives for brightness or dirt spots.
One German pulp mill uses a mixture of DTPA and DTMPA, a phosphonate that is heavily biodegradable and more adsorbable at the biosludge. As DTMPA accumulates on the biomass of the waste water treatment plant, it can be eliminated from the waste water and less chelating agents are released to the water body.

Groundwood
Several mill trials from Holzforschung Austria in oxidative bleaching of groundwood pulp have clearly shown that an elimination of DTPA leads to a brightness drop of 5 – 6 points in ISO brightness. Trials with the substitution of DTPA for some chemicals (sold by the suppliers as biodegradable) have shown that a reduction (e.g. from 0.3 to 0.05 %) of DTPA is possible though with brightness losses from 1 – 2 points. Phosphonate-based substitutes showed results similar to DTPA in some cases. If the alternative contains phosphonates, it may create operational problems in the clarification plant. Some mills have not observed these problems while applying phosphonates as eliminable alternative chelating agent achieving complexing properties close to DTPA. A pulp and paper mill in Germany has reduced considerably the amount of DTPA used in its groundwood line from 2 kg DTPA/t down to 0.4 kg DTPA/tonne of pulp.

The stepwise approach for reducing the emissions from the use of chelating agents is applicable to new and existing mills. Depending on the substitutes used, minor or more significant process adjustments may be required to guarantee the performance of the complexing agents. For example some adjustment to the process usually in terms of altering the pH or dosing point of chelant has been found to be necessary to optimise the process for the new blend.

Often the biodegradable alternatives to EDTA/DTPA are highly specific, i.e. different chelating agents have to be used for different pulping and bleaching processes. There is no 'one for all chelating agent' like EDTA/DTPA. Before application, there is a need for process adjustments and for the identification of the best fitting bleaching additive substances.

6 JUSTIFICATION FOR THE RISK MANAGEMENT OPTION

6.1 Need for (further) risk management

Table 8: SVHC Roadmap 2020 criteria

	Yes	No
a) Art 57 criteria fulfilled?		✓
b) Registrations in accordance with Article 10?	✓	
c) Registrations include uses within scope of authorisation?	✓	
d) Known uses not already regulated by specific EU legislation that provides a pressure for substitution?	(✓)	

DTPA has a high production volume (10,000 – 100,000 tonnes) and is wide-dispersive (numerous consumer uses). DTPA is potentially used in a wide number of industries including pulp and paper industries (main use), laundry detergents, cleaners, soaps, and textiles. This substance may be present in final products (< 2% in consumer cleaning products and < 0.1% in personal care products). Important uses (according to their tonnage) are regulated by specific EU legislation that provide a similar level of pressure for substitution as

authorisation (e.g for pulp and paper industry, see section "2.3 Regulatory context"). However many other uses, including consumer products, are not covered.

The members of the *amino carboxylic acid-based chelants category (including Na5DTPA)* possess hazard properties for human health (skin and eye irritation, repeated-dose toxicity and reproductive/developmental toxicity)[10]. These effects are associated with the chelation of metals and the subsequent toxicological effects related to metal deficiency.

Furthermore, the *amino carboxylic acid-based chelants category (including Na5DTPA)* members possess properties indicating a hazard to the environment.

Finally, the RAR performed by Germany have identified a need for limiting the risks to Environment for EDTA, another aminocarboxylic acid-based chelant[11] with similar uses.

6.2 Identification and assessment of risk management options

A – Do nothing in the framework of REACH

Directive 2008/1/EC concerning integrated pollution prevention and control (IED)

The BREF "Production of Pulp, Paper and Board, Final Draft July 2013" gives information regarding permitting and monitoring of DTPA in this activity sector: in particular some national regulations and regional competent authorities ask pulp mills within the area of their responsibility to reduce emissions of EDTA or DTPA to the receiving waters (e.g. in Austria or Germany), assessing the availability of substitutes case by case. If recipient rivers or lakes are used to provide drinking water, environmental officials set increasingly strict limits on permissible EDTA and DTPA concentrations.
The BREF for the "Textiles Industry, European Commission, July 2003" stated that complexing agents can often be avoided. Nevertheless, when they need to be used, compounds are available as an alternative: readily biodegradable or at least bioeliminable and that do not contain N or P in their molecule (e.g. polycarbonates, polyacrylates, gluconates, citrates and some sugar-acrylic acid copolymers). Costs are comparable, although higher quantities may be necessary in some cases.
OSPAR Convention for the protection of the marine environment of the North-East Atlantic recommends also that the waste water at the sites of occurrence must not contain EDTA, DTPA and phosphonates[12].

Regulation 1980/2000/EC on a revised Community eco-label award scheme

The objective of the Community eco-label award scheme is to promote products which have the potential to reduce negative environmental impacts.
EDTA and its salts shall not be included in the product, either as part of the formulation or as part of any mixture included in the formulation, according to criterion 3 of EU Ecolabel described in Commission Decision of 28 June 2011 on establishing the ecological criteria for the award of the EU Ecolabel to all-purpose cleaners and sanitary cleaners.

DTPA and its salts could be included in the criteria of the Ecolabel considering a similar hazard profile for the environment.

Directive 2000/60/EC establishing a framework for Community action in the field of water policy Water Framework Directive

[10] SIDS Initial Assessment Profile (COCAM 3, 16-18 October 2012).

[11] European Union Risk Assessment Report, Final Report 2004, Germany.

[12] PARCOM Recommendation 94/5 Concerning Best Available Techniques and Best Environmental Practice for Wet Processes in the Textile Processing Industry.

With regard to pollution prevention and control, Community water policy should be based on a combined approach using control of pollution at source through the setting of emission limit values and of environmental quality standards.

EQS (Environmental Quality Standard) have been developed for EDTA (INERIS, 2012):
- EQS surface water = 40 µg/L (maximum value = 78 µg/L);
- EQS marine water = 7.4 µg/L (maximum value = 7.8 µg/L).

In the same line, an EQS for DTPA with specific data on this substance could also be proposed as an EU threshold values to control the aquatic emissions of DTPA.

B - Classification & Labelling / SVHC identification

Considering toxicological data, a classification Repr. 1B may be supported according to CLP Regulation, with the following hazard statement:
H360D - May damage the unborn child

Such harmonized classification (Repr. 1B) has a direct impact in different regulations:
- On the health protection of workers from the risks related to exposure to CMR categories 1A and 1B, at least in France (the directive 2004/37/EC on the protection of workers from the risks related to exposure to carcinogens or mutagens at work does not consider reprotoxicity, on the contrary of the French worker legislation). Substitution and, if not technically feasible, collective protection measures are preferred to avoid/reduce occupational exposure. The Member States shall also establish arrangements for carrying out relevant health surveillance of workers.
- On the health protection of consumers: reduction of the concentration of DTPA in consumer products (concentration limit of 0.3 % according to CLP Regulation instead of e.g. < 2% in consumer cleaning products as mentioned in the registration report).
- Other restrictions in specific regulations, such as the Toy Safety Directive (2009/48/EC): CMR substances are no longer allowed in accessible parts of toys.

This classification could also lead to identify this substance as a substance of very high concern (SVHC), with a possibility to include it in Annex XIV according to Art. 57(c) of REACH Regulation.

C – REACH restriction

A restriction of DTPA and its salts, as permitted by REACH Regulation, could:
- restrict all uses of these substances;
- restrict only specific uses (e.g. leading to the most emissions into Environment).

The proportionality of these options has not been assessed in this RMOA. A restriction of all uses would however lead to high economic consequences due to the number of activity sectors concerned.

Option	Risk reduction (effectiveness)	Costs-effectiveness (proportionality)	Clarity of the obligations (practicality)	Regulatory consistency
Do nothing in REACH: application of directive 2008/1/EC (IED directive) and other sectoral regulations	Conform to risk reduction strategy adopted for the environment for EDTA. Focus on reducing existing emissions into environment (no action on upstream supply). Not effective for workers risk reduction.	Measures implemented at a national level: potential for inconstancies between Member States. Costs induced by monitoring (enforcement).	IED covers some but not all user sites: only large installations are affected.	Level of emission reduction achieved will depend on enforcement provided by each Member State.
Classification & Labelling / SVHC identification	Effective – indirectly - for workers risk reduction (more important hygiene measures for CMR 1A/. B substances). Information for women on developmental toxicity through labeling.	Annex VI dossier has already been prepared by Industry. It should be encouraged to submit it to ECHA.	Clear. SVHC identification leads to an information of consumers: Any supplier of an article containing a SVHC on the 'Candidate List' in a concentration above 0.1 % (w/w) has the duty to provide the recipient of the article with sufficient information to allow safe use of the article.	Harmonized classification within EU. SVHC identification / annex XIV inclusion lead to the same management measure within EU.
Restriction of all uses	Effective.	Very high production volume with expected high economic consequences. Alternatives for certain uses but not always technically feasible.	Clear.	Good.
Targeted restriction	Effective for Environment, if the most emitting uses are concerned (e.g. .for production of Pulp, Paper and Board).	Potentially moderate economic consequences: depending on the substitutes used, minor or	Clear.	Good.

RMOA DTPA salts.

Option	Risk reduction (effectiveness)	Costs-effectiveness (proportionality)	Clarity of the obligations (practicality)	Regulatory consistency
		more significant process adjustments may be required to guarantee the performance of the complexing agents.		

7 CONCLUSIONS ON THE MOST APPROPRIATE (COMBINATION OF) RISK MANAGEMENT OPTION(S)

For Human Health, based on the ability of the body to compensate for changes in zinc status and the minimal amount of zinc that could be affected by DTPA, it is unlikely that exposure to DTPA in the workplace will affect an individual's zinc status leading to adverse effects. The physicochemical properties of the substance (low vapour pressure, poor dermal absorption) and the results of the chemical safety assessment of Na5DTPA are consistent with this assumption.
Using a conservative approach, the use of consumer products give low RCR values according to the Lead registrant of Na5DTPA. The RCR values for the combined routes (oral, inhalation and skin contact) are low.
However, DTPA serves as chelating agent in a wide variety of consumer products and is considered persistent in the environment. The cumulative exposure (including drinking water, food, etc.) of the general population has not been calculated.

Even though Na5DTPA and DTPA Acid are not expected to cause direct ecotoxicological effects at the levels typically found in natural waters, but rather exert their influence by affecting mineral (metal ion) balance in aqueous or biological systems, their widespread use has raised concern about their ultimate fate in the environment. Their complex formation properties depending on environmental conditions - as pH, water hardness, metal concentrations - may affect the distribution and mobilization of heavy metals. Additionally, due to their persistency or slow transformation in the environment and their implication in eutrophication of natural water systems, chelants are a cause of concern and several research works on their replacement by chelating agents with improved biodegradability are currently under investigation.

Na5DTPA and DTPA Acid are widely used as chelating agents by industrials, professionals and consumers. As presented by the registrant in the CSR, the environmental risk assessment for DTPA Acid lead to acceptable risks for all emissions scenarios. For Na5DTPA, even if acceptable, the levels of environmental risk associated to the production, to the formulation, to the industrial uses of DTPA in pulp bleaching and washing, and to the use as a process chemical and as an intermediate are closed to the acceptability threshold of 1, particularly for the aquatic compartment. Several risk management measures, enhancing the biodegradation rate for example, have been used in the exposure scenarios but without any data or any description of their onsite technologies allowing such a reduction of emissions.

Consequently, and as it was previously applied for EDTA, there is a need for limiting the emissions considering the tonnage of Na5DTPA and DTPA Acid, their wide dispersive uses and their high persistency in the environment. **Risk reduction measures which are already applied for other chelant - EDTA could be taken into account**, even if it is already the case for some uses (e.g. in the framework of IED directive). The Commission Recommendation on risk measures for substances such as EDTA [COM Recommendation No 2006/283/EC] proposes in its Section 3 a number of measures for the reduction in EDTA emissions that are also applicable to other poorly biodegradable chelants as DTPA. Among these recommendations, the establishment of Environmental Quality Standards and national pollution reduction measures are foreseen. An EQS for DTPA could also be proposed as an EU threshold values to control the aquatic emissions of DTPA.

Finally, toxicological data seems sufficient to support **a classification Repr. 1B (H360D - May damage the unborn child)** according to CLP Regulation No1272/2008/EC: this would lead to a better information of pregnant women and a reduction of the concentration of DTPA in consumer products.

References

Most of references are extracted from Annex VI Proposal for CLH and from the CSR of the Lead registrant of Na5DTPA. For more details, check the bibliography provided in these reports (confidential study reports are not cited here).

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CONFIDENTIAL ANNEXES

Annex 1: DNEL derivation

DNELs developed by Lead registrant of Na5DTPA for workers

DNELs workers	Value	Starting point	Key effect	Other information
Acute - local effects (inhalation)	2.5 mg/m³	LOAEC: 22.5 mg/m³ (AF of 9)	irritation (respiratory tract)	subacute (inhalation: aerosol) (nose/head only)
Long-term - systemic effects (dermal)	11718 mg/kg bw/day	Adjusted starting point: 375000 mg/kg bw/day (AF of 32)	repeated dose toxicity	NOAEL: ca. 75 mg/kg bw/day (nominal)
Long-term - systemic effects (inhalation, aerosol - nebulized)	4.1 mg/m³	Corrected inh NOAEL: 33 mg/m³ (AF of 8)	repeated dose toxicity	NOAEL: ca. 75 mg/kg bw/day (nominal)
Long-term - systemic effects (inhalation, aerosol - dust)	5.7 mg/m³	Corrected inh NOAEL: 46 mg/m³ (AF of 8)	repeated dose toxicity	NOAEL: ca. 75 mg/kg bw/day (nominal)

DNELs developed by Lead registrant of Na5DTPA for the general population

DNELs for the general population	Value	Starting point	Key effect	Other information
Acute - local effects (inhalation)	2.5 mg/m³	LOAEC: 22.5 mg/m³ (based on AF of 9)	irritation (respiratory tract)	subacute (inhalation: aerosol) (nose/head only)
Long-term - systemic effects (dermal)	5859 mg/kg bw/day	Adjusted starting point: 375000 mg/kg bw/day (based on AF of 64)	repeated dose toxicity	NOAEL: ca. 75 mg/kg bw/day (nominal)
Long-term - systemic effects (inhalation)	1 mg/m³	Corrected inh NOAEL: 16 mg/m³ (based on AF of 16)	repeated dose toxicity	NOAEL: ca. 75 mg/kg bw/day (nominal)
Long-term - systemic effects (oral)	1.2 mg/kg bw/day	Corrected inh NOAEL: 76.8 mg/kg bw/day (based on AF of 64)	repeated dose toxicity	NOAEL: ca. 75 mg/kg bw/day (nominal)

Starting point (local effects)
In the short term inhalation study conducted with disodium EDTA there were local irritation effects noted at the dose level of 30 mg/m^3. This dose level is then converted from a 6 hr exposure (in the study) to an 8 hr exposure for the worker. This results in a starting point of 22.5 mg/m^3 chosen by the lead registrant of Na5DTPA for the derivation of an acute inhalation DNEL for local effects.

Starting point (systemic effects)
The lead registrant of Na5DTPA chooses as key study for DNEL derivation the NOEL from the 28-days oral toxicity study. The NOEL for this study is lower than that for the developmental toxicity study and the mode of action for toxicity is considered to be consistent for the different endpoints. This NOEL is considered by the registrant to be protective for both endpoints and no separate DNEL has been calculated for developmental toxicity. The starting point for the DNEL derivation is therefore 75 mg/kg bw/day.

Assessment factors (AF)
- Sub acute to Chronic = 2 (6 default in ECHA guidance R8)
- Allometric scaling = 4 (Conversion from a rat study to human exposure)

- Other inter species differences = 1
- Intra species differences = 8 (consumers), 4 (workers)

Much of the toxicity of DTPA is based upon the chelation of essential metals such as zinc. Due to the differences in nutritional status within the population, a factor of 8 is proposed for Consumer exposure. This factor indicates the potential variation in the intake of essential nutrients such as zinc in the worker and consumer populations, for example, zinc intake can vary from 4 mg to 22 mg/day.

- Total Assessment factor is 64 (32 for workers) for Oral / Dermal and 16 (8 for workers) for Inhalation

Workers DNELs
Acute Inhalation exposure, local effects
Starting point of 22.5 mg/m^3
Assessment factors: LOAEC to NOAEC = 3, Inter-individual variability = 3
DNEL = 22.5 / 9 = 2.5 mg/m^3

Long term exposure, systemic effects

Dermal
Dermal absorption of DTPA is estimated to be 0.001 %.
Oral absorption is estimated to be approximately 5 %.

Adjusted starting point = Oral NOEL * (oral bioavailability/dermal bioavailability) = 75*(5/0.001) = 375000 mg/kg bw
Dermal DNEL =375000/32
Dermal DNEL=11718 mg/kg bw/day

Inhalation of aerosol (nebulized)
For intestinal absorption an assumption of 5% has been used.
For inhalation: 20% (based on studies using nebulized DTPA solutions in humans)
According to R8 Guidance (ECHA, 2010):
Corrected inh NOAEL = oral NOAEL x [1/sRV(rat)] x [absorption (oral-rat) / absorption (inh-human)] x [sRV(human) / wRV]
Giving:
75 x [1/0.38 m^3 (8h)] x [5/20] x [6.7 m^3 (8h) / 10 m^3 (8h)] = 33 mg/m^3

Application of AF=8: Inhalation DNEL (liquid aerosol) = 33/8 = 4.1 mg/m^3

Inhalation of aerosol (dust)
For inhalation absorption the following is suggested: based on the particle size distribution, it is expected that 90% of the inhaled substance will be deposited in the upper respiratory tract, which will finally be taken up orally. Of this, only 5% will be absorbed in the gastrointestinal tract and become available systematically, i.e. 0.9 x 0.05 = 0.045. The other 10% may reach the alveoli and it is assumed that this will be absorbed completely (worst case). Therefore, the total inhalation absorption factor will be 0.045 + 0.10 = 0.145.
According to R8 Guidance (ECHA, 2010):
Corrected inh NOAEL = oral NOAEL x [1/sRV(rat)] x [absorption (oral-rat) / absorption (inh-human)] x [sRV(human) / wRV]
Giving: 75 x [1/0.38 m^3 (8h)] x [5/14.5] x [6.7 m^3 (8h) / 10 m^3 (8h)] = 46 mg/m^3

Application of AF=8: Inhalation DNEL (dust) = 46/8 = 5.7 mg/m^3

General population DNELs

Acute Inhalation exposure, local effects
Starting point of 22.5 mg/m^3
Assessment factors: LOAEC to NOAEC = 3, Inter-individual variability = 3
DNEL = 22.5 / 9 = 2.5 mg/m^3

Long term exposure, systemic effects

Dermal

Dermal absorption of DTPA is estimated to be 0.001 %. Oral absorption is estimated to be approximately 5 %.
Adjusted starting point = Oral NOEL * (oral bioavailability/dermal bioavailability) = 75*(5/0.001) = 375000 mg/kg bw
Application of AF=64: Dermal DNEL =375000/64
Dermal DNEL=5859 mg/kg bw/day

Inhalation of aerosol (nebulized)

For intestinal absorption a figure of 5% has been used
For inhalation: 20% (based on studies using nebulized DTPA solutions in humans)
According to R8 Guidance (ECHA, 2010):
Corrected inh NOAEL = oral NOAEL x [1/sRV(rat)] x [absorption (oral-rat) / absorption (inh-human)] x [sRV(human) / consRV]
Giving: 75 x [1/0.38 m^3 (8h)] x [5/20] x [6.7 m^3 (8h) / 20 m^3 (24h)] = 16 mg/m^3
Inhalation DNEL (liquid aerosol) = 16/16 = 1 mg/m^3

Oral

Unabsorbed DTPA in the gut will bind metals and prevent their absorption just as the absorbed DTPA will bind metals in the systemic circulation and increase their excretion. Therefore it is not necessary to take into account bioavailability following an oral dose when calculating the oral DNEL.
Oral DNEL = 75/64 = 1.2 mg/kg bw/day

Annex 2: Exposure estimation

1. Occupational exposure

As the availability of DTPA exposure data in the workplace is limited, the exposure assessment has used exposure models to estimate workplace exposures. In addition, as patterns of exposure to EDTA and DTPA are very similar, the exposure scenarios used in the EDTA EU Risk Assessment have been applied to assess exposure to DTPA (European Chemicals Bureau, 2004).

The following information is given in the CSR from Lead Registrant of Na5DTPA:

Oral exposures in the workplace

It is generally assumed that oral exposure to industrial chemicals in the workplace can be discounted and DTPA is no exception, making it unlikely that any oral exposure will occur during manufacturing or formulation processes. However, for the purpose of this CSA the possibility of some small contamination of food occurring within the workplace is considered as part of the exposure assessment. In the absence of data on the potential oral intake of dusty chemicals in the workplace, an exposure level of 25 mg/day is assumed. This assumption is based on a US-EPA estimate that the daily adult unintentional soil intake would fall within the range of 0 to 50 mg/day (US-EPA 1997). For the purpose of this assessment the midpoint of this range was used. For a 70 kg worker this corresponds to an oral dose of 0.35 mg/kg bw/day. It should be understood that an estimated exposure of up to **25 mg/day** is still likely to be a gross overestimate of actual worker exposure through the dietary route.

Absorption following oral exposure is approximately 5% (Stevens et al. 1962, Bondesson et al., 2007) therefore the actual systemic dose to DTPA following oral exposure in the workplace is 1.25 mg/day.

In summary assuming oral ingestion of 25 mg DTPA:

- Amount remaining in the Gastrointestinal Tract (GIT) is 23.75 mg/day
- Systemic exposure is 1.25 mg/day (= 1.25/70 = **0.018 mg/kg bw/day**)

Dermal exposures in the workplace

Data on dermal absorption of DTPA are not available. However, data on similar chelating agents suggest that the rate of absorption will be low. Dermal penetration data for EDTA has been reported by the European Chemicals Bureau (2004) as 0.001% absorption. Unpublished data from BASF (2007) reported 0.1% dermal absorption for Nitrilotriacetic acid (NTA). As DTPA has a higher molecular weight than EDTA but a similar log Kow it is proposed that dermal penetration of DTPA will be equivalent to or less than that of EDTA, i.e. approximately 0.001%.

Given this very low dermal penetration, systemic exposure via dermal exposure to DTPA is not considered to significantly add to a combined workplace exposure estimate. However to ensure dermal exposures are in fact insignificant a worst case estimate for dermal exposure of DTPA has been developed based on the assessment of EDTA by the EU (European Chemicals Bureau, 2004). In the dermal exposure estimate for EDTA 5 mg/cm^2/day dermal exposure and an exposed area of 840 cm^2 was considered appropriate. Using these values, the theoretical worst case dermal exposure for DTPA is 4,200 mg/person/day.

Taking into account the dermal absorption, the systemic dose for a 70 kg person would be:
4.200 mg/day x 0.001% / 70 kg = **0.0006 mg/kg bw /day**

Inhalation exposures in the workplace

DTPA is sold either as a liquid or a solid (a crystalline solid powder). The manufacture and major industrial use of liquid forms of DTPA are not anticipated to form aerosols. For example, in the paper and pulp industry DTPA is supplied as a liquid. Due to the enclosed nature of the production process, the low volatility of liquid DTPA and the use of suitable personal protective equipment by the work force (goggles, gloves and respiratory protection), the potential for occupational exposure to liquid DTPA during production and use

in the paper and pulp industry is considered to be minimal. A similar conclusion was reached in the EDTA EU Risk Assessment report (European Chemicals Bureau 2004).

Na5DTPA is mainly available and processed in liquid solutions. The vapour pressure of Na5DTPA is low, so exposure to vapours is expected negligible. When aerosol/mist formation is likely to occur, this has been indicated and a separate estimate for the aerosol exposure has been made in the CSR (using the ECETOC TRA v2 tool, applying medium dustiness for the solid to estimate the concentration).

Example of assessment parameter default values (for Industrial use in cleaning products):

Fugacity: medium dustiness
Type of Use: industrial
Concentration: > 25 %
Local Exhaust Ventilation: none
Duration of Exposure: > 4 hours/day
Respiratory Protection Equipment: none

Maximum resulted inhalation exposure: **2 mg/m^3** (using ECETOC TRA v2).

There are some other applications where aerosols of DTPA-containing solutions might be formed (such as agricultural spraying), however the concentration of DTPA in these solutions are typically very low (< 1%). In addition, due to the hazards posed by other components of the solutions (pesticides and fertilizers) it is assumed that workers applying these products wear goggles, gloves and respiratory protection (European Chemicals Bureau, 2004). Thus exposures to aerosols containing DTPA are not expected to be significant.

Inhalation of DTPA powder in the air is likely to be the most significant source of inhalation exposure in the workplace. Although DTPA powder is manufactured in an enclosed process, there is potential for inhalation exposure when the powder is transferred into containers for transport and when the powder is transferred from transport containers into formulating vessels. The manufacture and use of DTPA is very similar to EDTA and the EDTA EU Risk Assessment report (European Chemicals Bureau, 2004) also identified the potential for exposure to the powdered form of that chelating agent.
The data in Table below presents data on particle size distribution from three DTPA powder producers (Akzo Nobel, personal communication 2008, DOW, personal communication 2008, Dabeer, personal communication 2008).
Of these three manufacturers, Akzo is the only company that manufactures DTPA Acid powder in the EU. Dow manufactures in the US and Latin America, whilst Dabeer no longer produces the DTPA acid powder. Therefore this data on particle size is considered to be representative of the DTPA powder in use globally.

Akzo Nobel Data			Dow Data		Dabeer Data		BASF Data	
Size (µm)	Percentage by weight		Size (µm)	Average Percentage (by weight)	Size (µm)	Average percentage (by weight)	Size (µm)	Average percentage (by weight)
	Maximum Percentage	Minimum Percentage						
355	25	10	>355	10.0	> 800	1.5	< 1589	100.0
250	30	10	250 - 355	13.5	800-200	5.5	< 1002	99.3
180	20	5	180 - 250	15.0	200-150	17.3	< 502	94.6
125	15	10	125 - 180	10.0	150-100	52.0	< 200	76.6
90	20	5	90 - 125	6.5	100-71	23.7	< 100	51.5
63	20	5	53 - 90	17.2	71-63	0.2	< 50	30.9
< 63	25	5	< 53	29.0	63-40	0.0	< 20	12.7
< 10	4	0					< 10	5.3
							< 4	1.3
							< 2	0.1

Table: Particle Size Distribution in DTPA Powder (Annex XV C&L Proposal, 2009)

Whilst the actual concentrations of DTPA in the air are not monitored as a standard, the total dust concentration in the air is kept below 2 mg total dust per m^3 air (personal communication Akzo Nobel). Since Akzo are the only EU manufacturer of DTPA powder, the estimated concentration of DTPA powder in the air during manufacture is taken as 2 mg/m^3. While dust samples will contain a variety of particles, for this assessment a conservative assumption is that all the dust is DTPA and that inhalation exposure of **2 mg/m^3** represents the situation in the EU and globally.

2. Consumer exposure and Man exposed via the environment

The concept of a "sentinel" product" is used by the Lead registrant to determine the safety of DTPA containing products. The identification of "sentinel" products has been performed in two steps. Firstly, for each of the PCs an example consumer product is identified that is typical for the product category (use of large amounts of product, large potential for exposure by one or more routes). Secondly, the number of products is reduced by selecting the example products that have the highest "potential for exposure" (sentinel products). One sentinel product is assigned to each PC. The idea is that if exposures to these products are found to have acceptable risk management ratios then the products in the various PCs (being lower) will also have acceptable risk management ratios.
The 2 "sentinel" products are hard surface cleaners and house paints. Consumer exposure has been predicted with ConsExpo v4.1 model.

The bioaccumulation potential of this substance is low, therefore secondary poisoning is considered negligible by the lead registrant of Na5DTPA. However, DTPA serves as chelating agent in a wide variety of consumer products and is considered persistent in the environment. The cumulative exposure – represented by the use of consumer products / drinking water / food consumption - has not been calculated.

Monitoring data of the drinking water along the Ruhr indeed reveal that concentrations of some µg/l of EDTA and DTPA are regularly detected in drinking water. During 2007 and 2008, about 50 % of the values measured were below the limit of detection. During the monitoring period 2001-2008, the maximum value measured in the Rhine at the German-Dutch border (Lobith) amounted to 18 µg/l. In the R. Main at Bischofsheim, DTPA was measured in all samples, the maximum value during 2007 to 2008 amounted to 13 µg/l, in the R. Ruhr the maximum concentration amounted to 21.6 µg/l. Contrary to EDTA, no increase in concentration is measured downstream the Rhine (ICPR 2012).

Annex 3: Main calculated RCR for DTPA (occupational exposure)

Exposure route	Estimated concentration	DNEL	RCR
Oral	0.018 mg/kg bw/day	1.2 mg/kg bw/day*	0.015
Dermal	0.0006 mg/kg bw/day	11718 mg/kg bw/day	5.10^{-8}
Inhalation	2 mg/m^3 (aerosol / dust)	2.5 mg/m³ (aerosol, subacute) 5.7 mg/m³ (Na5DTPA dust) 4.5 mg/m³ (DTPA Acid dust)	0.8 0.35 0.44

*As no DNEL has been derived by Lead registrant for the oral route for workers, the DNEL of the general population has been used in a conservative approach.