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Environmental Protection Agency

Survey of Trisodium nitrilotriacetate

A report under the LOUS review project

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Trisodium nitrilotriacetate

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Preface

Background and objectives

The Danish Environmental Protection Agency's List of Undesirable Substances (LOUS) is intended as a guide for enterprises. It indicates substances of concern whose use should be reduced or eliminated completely. The first list was published in 1998 and updated versions have been published in 2000, 2004 and 2009. The latest version, LOUS 2009 (Danish EPA, 2011) includes 40 chemical substances and groups of substances which have been documented as dangerous or which have been identified as problematic using computer models. For inclusion in the list, substances must fulfil several specific criteria. Besides the risk of leading to serious and long-term adverse effects on health or the environment, only substances that are used in an industrial context in Denmark in quantities over 100 tonnes per year, are included.

Over the period 2012-2015 all 40 substances and substance groups on LOUS will be surveyed. The surveys include collection of available information on the use and occurrence of the substances, internationally and in Denmark, information on environmental and health effects, on alternatives to the substances, on existing regulation, on monitoring and exposure, and information regarding on going activities under REACH, among others.

On the basis of the surveys, the Danish Environmental Protection Agency (Danish EPA) will assess the need for any further information, regulation, substitution/phase out, classification and labelling, improved waste management or increased dissemination of information.

This survey concerns the substance Trisodium nitrilotriacetate (in this report abbreviated as Na_3NTA), which is the most commonly used salt of the aminocarboxylic acid nitriloacetate (NTA). In terms of toxicology and ecotoxicology it is NTA that determines the hazard of the substance. Other salts of NTA do exist (disodium nitrilotriacetate (NA_2NTA), but the toxicological literature and reports on hazards and risks often simply refer to the aminocarboxylic acid, NTA. . The present report focusses on Na_3NTA but consider also available information on NTA and other NTA salts where relevant. In these cases the name of the substance is mentioned

The entry on Na_3NTA in LOUS in 2009 is based on the classification as Carc 2 according to the EU Regulation (EC) No 1272/2008[1] and a yearly consume in Denmark of more than 100 tonnes. Moreover, the substance is applied in high volumes in the EU and is registered under REACH as a monoconstituent substance (10,000-100,000 tonnes).

The main objective of this study is, as mentioned, to provide background for the Danish EPA's consideration regarding the need for further risk management measures.

[1] Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures

The process

The survey has been undertaken by DHI and Nordic Institute of Product Sustainability, Environmental Chemistry and Toxicology (NIPSECT) from April to October 2013. The work has been followed by an advisory group consisting of:

- Annette L. Gondolf (Danish EPA)
- Katrine Smith (Danish EPA)
- Christina Ihlemann (Danish EPA)
- Ulla Hansen Telcs (Confederation of Danish Industry)
- Nikolai Stubkjær Nielsen (Confederation of Danish Industry)
- Anette Ravn Jensen (Danish Working Environment Authority)
- Bente Fabech (Danish Veterinary and Food Administraion)
- Charlotte Legind (Danish Veterinary and Food Administraion)
- Allan Astrup Jensen (NIPSECT)
- Jens Tørsløv (DHI)
- Tina Slothuus (DHI)

Please note that the report does not necessarily reflect the views of the members of the advisory group".

Data collection

The survey and review is based on the available literature on the substances, information from databases and direct inquiries to trade organisations and key market actors.

The data search included (but was not limited to) the following:

- Legislation in force from Retsinformation (Danish legal information database) and EUR-Lex (EU legislation database);
- Ongoing regulatory activities under REACH and intentions listed on ECHA's website (incl. Registry of Intentions and Community Rolling Action Plan);
- Data on harmonised classification (CLP) and self-classification from the C&L inventory database on ECHAs website;
- Data on ecolabel criteria from the Danish ecolabel secretariat (Nordic Swan and EU Flower)
- Pre-registered and registered substances from ECHA's website;
- Data on production, import and export of substances in mixtures from the Danish Product Register (confidential data, not searched via the Internet);
- Date on production, import and export of substances from the Nordic Product Registers as registered in the SPIN database;

Besides, direct enquiries were sent to Danish and European trade organisations and a few key market actors in Denmark.

Summary and conclusions

Trisodium nitrilotriacetate (Na_3NTA) is included on LOUS in 2009 because it has a harmonized classification as Carc. 2 according to the CLP regulation (Carc. Cat. 3; R40 according to Directive) 67/548/EEC) and is used in high volumes (> 100 t) in Denmark.

According to the most recent data from the Danish product Register Na_3NTA is applied in products on the Danish market at an approximate volume of 50.5 tonnes. Data from the Nordic SPIN database show that the trend in Denmark and the Nordic Countries is a decreased use of Na_3NTA in tonnage as well as number of preparations containing Na_3NTA. In Denmark only three product categories containing Na_3NTA were reported in 2011: complexing agents, cleaning/washing agents and non-agricultural pesticides/ preservatives. The registered volumes used in these products indicate a steep decrease in the use over a 5 – 10 years horizon. The observation is in accordance with information from The Danish Association for Soaps, Detergents and Maintenance Products (SPT) who states that NTA has increasingly been replaced by other substances and is today phased out of cosmetics, detergents and all-purpose cleaners.

According to data on the use of Na_3NTA around year 2000, which were supplied by the producers and importers for the European risk assessment report, the consumption in Europe in 2000 was 32,040 tonnes/year. A similar figure was obtained by European Chemical Industry Council (CEFIC) who estimated that 26,756 tonnes Na_3NTA were sold in the EU in 1999. The difference can be explained by exports and/or imports of Na_3NTA containing formulations. A jointly submitted REACH registration dossier accounts for a manufactured volume in EU of 4,400 tonnes in per year in 2010. This indicates a reduced use of Na_3NTA within the EU.

NTA and its sodium salt are used to soften water and to remove traces of alkaline earth metals and heavy metals. They are often included in detergent and cleaner formulations for household or industrial use. In Denmark the registered uses are as complexing agents, cleaning/ washing agents and non-agricultural pesticides/preservatives. In recent years, however, especially the use in non-agricultural pesticides/preservatives has decreased markedly and was in 2011 only 0.4 tonnes. The registered volume for the two other main product categories as complexing agents and cleaning- and washing agents, has also decreased dramatically over the past 10 years and was in 2011 38 tonnes and 14 tonnes respectively

The main source of release of Na_3NTA to the environment is waste water from the formulation and use of Na_3NTA containing products. Na_3NTA is readily biodegraded and a large percentage (up to more than 95%) is removed in waste water treatment plants. The concentration of Na_3NTA in sewage sludge is expected to be low due to its biodegradability and tendency to remain in the water phase. No recent studies on contaminants in sludge have included measurements for NTA and its salts. Once Na_3NTA is released to the aquatic environment it is expected to remain in the water phase and is not expected to distribute to the sediment compartment.

Furthermore, based on the available data it is concluded that Na_3NTA is neither a PBT nor a vPvB substance.

An EU Risk Assessment Report from 2005 concluded that the environmental risk for all life-cycle steps, exposure routes and targets were adequately controlled. This conclusion is strengthened by the observed general trend of a reduced production and use of Na_3NTA. The risk assessment report concluded that for the environment there is no need for further information/ testing and for risk reduction measures beyond those which are being applied already. The current review has not identified information that can question this conclusion.

The available toxicological studies show that the acute oral toxicities of NTA and its sodium salts are low but sufficient for a classification as harmful. NTA and its salts are mildly irritating to skin, eyes and airways.

In 1998 International Agency for Research on Cancer (IARC) concluded that there was inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of NTA and its salts. The overall evaluation was that the substances were possibly carcinogenic to humans (Group 2B).

Since NTA is widely used in cleaning agents for household and industrial use, there is a potential for direct exposures of both consumers and workers. Workers may be exposed dermally and by inhalation during production and formulation of detergents and workers and consumers may be exposed to dust from dish-washing powder, and the use of aerosol spray cans or high-pressure application of aqueous preparations containing NTA.

Indirect exposures via drinking water, ambient air and food and seems insignificant. There is no available bio-monitoring data.

Based on the Risk Assessment report of Na_3NTA finalised in 2008 a risk reduction strategy was formulated. The strategy focused on the possible risk to workers and recommended a harmonised classification of Na_3NTA and establishment of a European Community Occupational Exposure Limit value (OEL). An EU harmonised classification, including Carc. 2, is now in place, but no OEL has been established at Community level.

The EU Scientific Committee for Consumer Safety estimated a possible risk for NTA used in cosmetics. NTA and its salts are therefore banned in cosmetics in the EU.

Na_3NTA was introduced as an alternative to phosphate in detergents and all-purpose cleaners in order to avoid eutrophication of surface waters. Because of the classification as a Carc 2 substance, alternatives have been introduced, e.g. zeolites, polycarboxylates, sodium citrate, citric acid, phosphonate and EDTA. None of identified alternatives are classified as carcinogenic, mutagenic or toxic for the reproduction. Neither are they classified as Persistent, Bioaccumulative and Toxic in the environment, are endocrine disruptors, or have properties of similar concern.

Ultimately it is the specific technical requirements as well as economic considerations that will determine the choice of alternative.

Sammenfatning og konklusion

Trinatrium nitrilotriacetat (Na_3NTA) blev optaget på LOUS i 2009 p.g.a. stoffets harmoniserede klassificering som Carc. 2 i henhold til CLP reguleringen (Carc. Cat. 3; R40 i henhold til Direktiv 67/548/EEC) og fordi det anvendes i store mængder (> 100 t) i Danmark.

Ifølge de nyeste oplysninger fra det Danske Produktregister anvendes Na_3NTA i produkter på det danske marked i en mængde svarende til 50,5 tons. Data fra den nordiske SPIN database viser, at tendensen i Danmark såvel som i de øvrige nordiske lande er et fald i anvendelsen af Na_3NTA både mht. til tonnagen, der anvendes, såvel som antallet af præparater der indeholder Na_3NTA. I Danmark blev Na_3NTA således kun registreret anvendt i 3 produktkategorier med en samlet tonnage i 2011 på 52,4 tons hvilket repræsenterer et dramatisk fald set over en 5 – 10 årig horisont. Dette er i overensstemmelse med oplysninger fra den danske brancheorganisation for Sæbe, Parfume og Teknisk/Kemiske artikler (SPT), som oplyser, at NTA i stigende grad er blevet erstattet af andre stoffer, og at det i dag er blevet udfaset af kosmetikprodukter, detergenter og rengøringsmidler.

Jævnfør data for anvendelsen af Na_3NTA omkring år 2000, og som er blevet gjort tilgængelig af producenter og importører i forbindelse med udarbejdelsen af den europæiske risikovurderingsrapport, er forbruget i Europa i år 2000 på 32.040 tons/år. Lignende oplysninger stammer fra CEFIC (European Chemical Industry Council), som har beregnet at 26.756 tons Na_3NTA blev solgt i EU i 1999. Forskellen kan forklares ud fra eksport og/eller import af formuleringer, der indeholder Na_3NTA. Et fælles REACH registreringsdossier redegør for en produceret mængde på 4.400 tones pr. år i 2010. Dette indikerer en reduktion i anvendelsen af Na_3NTA indenfor EU.

NTA og dets natriumsalte anvendes til at blødgøre vand og til at fjerne spor af metaller, herunder tungmetaller. De anvendes ofte i detergenter og rengøringsmidler, som anvendes privat og i industrien. I Danmark er de registrerede anvendelser: kompleksbindere, rengørings-/vaskemidler, ikke landbrugsmæssige pesticider/ konserveringsmidler. I de seneste år, er især anvendelsen indenfor ikke landbrugsmæssige pesticider/ konserveringsmidler faldet markant og i 2011 blev kun 0,4 tons Na_3NTA anvendt indenfor denne produktkategori. De tilsvarende tonnager registeret i kompleksbindere og rengørings-/vaskemidler viser også et fald i anvendelsen over en årrække og var henholdsvis 38 og 14 tons Na_3NTA i 2011.

Den største kilde til frigivelse af Na_3NTA til miljøet er spildevand fra formuleringen og anvendelsen af produkter, der indeholder Na_3NTA. Na_3NTA er let bionedbrydeligt og en stor procentdel (op til 95 %) fjernes i renseanlæg. Koncentrationen af Na_3NTA i spildevandsslam forventes at være lav pga. stoffets nedbrydelighed, og pga. at stoffet vil forblive i vandfasen. Ingen nyere studier vedrørende miljøfremmede stoffer i slam har omhandlet NTA og dets salte. Når Na_3NTA frigives til vandmiljøet forventes det at forblive i vandfasen og ikke at fordeles til sedimentet.

Endvidere, på baggrund af tilgængelige data kan det konkluderes, at Na_3NTA ikke er et PBT-stof ej heller et vPvB-stof.

En EU risikovurderingsrapport fra 2005 konkluderede, at den miljømæssige risiko for alle stadier i livscyklussen, eksponeringsveje og mål var tilstrækkeligt kontrolleret. Denne konklusion underbygges af den generelle tendens til en reduceret produktion og anvendelse af Na_3NTA.

Risikovurderingsrapporten konkluderer, at for miljø er der ikke brug for yderligere informationer /tests samt risikoreducerende tiltag ud over de allerede anvendte. Den aktuelle undersøgelse har ikke identificeret oplysninger, der kan sætte spørgsmålstegn ved denne konklusion.

Tilgængelige toksikologiske studier viser, at den akutte orale toksicitet af NTA og dets natriumsalte er lav men tilstrækkelig til klassificering som skadelig. NTA og dets salte er mildt irriterende for hud, øjne og luftveje.
I 1998 konkluderede det Internationale Agentur for Kræftforskning (IARC), at der ikke var tilstrækkeligt bevis for mennesker, men tilstrækkeligt bevis fra forsøgsdyr for NTA og dets saltes kræftfremkaldende effekter. Den samlede evaluering var, at stofferne var potentielt kræftfremkaldende for mennesker (gruppe 2B).

Eftersom NTA er meget anvendt i rengøringsmidler til både private og til industrien, er der en potentiel eksponering af både forbrugere og arbejdere. Arbejdere kan blive eksponeret via huden eller via inhalation under produktionen og formuleringen af detergenter, og arbejdere og forbrugere kan blive eksponeret via støv fra pulver til opvask og anvendelsen af aerosolsprays samt anvendelsen af vandige opløsninger, der indeholder NTA.

Indirekte eksponering via drikkevand, luften samt føden virker ubetydelig. Der er ingen tilgængelige moniteringsdata.

På baggrund af risikovurderingsrapporten for Na_3NTA, som blev afsluttet i 2008, blev der formuleret en strategi for risikobegrænsning. Strategien fokuserer på den mulige risiko for arbejdere og anbefalede en harmoniseret klassificering af Na_3NTA og etableringen af en fælles europæisk grænseværdi for arbejdsmiljøet (OEL). En EU-harmoniseret klassificering som Carc. 2 er etableret. Der er på nuværende tidspunkt ingen OEL i EU-regi.

EU's Videnskabelige Komité for Forbrugersikkerhed har anslået en mulig risiko for anvendelsen af NTA i kosmetik. NTA og dets salte er derfor ikke tilladt i kosmetik i EU.

Na_3NTA blev introduceret som et alternativ til phosphat i detergenter og rengøringsmidler for at undgå eutrofieringen af overfladevand. På baggrund af stoffets klassificering som Carc. 2 er mulige alternativer introduceret, herunder zeolitter, polycarboxylater, natriumcitrat, citronsyre, phosphonat og EDTA. Ingen af disse har en klassificering som carcinogene, mutagene eller reproduktionstoksiske, er persistente, bioakkumulerende og toksiske i miljøet, har hormonlignende egenskaber, eller har andre kritiske egenskaber, som gør dem problematiske i samme grad som disse.

Valg af alternativ til Na_3NTA vil derfor afhænge af de specifikke tekniske krav til de forskellige anvendelser af stoffet samt økonomiske overvejelser.

1. Introduction to the substance

1.1 Definition of the substance

Trisodium nitrilotriacetate (Na_3NTA) is included on LOUS because it is classified as Carc. 2, H351: Suspected of causing cancer, according to the EU Regulation (EC) No 1272/2008 (Carc. 3 R40 according to EU Regulation (EC) No 67/548/EEC), and because the registered use of Na_3NTA was over 100 tonnes per year in Denmark (2007 – 2008).

Na_3NTA has under REACH been registered as a mono constituent substance with a production/import volume in EU within the range of 10,000-100,000 tonnes per year.

NTA is produced and used mainly as sodium salt (Na_3NTA) or as acid (H_3NTA). In the literature doses, amounts and concentrations are mostly referred as Na3NTA.

Na_3NTA is available as anhydrous as well as monohydrate, dihydrate and trihydrate. The hydrated forms are all covered by the same EC number: 225-768-6. Table 1.1 lists the CAS and EC numbers of Na_3NTA, Na_2NTA and NTA. The present report focuses on Na_3NTA, but considers as well disodium salts and NTA where relevant. In such cases reference is made to these substances.

TABLE 1.1
NAME AND OTHER IDENTIFIERS OF TRISODIUM NITRILOTRIACETATE, NA_3NTA (CAS: 5064-31-3) DISODIUMNITRILOTRIACETATE, NA_2NTA (CAS: 15467-20-6) AND NITRILOTRIACETIC ACID (NTA) (CAS: 139-13-9) (EUROPEAN COMMISSION, 2005 AND IARC MONOGRAPHS VOLUME 73)

Substance	Synonyms	EC nr	CAS No.	Molecular formula	Molecular weight
Trisodiumnitrilotriacetate (Na_3NTA)	Nitrilotriacetic acid trisodium salt; NTA trisodium salt; NTA, trisodium salt; trisodium nitrilotriacetate; trisodium 2,2′,2′′-nitrilotriacetate; trisodium NTA	225-768-6	5064-31-3	$C_6H_6NNa_3O_6$	257.1 g/mol
Disodium-nitrilotriacetate (Na_2NTA)	Disodium hydrogen nitrilotriacetate; disodium nitrilotriacetate; nitrilotriacetic acid disodium	239-484-5	15467-20-6	$C_6H_6NNa_2O_6$	235.1 g/mol

Substance	Synonyms	EC nr	CAS No.	Molecular formula	Molecular weight
	salt; NTA, disodium salt				
Nitrilotriacetic acid (NTA)	Nitrilo-2,2′,2′′-triacetic acid; nitrilotris(methylenecarboxylic acid); NTA; triglycine; triglycollamic acid; α,α′,α′′-trimethylaminetricarboxylic acid	205-355-7	139-13-9	$C_6H_6NNaO_6$	213.1 g/mol

1.2 Physico- chemical properties

Trisodium nitrilotriacetate (Na_3NTA, CAS: 5064-31-3) is a colourless crystalline powder at room temperature and normal pressure. It is characterised by a high water solubility at room temperature (640 g/L at 20 °C) and a low vapour pressure ($1*10^{-7}$ Pa L at 25 °C). Based on a calculated Log P_{ow} of -2.6 it is expected to have a low bioaccumulation potential. Other key intrinsic physical-chemical properties of Na_3NTA are presented in the Table 1.2.

TABLE 1.2
PHYSICO-CHEMICAL PROPERTIES OF TRISODIUM NITRILOTRIACETATE (NA_3NTA) (CAS: 5064-31-3)

Property		Reference
Physical state	Crystalline powder	European Commission, 2005
Melting point	410°C with decomposition above 200°C	European Commission, 2005
Boiling point	Not applicable	European Commission, 2005
Relative density	1.77 at 20°C	European Commission, 2005
Vapour pressure	$1*10^{-7}$ Pa 25 °C (Calculated)	REACH Registration data
Surface tension	Not determined	European Commission, 2005
Water solubility (mg/L)	About 640 g/L at 20°C	European Commission, 2005
Log P (octanol/water)	-2.6 (Calculated)	European Commission, 2005

Nitrilotriacetic acid (NTA, CAS: 139-13-9) has a water solubility of 1.28 g/L at 25 °C and an estimated vapour pressure of $9.54*10^{-7}$ Pa L at 25 °C (QSAR calculation). Based on a calculated Log P_{ow} of -3.81 it is expected to have a low bioaccumulation potential. Other key intrinsic physico-chemical properties of NTA are presented in Table 1.3.

TABLE 1.3
PHYSICO-CHEMICAL PROPERTIES OF NTA (CAS: 139-13-9)

Property		Reference
Physical state	Flakes	REACH registration data (2013)
Melting point	242 °C at 1 atm	REACH registration data (2013)
Boiling point	429 °C at 1 atm (QSAR)	REACH registration data (2013)
Relative density	> 1 g/cm^3 at 25 °C	REACH registration data (2013)
Vapour pressure	9.54*10^{-7} Pa at 25 °C (QSAR)	REACH registration data (2013)
Surface tension	No data	No data
Water solubility (mg/L)	1.28 g/L at 25 °C pH =2.3	REACH registration data (2013)
Log P (octanol/water)	-3.81 at 25 °C (QSAR)	REACH registration data (2013)

No available information was found on the physical-chemical properties of Na_2NTA. The CAS number (CAS no.: 15467-20-6) is not, currently, registered under REACH.

1.3 Salt and complex formation

When dissolved in water, Na_3NTA dissociates. The carboxylic acid, NTA, forms salts with various available cat-ions.

NTA in its fully ionized form has four functional groups. Three carboxylates and one amine groups are available for complexing with an appropriate metal ion. This phenomenon where more than one of the NTA functional groups is involved in binding with a central metal ion is known as chelation. For example, the structure of the Fe^{3+} /NTA_3- complex involves simultaneous binding of the three carboxylate groups and the amine group to the Fe^{3+} ion. Other metal ions show intermediate degrees of complexation with NTA in its ionized (salt) form in solution.

Complexes are formed in water between metal ions and NTA. The proportion of metal ions complexed in a given solution depends on a number of factors, and the complex is always in equilibrium with uncomplexed metal ion and NTA (IARC, 1990).

The extent of metal complex formation in solution depends on the concentrations of the ionized forms of NTA and the metal ion, and on the formation constant (inverse of dissociation constant) of the complex.

Binding of metal ions to NTA makes the metals less available for aquatic organisms and since it is the metal ion which is most often associated with a toxic effect, complexing may reduce toxicity. Similarly the binding of Ca^{2+} softens the water, and NTA is therefore used together in detergents to increase the effectiveness of the tensides that otherwise would be less active because of the presence of Ca^{+}.

2. Regulatory framework

2.1 Legislation

This section gives an overview of how Na_3NTA is addressed in existing and forthcoming EU and Danish legislation, international agreements and eco-label criteria.

2.1.1 Existing legislation

The current regulation of Na_3NTA, which is listed in Table 2.13 below, includes registration under REACH, classification according to the CLP regulation and the regulation of the use of chemicals in the workspace, i.e. the exposure to chemicals agents at work places as well as the exposure to carcinogens at work places. Furthermore, NA_3NTA is also considered in both the Nordic and the EU-eco-labeling criteria for several categories of products.

NTA was first evaluated by IARC in 1990 and placed in IARC group 2b as possible carcinogenic to humans based on evidence from studies on experimental animals. The Danish working environment Authorities included in 1993 NTA on the list of substances subject to the regulation of carcinogenic substances in the work place.

TABLE2.1
LEGISLATION ADRESSING NA_3NTA

Legal instrument	EU	Requirements as concerns Na_3NTA and national implementation
General legislation		
REACH regulation	REGULATION (EC) No 1907/2006 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 18 December 2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)	Registration of production import and uses. Tonnage band: 10,000 – 100,000 tonnes per year
CLP regulation	REGULATION (EC) No 1272/2008 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 December 2008 on classification, labelling and packaging of substances and mixtures	EU harmonised classification.
Regulation addressing substances and products (workers and consumers)		
Directive on	COUNCIL DIRECTIVE 98/24/EC of	On the protection of the health

Legal instrument	EU	Requirements as concerns Na_3NTA and national implementation
Chemicals Agents at Work	7 April 1998 on the protection of the health and safety of workers from the risks related to chemical agents at work	and safety of workers from the risks related to chemical agents at work (fourteenth individual Directive within the meaning of Article 16(1) of Directive 89/391/EEC) . There is no Occupational Exposure Limit established for Na_3NTA or NTA. *Implemented in Denmark by: Statutory Order No. 292; 26. April 2001. "Bekendtgørelse om arbejde med stoffer og materialer (kemiske agenser)"*
Executive Order on the Performance of Work	Danish Executive Order No. 559 of 17 June 2004	Section 16. Any unnecessary effect of substances and materials shall be avoided. Therefore, the effect of substances and materials during work shall be reduced to the lowest level reasonably practicable taking account of technical progress, and any limit values fixed shall be complied with.
Executive order approval of disinfectants etc. in certain food etc.	Danish Executive Order no 134. Of 11 February 2013	The Danish Food Autority positive list of permitted substances for use as corrosion derogatory agents for steam boilers. Na_XNTA (CAS: 10042-84-9), is permitted in a concentration not exceeding 5 mg/kg in water applied in steam boilers within the food industry. However the fume must not come into contact with the raw milk and dairy products

Legal instrument	EU	Requirements as concerns Na_3NTA and national implementation
Carcinogens Directive	DIRECTIVE 2004/37/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 29 April 2004 on the protection of workers from the risks related to exposure to carcinogens or mutagens at work.	On the protection of workers from the risks related to exposure to carcinogens or mutagens at work (Sixth individual Directive within the meaning of Article 16(1) of Council Directive 89/391/EEC) *Implemented in Denmark by Statutory Order No 908; 27 September 2005: "Bekendtgørelse om foranstaltninger til forebyggelse af kræftrisikoen ved arbejde med stoffer og materialer" Appendix 1.*
Eco-labelling: Nordic Swan criteria European Flower criteria		Detergent Ingredient Database (DID) list. The DID-list is a list of information regarding the toxicity and biodegradation potential of a chemical substance. The information is used when applying for the two Eco-labels: Nordic Swan and EU Flower.
Cosmetics Directive	COUNCIL DIRECTIVE of 27 July 1976 on the approximation of the laws of the Member States relating to cosmetic products (76/768/EEC) Article 4b	The use in cosmetic products of substances classified as carcinogenic, mutagenic or toxic for reproduction, of category 1, 2 and 3, under Annex I to Directive 67/548/EEC shall be prohibited.
Biocidal Products Regulation	REGULATION (EU) No 528/2012 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 May 2012 concerning the making available on the market and use of biocidal products From September 2013, the Biocidal Products Regulation (BPR, Regulation (EU) 528/2013) has replaced the Biocidal Products Directive (DIRECTIVE 98/8/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 16 February 1998 concerning the placing of biocidal products on the	The Biocidal Products Regulation (528/2012) introduces new types of authentication and ensures a more rapid approval process. NTA (CAS no. 139-13-9) is included in Annex I : 'List of active substances identified as existing' of the Commission regulation 1451/2007 on biocides, referring to the work programme under the previous Biocidal Products Directive (Directive 98/8/EC). None of the three CAS numbers: 139-13-3; 5064-31-3; 15467-20-6

Legal instrument	EU	Requirements as concerns Na_3NTA and national implementation
	market).	are included in Annex II: ‘on active substances to be examined under the review programme’ of this Directive.
Regulation addressing waste		
Waste Framework Directive	DIRECTIVE 2008/98/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 19 November 2008 on waste and repealing certain Directives	NTA is as a consequence of its classification as Carc. 2 included in ANNEX III: Properties of waste which render it hazardous. Implemented in Denmark by Statutory Order No 1309/18/12: “Bekendtgørelse om affald” NTA is as a consequence of its classification as Carc. 2 included in Annex 4: Properties and weight % which classifies waste as hazardous
Regulation addressing emissions to the environment		
Water Framework Directive	DIRECTIVE 2000/60/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 23 October 2000 establishing a framework for Community action in the field of water policy	NTA or its sodium salts are not on the amended list of priority substances NTA is however as a consequence of its classification as Carc. 2 included in the ANNEX VIII Indicative list of the main pollutants
International agreements		
Waste framework directive	DIRECTIVE 2008/98/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 19 November 2008 on waste and repealing certain Directives	The Directive states that waste which contains NTA in a concentration which calls for classification also classifies it as hazardous waste.
Basel convention	Basel Convention ON THE CONTROL OF TRANSBOUNDARY MOVEMENTS OF HAZARDOUS WASTES AND THEIR DISPOSAL	Basel Convention regulates wastes classified as hazardous (Annex III): *Substances or wastes which, if they are inhaled or ingested or if they penetrate the skin, may involve delayed or chronic effects,*

Legal instrument	EU	Requirements as concerns Na_3NTA and national implementation
		including carcinogenicity.

2.1.2 Classification and labelling

2.1.2.1 Harmonised classification in the EU

Based on an Annex XV transitional dossier submitted by The Netherlands in 2008, NTA was classified as Carc. Cat 3 in the 31st adaptation of the Annex I to the Directive 67/548/EEC (September 2009). The Carc. Cat 3 corresponds to a CLP classification as Carc 2.

The classification as Carc. 2 has implications for the regulation of the substance in 'downstream' legislation. The Cosmetics Directive prohibits the use of substances classified as Carc. 1A, 1B and Carc. 2 in cosmetic products. Furthermore, NTA and its salts if contained in wastes in concentrations at or above 5% will render the waste as hazardous according to the Waste Framework Directive and the Basel Convention (rf. Table 2.1).

Table 2.2 shows the harmonised classification and labelling for Na_3NTA according to the CLP regulation.

Na_3NTA (CAS no. 5064-31-3, EC 225-768-6) is classified:

- acute toxic in category 4 with a cut-off value of 1%,
- an eye irritant in category 2, and as
- a carcinogen in category 2 with a specific concentration limit of 5%.

The Hazard statements are:

- Harmful if swallowed (H302)
- Causes serious eye irritation (H319)
- Suspected of causing cancer (H351)

The Classification of Na_3NTA is summarised in Table 2.2 below

TABLE 2.2
HARMONISED CLASSIFICATION ACOORDING TO ANNEX VI OF REGULATION (EC) NO 1272/2008 (CLP REGULATION)

Index No	International chemical identification	CAS No	Classification	
			Hazard Class and Category Code(s)	Hazard statement Code(s)
225-768-6	Trisodium nitrilotriacetate (Harmonised Classification)	5064-31-3	Acute Tox. 4 Eye Irrit. 2 Carc. 2	H302 H319 H351

Further it needs be labeled with warning pictograms:

And the Precautionary Statements:
P201: Obtain special instructions before use.
P202: Do not handle until all safety precautions have been read and understood.
P264: Wash … thoroughly after handling (Manufacturer/supplier to specify parts of the body to be washed after handling).
P270: Do not eat, drink or smoke when using this product.
P280: Wear protective gloves/protective clothing/eye protection/face protection.
P281: Use personal protective equipment as required.
P301/312: IF SWALLOWED: Call a POISON CENTER or doctor/physician if you feel unwell.
P305/351/338: IF IN EYES: Rinse cautiously with water for several minutes. Remove contact lenses, if present and easy to do. Continue rinsing.
P308/P313: IF exposed or concerned: Get medical advice/attention.
P330: Rinse mouth.
P337/313: If eye irritation persists: Get medical advice/attention.
P405: Store locked up.
P501: Dispose of contents/container to … (… in accordance with local/regional/national/ international regulation (to be specified).

According to Annex VI of Regulation 1272/2008/EC, there is a specific concentration limit for Na_3NTA (CAS 5064-31-3) of ≥ 5 w% when included in mixtures. If the substance is included in mixtures in a concentration exceeding this limit the mixture must also be classified.

2.1.3 REACH

Na_3NTA is registered under REACH as mono constituent substance[2] (10,000-100,000 tonnes). The registration dossier therefore has to comply with the information requirement in REACH Annex VI-X, i.e. the highest level in REACH regarding information covering physico-chemical, toxicological- and ecotoxicological properties. The substance does not appear on the candidate list of Substances of very High Concern (SVHC) or the Community Rolling Action Plan (CoRAP) for substance prioritised for evaluation. Further, no Registry of Intention (ROI) for consideration of preparing an

2 A mono-constituent substance is a substance, defined by its quantitative composition, in which one main constituent is present to at least 80% (w/w)

Annex XV dossier (regarding identification of SVHC or a restriction proposal) has been made by a member state.

2.1.4 Other legislation/initiatives

An Annex XV transitional report on Na_3NTA is available from the ECHA homepage. The report is based on the EU Risk Assessment Report from 2008 and refers to the risk reduction strategy presented by the German authorities also in 2008. The risk assessment strategy proposes a harmonised classification (which was adopted in the 31st ATP of the Directive 67/548/EEC). Furthermore, it was proposed to establish at community level an occupational exposure limit value for NTA according to Directive 98/24/EEC.

2.2 International agreements

No international agreement specifically mentioning sodium salts of NTA has been identified. The Basel convention, however, covers waste containing substances classified as Carc. 2 at concentrations higher than the specific concentration limit for classification of mixtures mentioned in the CLP regulation (i.e. Carc. 2 at >5% Na_3NTA).

2.3 Eco-labels

Table 2.3 gives an overview of Nordic and EU eco-labeling criteria addressing NTA and its salts as an ingredient. Furthermore, Na_3NTA is classified with H302, H319 and H351 and almost all remaining criteria documents do not allow substances classified as H302 (R22: Harmful if swallowed) and/or H319 (R36 Cause serious eye irritation) and/or H351 (R40: Suspected of causing cancer).

TABLE 2.3
ECO-LABELING CRITERIA WHICH DO NOT ALLOW NTA AND ITS SALTS IN ECOLABELLED PRODUCTS.

Eco-label	Criteria document title	Document number
EU-Flower	All-purpose cleaners and sanitary cleaners	2011/383/EU
	Industrial and Institutional Laundry Detergents	2012/721/EU
	Laundry detergents	2011/264/EU
	Soaps, shampoos and hair conditioners	2007/506/EC
	Hand dishwashing detergents	2011/382/EU
	Detergent for dishwasher	2011/263/EU
	Industrial and Institutional Automatic Dishwasher Detergents	2012/720/EU
Nordic-Swan	Cleaning agents for use in the food industry	Version 1.5
	Laundry detergent for professional use	Version 2.2
	Floor care products	Version 4.1
	Textile services	Version 2.0
	Cleaning services	Version 2.3

Eco-label	Criteria document title	Document number
	Industrial cleaning and degreasing agents	Version 2.4
	Cleaning products	Version 5.0
	Dishwasher detergents	Version 5.2
	Dishwasher detergents for professional use	Version 2.3
	Vehicle wash installations	Version 2.2
	Car and boat care products	Version 5.1

2.4 Summary and conclusions

The current regulation of Na_3NTA includes registration under REACH, classification according to the CLP regulation as well as the regulation of use of chemicals in the workspace, i.e. the Directives pertaining to exposure to chemical agents at work and to carcinogens at work.

The EU directives concerning the use of chemicals in the workspace (Council Directive 98/24/EC) and the work with carcinogenic substances (Directive 2004/37/EC) are implemented in Denmark by national legislations (Statutory Order No. 292; 26. April 2001 and Statutory Order No 908; 27. September 2005). The EU legislation concerning waste (Directive 2008/98/EC) is implemented in Danish legislation (Statutory Order No 1309/18/12).

Na_3NTA has a harmonised classification as Carc. 2 according to the CLP regulation. Following the EU risk assessment report from 2008, a risk reduction strategy was developed by the German rapporteur and a transitional dossier was prepared in 2009. A harmonised classification was proposed (and later adopted) as well as establishing at community level an occupational exposure limit value for NTA. However, no indicative or community OEL has been established.

The harmonised classification as Carc. 2 triggers a ban of the use in cosmetics and the substance is not allowed in eco-labeled products as detergents and cleaning agents (EU flower and the Nordic Swan).

3. Manufacture and uses

3.1 Manufacturing

3.1.1 Manufacturing processes

The manufacture of Na_3NTA is today based on a one-stage alkaline and two-stage acid process based on the cyanomethylation of ammonia (or ammonium sulphate) with formaldehyde and sodium cyanide (or hydrogen cyanide).

The two-stage process is as follows:

$$NH_3 + 3HCHO + 3NaCN \longrightarrow N(CH_2CN)_3 + 3NaOH$$

$$N(CH_2CN)_3 + 3NaOH + 3H_2O \longrightarrow N(CH_2COONa)_3 + 3NH_3$$

This synthesis can be carried out batch wise or continuously, where the continuous process is more economical. The resulting solution is sold directly as a solution (40 wt %) or used in the production of Na_3NTA in powder form, or acidified to pH 1 - 2 to yield the acid (H_3NTA). The significant yield of by-products in the alkaline process has in recent years led to the construction of plants based on the acid process, which features much lower by-product levels. The acid process is associated with stringent safety requirements due to the use of hydrogen cyanide, which is highly toxic and requires enclosed production equipment, and further may lead to corrosion of equipment. In the first stage, ammonia is reacted with formaldehyde to give hexamethylenetetramine, which is then reacted with hydrogen cyanide in sulfuric acid solution to yield triscyanomethylamine. Triscyanomethylamine is sparingly soluble in the acidic solution and is filtered off, washed, and saponified with NaOH to give Na_3NTA. The resulting solution has far lower by-product content than the solution from the alkaline method (European Commission, 2005).

3.1.2 Manufacturing sites

There are five producers and/or importers of NTA in Europe (European Commission, 2008):

- Akzo Nobel Chemicals B.V., Herkenbosch (NL)
- Akzo Nobel Chemicals B.V., Kvantorp (SWE)
- BASF AG, Ludwigshafen (GER)
- Dow Europe S.A., Seal Sands (UK)
- Solutia Europe S.A. (BEL)

It is likely that one or more of these companies are both producing and importing NTA. Information on manufacturing sites outside Europe has not been identified.

3.1.3 Manufactured volumes

According to a report published by the European Commission "*Concerning the biodegradability of the main non-surfactant organic detergent ingredients*" (EU Commission, 2009), the EU consumption of NTA was > 20.000 tonnes/year (mainly industrial detergents). According to information received from the international Association for Soaps, Detergents and Maintenance Products (A.I.S.E.), which is the official representative body of this industry sector in Europe, the use of NTA has been significantly reduced. The main reason is the reclassification to Carc. Cat. 3 according to Directive 67/548/EEC, which has been carried forward under the current CLP regulation as a Carc. 2 classification (pers. communication A.I.S.E, May 2013).

According to the Danish Association for Soaps, Detergents and Maintenance Products (SPT), NTA and its salts are not used as ingredients in Denmark, and recent contact to their members confirms that it is not applied in cosmetics, detergents and all-purpose cleaners (pers. communication SPT, May 2013). Furthermore, the organisation informs that NTA was phased out and replaced by other substances with a similar function of the professional market in Denmark under the SPT certificate in 2008/2009 (SPT 2008/2009). The SPT certificate is a certificate which aims at reducing environmentally hazardous substances and substances with a high (eco)toxicity. In this certificate, NTA is specifically mentioned by name. The certificate is given to suppliers of all-purpose cleaners who deliver products of high performance and a minimal environmental influence (the specific requirements for obtaining the certificate were not available for this report).

A.I.S.E. reports they have very limited or no tonnage data. Compared to many other ingredients, the volumes of NTA used in this sector are considered as relatively small (pers. communication A.I.S.E, May 2013).

3.2 Import and export

3.2.1 Import and export of Na_3NTA in Denmark

The Danish product register has records on the numbers of products containing NTA and its salts as well as the corresponding tonnages of products. In Denmark there is no requirement to register cosmetic products, and this product type is not included in the register.

Based on the information from the Danish Product Register on the numbers of products containing NTA and the corresponding tonnages which have been reported, it can be seen that it is mainly Na_3NTA which is applied in the products on the Danish market (Table 3.1). The total volume represents both import and production, and the differences between the total volume of Na_3NTA in products (55.9 tonnes Na_3NTA /year) and the product volume for export (4.4 tonnes Na_3NTA /year) is the amount of Na_3NTA in products applied on the Danish market (i.e. 50.5 tonnes Na_3NTA /year (in 2011)).

TABLE 3.1
INFORMATION FROM THE DANISH PRODUCT REGISTER REGARDING THE NUMBER OF PRODUCTS, AND THE CORRESPONDING TONNAGES, WHICH CONTAIN NA3NTA (DATA EXTRACTED 2013.09.12), NA2NTA AND NTA (DATA EXTRACTED 2013.05.07)

	Na_3NTA (CAS no. 5064-31-3)	NA_2NTA (CAS no. 15467-20-6)	NTA acid (CAS no. 139-13-9)
Numbers of products	309	5	14
Total volume of products (tonnes /year)	55.9	< 1	1
Total volume of products for export (tonnes/year)	4.4	0	<1
Consumption on the Danish market (Calculated as the total volume minus the total volume of products for export (tonnes/year))	**50.5**	**< 1**	**1**

3.2.2 Import and export of Na_3NTA in EU

According to industry producers and importers the consumption of Na_3NTA in the EU was 32,040 tonnes in year 2000. The data were supplied by the producers and importers for the development of the EU risk assessment on NTA (European Commission, 2008). The EU production was estimated to 36,090 tonnes/year (calculated as Na_3NTA), 6,040 tonnes/year was imported, and 10,090 tonnes/year was exported to outside EU (Table 3.2). Similar figures were reported by the European Chemical Industry Council (CEFIC), who estimated that 26,756 tonnes/year were sold in the EU in 1999 (Table 3.3). The difference between these data on the overall consume in the EU can be explained by exports or imports of Na_3NTA containing formulations.

TABLE 3.2

TONNES OF NA_3NTA PRODUCED, IMPORTED, AND EXPORTED IN THE EU IN 2000. THE DIFFERENCE BETWEEN THE SUM OF THE PRODUED AND IMPORTED AMOUNT OF NA_3NTA AND THE EXPORTED AMOUNT REPRESENTS THE CONSUMPTION IN EU (EUROPEAN COMMISION, 2005).

EU	Tonnes
Produced	36,090
Imported	6,040
Exported	10,090
Consumed in Europe	**32,040**

According to the data supplied by the producers and importers for the risk assessment report this number was 26,756 tonnes/year. The NTA amounts (calculated as Na_3NTA) marketed in a number of European countries in 2000 are given in the Table 3.3. The figures are derived from sales information of the producers. A direct correlation to the consumption volume is therefore not precise; however, the figures may be regarded as an approximation for the consumption in Europe.

In the EU Risk Assessment Report there is no information to why some countries are reported in groups. According to the data, the sales numbers were the highest in the UK (7,274 tonnes), followed by Spain/Portugal/Greece (5,108 tonnes) and Germany (3,396 tonnes) (European Commission, 2005).

TABLE 3.3

NA_3NTA SALES IN WESTERN EUROPEAN COUNTRIES (DATA PROVIDED BY CEFIC, 2000) (EUROPEAN COMMISION, 2005

Country	Sales [t] in 1999
Germany	3,396
Belgium / Luxembourg	1,814
The Netherlands	2,055
France	1,838
Italy	8,25
UK	7,274
Ireland / Denmark	561

Country	Sales [t] in 1999
Spain / Portugal / Greece	5,108
Finland	Not published
Norway	0
Sweden	1,734
Austria	Not published
Switzerland	631
Total Western Europe	**26,756**

In Europe substances manufactured or imported in quantities of 1 tonnes or more have to be registered. This is done by sending in a registration dossier to ECHA (The European Chemical Agency). According to the registration dossiers recently submitted to ECHA the manufacture and import volume of Na_3NTA was 4400 tonnes in EU27 in 2010 (REACH registration data, 2013).

Thus, compared to the tonnages listed in the Tables 3.2 and 3.3, there has been a steep decline of the use of Na_3NTA from 2000 to 2010 - in agreement with the information received from A.I.S.E (Section 3.1.3).

3.3 Use

NTA is an aminocarboxylic acid with three functional groups which enable it to participate in complexation reactions. The most important property of NTA is to form water-soluble complexes with multivalent metal ions over a wide pH range (i.e. function as a complexing agent).

According to the LOUS-list from 2009, NA_3NTA is applied in products like biocides, complexing agents, pH-regulators and all-purpose cleaners.

NTA and its sodium salt are used to soften water and to remove traces of alkaline earth metals and heavy metals. They are often included in detergent and cleaner formulations for household or industrial use (European Commission, 2005). Around 67 % of the total European consumption of trisodium nitrilotriacetate are applied in cleaning agents for household and industrial use, 29 % of the marketed amount are used in other industrial categories, for example in uses as water softener, about 3.7 % are used for the textile cleaning industry and household (European Commission, 2008).

According to German data, Na_3NTA is used in all-purpose cleaners (up to 15 %), oven cleaners (up to 6 %), floor cleaners and polish (up to 20 %), machine dishwashing products (up to 7.5 %), glass cleaners (up to 8 %), bathroom cleaners (up to 7.5 %), hand dishwashing products (up to 0.8 %), laundry products (up to 3 %), and carpet cleaners (up to 3.5 %) (European Commission, 2008). In addition, Na_3NTA is used in car care product, including insect remover sprays (30%). It is also used in cosmetics (up to 5%) (SCCS, 2010). These uses will mainly result in consumer exposure of the skin fgby powder or liquids and inhalation of dust and aerosols, e.g. self-service at car washing stations, use of spray cans with NTA and hobby cleaning with the use of high-pressure equipment may increase the non-professional exposures considerably. No data are, however, available.

It is known that the effects of a biocide can sometimes be increased by using it in combination with a complexing agent. Bactericidal preparations often prove to be much less effective under practical conditions of use than when tested under laboratory conditions. This is because the bactericidal activity of a biocide can be adversely affected by the hardness of the water in which it is used. The addition of a complexing agent (like NTA), which binds calcium and magnesium ions, counteracts this effect. Moreover, according to producers of biocides, a chelating agent may increase the permeability of the membrane of the bacteria to biocides (www.SureChem.org).

The REACH registration dossier indicates that Na_3NTA is used in products applied within industry by professional workers as well as by consumers. Identified uses are textile dyes, intermediates water softeners, washing- and cleaning products, etc. (Table 3.4).

TABLE 3.4
IDENTIFIED USES OF NA_3NTA (REACH REGISTRATION DATA, 2013)

	Industrial use	Professional use	Consumer use
	Textile dyes Intermediate in formulation of other chelates Water softener Cleaning of equipment Metal working fluids	Laboratory chemicals Washing and cleaning products	Washing and cleaning products

According to the Danish SPT, NTA has been phased out of cosmetics and all-purpose cleaners. Regarding the European market A.I.S.E states: *NTA is relevant for our sector, for institutional applications: kitchen applications. This is believed to constitute the majority of NTA volumes used in our sector. It is used, to a relatively small extent, for private household applications as one of the ingredients involved in phosphate replacement for laundry detergents, as a complexing agent* (per. communication A.I.S.E., June 2013).

3.4 Historical trends in use

For information on the use of Na_3NTA (5064-31-3), the Danish Product Register and the SPIN database were consulted. The SPIN data base collects information on the use of substances in products in the Nordic countries (The database contains summary data from the Product Registries of Norway, Sweden, Denmark and Finland from 1999 and onwards).

According to the Spin database, Na_3NTA was included in products like non-agricultural pesticides and preservatives, cleaning- and washing agents, pH-regulation agents, complexing agents, reducing agents, surface active agents, surface treatment, laboratory chemicals, and solvents in the Nordic countries in 2011.

Table 3.5 shows the use categories i.e. products types and the corresponding tonnages of products containing NA_3NTA (CAS: 5064-31-3) in Denmark from 2000-2011 (SPIN, 2013). Figure 1 highlights the three main product categories in which Na_3NTA is applied: non-agricultural pesticides/preservatives, complexing agents and cleaning- and washing agents. In recent years, however, especially the use in non-agricultural pesticides/preservatives has decreased markedly and was in 2011 only 0.4 tonnes. The tonnages registered used in the two other main product categories, complexing agents and cleaning- and washing agents, have also decreased dramatically in the past 10 years and were in 2011 38 tonnes and 14 tonnes respectively .

TABLE 3.5

USE CATEGORIES AND AMOUNT IN TONNES NA_3NTA (CAS: 5064-31-3) APPLIED IN DENMARK FROM YEAR 2000-2011 (SPIN, 2013)

Use category/Year	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Complexing agents	145	110	108	226	5,7	5,7	113	113	212	42,3	38	38
Cleaning/washing agents	1318	120	141	209	121	124	143	144	45,5	29,5	17	14
Non-agricultural pesticides /preservatives	1,1	0	1,2	1,2	0,5	0,4	122	122	131	153	152	0,4
Surface treatment	0,3	0	0,3	0,1	0,1	0,1	0,1	0,1	0,1	0	0	0
Adhesives, binding agents	0	0	0	0	0	0	0	0	0	0	0	0
Colouring agents	1	1	0,2	0,2	0	0	0,1	0,1	0,1	0	0	0
Surface-active agents	0	0	0,2	0	0	3	0,6	0,6	0	0,2	0	0
Reprographic agents	0,1	0	0	0	0	0	0	0	0	0	0	0
Others	1,6	2	2,9	0	0	0	0	0	0	0	0	0

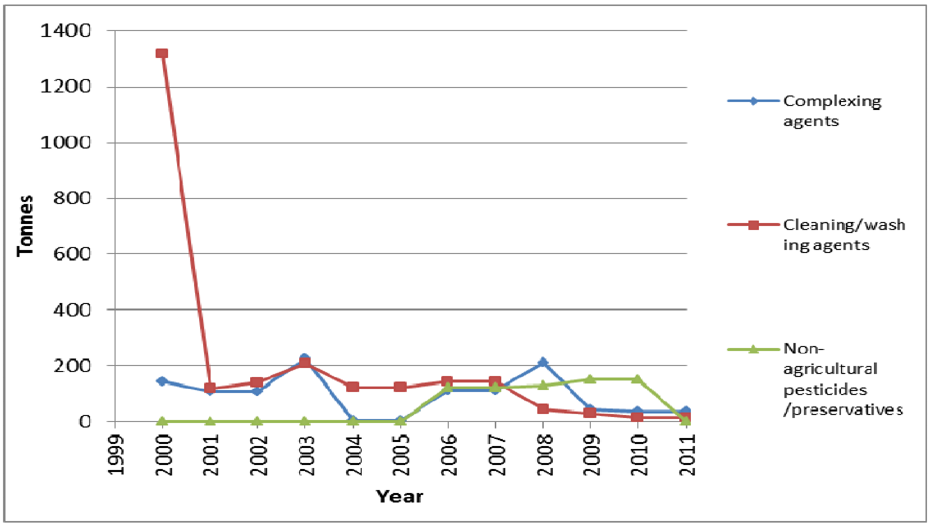

FIGURE 1

MAIN USE CATEGORIES IN WHICH Na_3NTA (CAS NO.: 5064-31-3) IS APPLIED IN DENMARK (SPIN, 2013).

Figure 2 below displays the numbers of preparations containing Na_3NTA and Figure 3 the tonnage of Na_3NTA in preparations in the Nordic countries from year 1999-2011 (SPIN, data extracted April 2013). The trend in all Nordic countries has been a fluctuation in the numbers of preparations containing NA_3NTA, and especially in Denmark and Sweden there has been a high number. However, it appears that the number is currently decreasing for all Nordic countries.

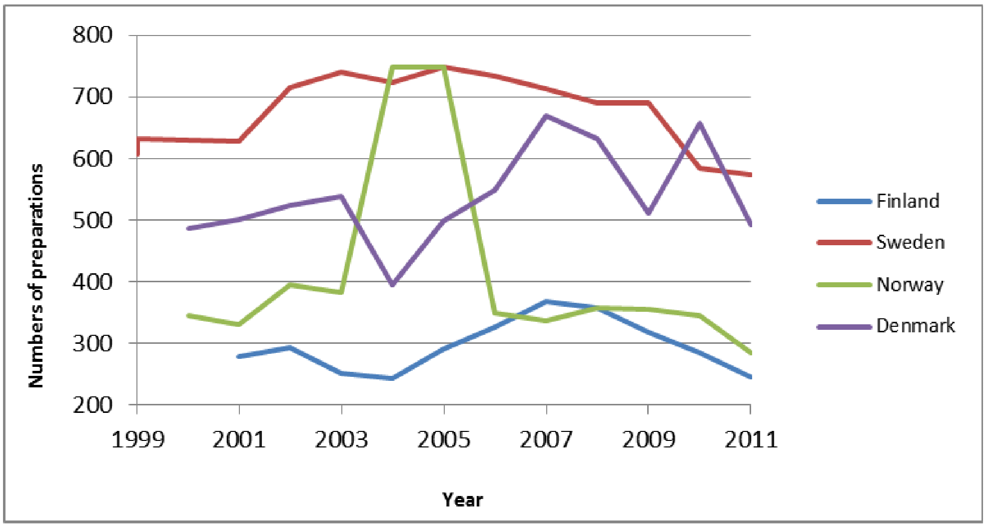

FIGURE 2
NUMBERS OF PREPARATIONS IN THE NORDIC COUNTRIES CONTAINING Na_3NTA (CAS NO.: 5064-31-3) (1999-2011) (SPIN, 2013)

Figure 3 shows that the tonnage of Na_3NTA in preparations on the Nordic markets has decreased in the period up to 2011 (Finland up to 2010). According to the SPIN database 52.4 tonnes was marketed in Denmark in 2011.

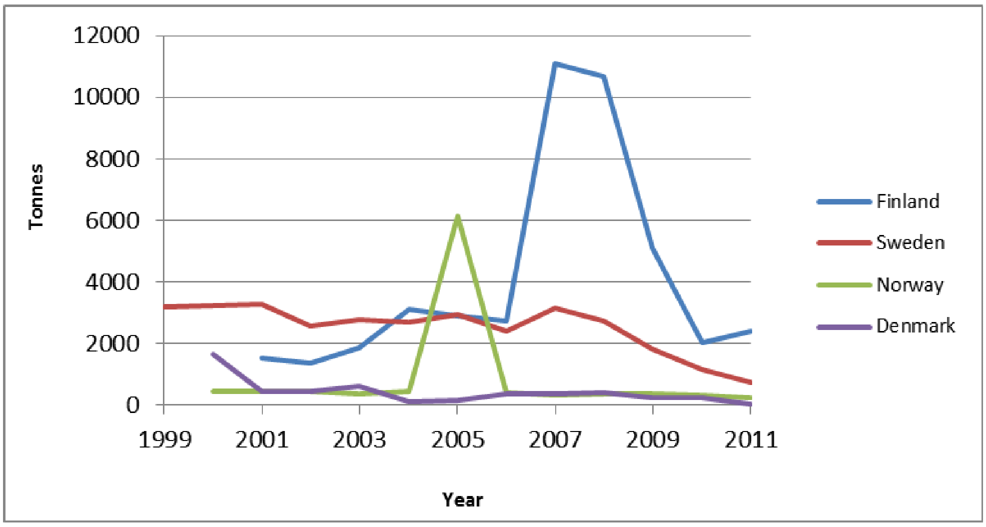

FIGURE 3
TONNES OF Na3NTA IN PREPARATIONS IN THE NORDIC COUNTRIES (CAS NO.: 5064-31-3) (1999-2011) (SPIN, 2013)

3.5 Summary and conclusions

Information regarding Na_3NTA application in preparations in Denmark and Europe was obtained by consulting the Danish Product Register, the Nordic SPIN database as well as SPT (The Danish Association for Soaps, Detergents and Maintenance Products) and A.I.S.E. (the official representative body of this industry sector in Europe).

NTA and its sodium salt are used to soften water and to bind traces of alkaline earth metals and heavy metals. They are often included in detergent and cleaner formulations for household or industrial use. The REACH registration dossier indicates that Na_3NTA is used in products applied in industry and by professionals in textile dyes, water softener, cleaning agents and metal working fluids. Consumer uses include washing and cleaning agents.

In Denmark, the main use categories registered in the SPIN data base are: complexing agents, cleaning/ washing agents and non-agricultural pesticides/preservatives. According to the LOUS list (2009) NTA is also used as pH-regulator and in biocide formulations. NTA itself does not have biocidal properties, but it is known that complexing agents can increase the effects of a biocide.

According to the information from the Danish Product Register it is mainly Na_3NTA, which is applied in products on the Danish market. The difference between the total tonnage of NTA used in marketed products (55.9 tonnes) and the tonnage used in products for export (4.4 tonnes) indicates that the amount of NA_3NTA on the Danish market is 50.5 tonnes in 2010. The general trend in Denmark and the Nordic countries is a decline in tonnes of Na_3NTA in preparations and also the numbers of preparations containing Na_3NTA.

The Danish Association for Soaps, Detergents and Maintenance Products (SPT) states that NTA has been phased out of cosmetics, detergents and all-purpose cleaners.

Information from producers and importers included in the EU risk assessment report states that 32,040 tonnes/year was consumed in Europe in 2000. Similar figures are provided by CEFIC who states 26,642 tonnes/year was sold in the EU in 1999. According to the REACH registration dossier, the manufacture and import of Na_3NTA in EU in 2010 was 4400 tonnes.

It needs to be noted that in contrast to the information received from industrial sector organisations claiming that NTA is phased out, there is still a significant, but reduced use of Na_3NTA in Denmark and the EU. This includes use in consumer products. The overall trend is, however, in the direction of a lower number of products and smaller tonnages.

4. Waste management

4.1 Waste from manufacture and use of Na_3NTA

The main release to the environment is through release of waste water both from the formulation processes and the use of products containing Na_3NTA.

4.2 Waste products from the use of Na_3NTA in mixtures and articles

Due to the use of Na_3NTA (complexing agent and cleaning/washing agents) the main release to the environment is via waste water from formulation and use of products containing Na_3NTA. Release of solid waste containing NTA is not expected.

4.3 Release of Na_3NTA from waste disposal

Na_3NTA is readily biodegradable (section 5.1), and most of the Na_3NTA in wastewater will be removed in the waste water treatment plants. This is confirmed by monitoring data showing a removal efficiency of more than 95%. Na_3NTA released to the aquatic environment is anticipated to remain in the water phase.

In the literature concentrations of NTA in waste water sludge mainly from Central- and Northern Europe as well as Northern America have been reported in the range of 10-50 mg NTA/kg dry weight (Danish EPA, 1995). The data are around 20 years old and most probably do not reflect the current situation. More recent surveys of sludge do not include information on NTA. Due to the degradability of the substance, it can be anticipated that Na_3NTA contained in sludge and subsequently applied on agricultural soils will degrade after application and mixing in the aerobe zone. No data are available on NTA in soil.

4.4 Hazardous waste

According to the EU waste legislation, implemented in Denmark by the Danish Statutory Order on waste (Danish Ministry of Environment, 2012), waste is considered as hazardous if it contains a certain concentration of a hazardous chemical substance. The concentration level in wastes that render a waste hazardous corresponds to those used for the classification of mixtures of substances[3]. *Carc. 2* is one of the characteristic ones mentioned with a limit of 1 % ww. If the waste contains a mixture including one or more chemical substances that meet the properties, the assessment must take into account the total content of these elements.

4.5 Summary and conclusions

The main source of Na_3NTA to the environment is waste water from formulation and use of products containing Na_3NTA. A large percentage (up to >95%) of Na_3NTA is expected to be removed in the waste water treatment plants. Recent measurement of Na_3NTA in sludge is not available, but concentrations in sludge between 10-50 mg NTA/kg dry weight have been reported in 1995. Once Na_3NTA is released to the aquatic environment it is expected to remain in the water phase and is not expected to distribute to the sediment compartment.

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[3] Directive 1999/45/EC of the European Parliament and of the Council of 31 May 1999 concerning the approximation of the laws, regulations and administrative provisions of the Member States relating to the classification, packaging and labelling of dangerous preparations

5. Environmental effects and exposure

A European Commission Risk Assessment Report was carried out by the Commission in 2005 with Germany as the Rapporteur (European Commission 2005). Information retrieved from this report is included in the sections below. The report covers the same general uses as identified in this report, i.e. textile cleaning and cleaning agents, and the main conclusions from the EU Risk Assessment regarding the environment were:

For all life-cycle steps, the PEC/PNEC ratios are below 1 for all environmental compartments. Therefore, a risk for the environment is not expected. There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already (European Commission 2005).

Furthermore, in the current report it is concluded that Na_3NTA does not fulfil the requirements for P, B and T criteria and is therefore neither a PBT nor a vPvB-substance.

5.1 Environmental hazard

5.1.1 Classification

A harmonised classification is available for Na_3NTA (CAS No. 5064-31-3) addressing health. No harmonised classification is however available for the environment.
There are 1,267 notified classifications reported by industry. 829 of these notified classifications are identical to the harmonized classification and none of the notified classifications addresses the environment.

A notified classification and labelling of nitrilotriacetic acid (CAS No. 139-13-9) is available from the ECHA CLP inventory:

- Acute chronic 3

Hazard statements:

- Harmful to aquatic life with long lasting effects (H412).

There is no notified classification for the disodium salts (CAS. No 1567-20-6).

5.2 Fate and distribution in the environment

5.2.1 Abiotic degradation:

Photolysis

The Fe(III)NTA complex was found to undergo photolysis when exposed to sunlight. In a 1 mM aqueous solution irradiated with sunlight in July (t = 25 – 30°C), the concentration of NTA decreased rapidly over a period of 9 hours. As reaction products, iminodiacetate (IDA), CH2O and CO2 were detected. IDA is very slowly degraded to glycine under the same test conditions. Complexes with other metals were irradiated for a week: while no significant change was found for Pb(II) and Cd(II), a marginally decrease for Cr(III) and a marked (70%) decrease for Cu(II) was observed.

Hydrolysis

There is no reported information on hydrolysis. The REACH registrant has waived the endpoint using the justification "scientifically unjustified". The reason is that the substance is readily biodegradable and testing for hydrolysis is therefore not necessary (REACH Registration data, 2013).

5.2.2 Biotic degradation:

Aerobe degradation

In the OECD Test Guideline no. 301 addressing aerobe degradation, a test substance is considered to be readily biodegradable if the pass level of the test corresponding to 70% removal of DOC (Dissolved Organic Carbon) or 60% of ThOD (Theoretical Oxygen Demand) or $ThCO_2$ production for respirometric tests is reached.

A series of laboratory degradation tests are available for Na_3NTA. In these tests Na_3NTA was found to be readily biodegradable (biodegradation ranging between 75 and 100%) (European Commission, 2005).

A degradation constant of 0.672 h^{-1} is reported for non-complexed NTA in the risk assessment report (European Commission, 2005).

Degradation of complexed NTA

It was demonstrated by several investigations that biodegradation of NTA can be influenced by the presence of metals, and the degradation also depends on which metals are present. The available investigations evaluated in the risk assessment report show that degradation constants vary between 0 h^{-1} (complexed with mercury (Hg^{2+})) and 0,072 h^{-1} (complexed with lead (Pb^{2+})) (European Commission, 2005).

Both in waste water and surface water, heavy metal ions may be present at concentrations, which may inhibit degradation. For environmental exposure assessment, where high concentrations of calcium or metal ions could be present, e.g. sediments, the degradation properties of the complexed NTA instead of the non-complexed NTA have to be taken into account (European Commission, 2005). However, it must also be mentioned that non-degradable complex species can be transformed into degradable compounds by metal exchange reactions.

5.2.3 Adsorption/desorption

According to the REACH registration data, 2 reliable studies are available on adsorption/desorption (no standard guidelines were followed). Na_3NTA (5064-31-3) is not strongly adsorbed to soil and sand. As a cut-off value a Log Kow <3 can be applied (not binding strongly to sediment and soil) (ECHA, 2013) corresponding to a Kd of approximately <20-50. Reported Kd values vary depending on the type of soil studied, Kd=0.22 (sand) and Kd =2.8 (loam).This is in agreement with the high water solubility of the substance (REACH Registration data, 2013).

5.2.4 Elimination in sewage treatment plants

Several studies on the elimination of H_3NTA/ NTA in sewage treatment plants (STP) have been conducted and reported in the EU risk assessment report. Some studies report the removal of "NTA" without further identification of the test substance, others report the removal of "H_3NTA". However, these results show that NTA is generally efficiently removed in municipal treatment plants with rates up to over 95% under normal operation conditions. The reported results indicate that the removal rate from treatment plants depends on the temperature. This is due to the overall lower biological activity at low temperatures leading to lower degradation rates of all organic substances. Results are summarised in the table below (Table 5.1).

TABLE 5.1
MEASURED ELIMINATION OF NTA/H_3NTA IN SEWAGE TREATMENT PLANTS (EUROPEAN COMMISSION, 2005)

Country	Concentration in influent	Concentration in effluent	Removal rate [%]
Netherland	Added H_3NTA up to 40 mg/L	-	93-98.9
Germany	196-562 µg NTA/L	6.6-23.1 µg/L	93.2-98.5 (winter, t = 11-13°C)
Switzerland	300-1,500 µg NTA/L	-	97
Canada	-	-	>95 (summer) <50 (winter t = 0.5-3°C)
Experimental study, Location not stated	15 mg H_3NTA/L	-	98 (t = 10-17.5°C) 85 (t< 6°C)
Experimental study, Location not stated	20 mg NTA/L 40 mg NTA/L	-	70-80 (t> 10°C) 60-70 (t<10°C) 67-82 (t> 10°C) <50-67 (t<10°C)

"-": No information

5.2.5 Biodegradation in natural waters

The biodegradation of NTA has been studied in natural waters. The available studies demonstrate that NTA is biodegraded in freshwaters with half-life in the range of several hours to some days, after an acclimation period in the range of days to weeks. For the exposure calculations in the risk assessment report, a half-life of 5 days is used. There is no further argumentation for applying this value in the report (European Commission, 2005).

Degradation is considerably influenced by temperature. NTA degradation was studied in a Canadian creek receiving municipal sewage from a biological treatment plant. The study was designed to determine the influence of temperature under summer and winter extremes. During the summer period, the NTA concentration was consistently less than the detection limit of 10 µg/L. During winter when the stream temperatures ranged from 0.5 to 3°C and NTA removal through the treatment plant was less than 50% (Tabel 5.1), the downstream concentrations averaged to 106 µg/L (European Commission, 2005).

The effects of salinity and Dissolved Organic Carbon (DOC) on the kinetics of degradation of NTA were studied in a Canadian river estuary with a prior history of NTA exposure. Degradation occurred immediately with no apparent lag phase, indicating that the microbial communities were adapted as a result of prior NTA exposure. There was no consistent effect of salinity (range 4 – 19%) or DOC (range 2-12 mg/L) levels on NTA degradation rates. Degradation followed first-order kinetics and the estimated mineralisation half-life was about 2 days. No details on the test conditions are given in the risk assessment report (European Commission, 2005).

5.2.6 Biodegradation in soil

In the GWSS slurry (10 g soil + 10 ml groundwater), NTA (initially 5 µg/l) was degraded with half-lives of 155 hours under anaerobic conditions and 128 hours under aerobic conditions. Similar results were obtained with groundwater samples from a septic tank plume. The biodegradation activity was generally highest in the area immediately to the septic tank tile field: nearest the tile field a half-life of 0.78 days was determined, while in 40 m distance the half-life decreased to 9 days (European Commission, 2005).

5.2.7 Biodegradation in sediment

The only available study demonstrated an NTA degradation half-life of 1 day. The study was conducted at a temperature of 30°C which is far above typical environmental conditions, thus the real degradation rate is possibly lower. No studies with anaerobic sediments are available. Half-lives are estimated to be 20 d (European Commission, 2005).

5.2.8 Biodegradation in sludge

NTA was found to degrade in anaerobic sludge, and a study where H_3NTA was added at a concentration of 10-30 mg /L is reported in the risk assessment report. However, it should be noted that this study was performed at 35°C which is quite high for Danish conditions. No half-life is reported for this study (European Commission, 2005).

Half-life values applied in the exposure assessment are summarised in Table 5.2 below.

TABLE 5-1
BIODEGRADATION HALF-LIFES OF NTA USED IN THE EXPOSURE ASSESSMENT

Parameter	Half-life
Water	5 days
Sediment (aerobe)	9 days*
Sediment (anaerobe)	20 days
Soil	9 days
Air	∞

*the value for soil is applied in the risk assessment for sediment
∞: No relevant releases to air are expected therefore no degradation expected in this compartment

5.3 Effects in the environment

5.3.1 Effects in the aquatic compartment

Information on the ecotoxicological effects of Na_3NTA is reported in the EU RAR, and the results from tests showing the highest toxicity towards freshwater organisms within a trophic level are reported in Table 5.3.

Tests on acute lethal toxicity to fish have resulted in 96-hour LC_{50} values in the range of 98 – 487 mg/L. Long term toxicity tests with fish are also reported. The lowest no observed effect concentration (NOEC) reported was > 54 mg/L (also the highest concentration tested) and was reported from a test of 224 days duration. Also an EC1 = 20.2 mg/L and an EC10 =96 mg/L are reported from a study with *Onchorhynchus mykiss* and *Lepomis macrochirus*, respectively (European Commission, 2005).

Effect Concentrations (EC_{50}-values) in the range of 79 - >1,000 mg/L (24-96 hours exposures) are reported from acute toxicity test with crustaceans. The lowest no observed effect concentration (NOEC) was found in a long term test (21 weeks exposure) with *Gammarus pseudolimnaeus*, which resulted in a NOEC = 9.3 mg/L Na_3NTA. This value is applied in the calculation of the Predicted No Effect Concentration (PNEC) (European Commission, 2005).

Results from tests with algae were reported with EC_{50}-values (96-120 hours) ranging from 133 to >560 mg/L. NOEC values were reported as 5-80 mg/L, where the higher NOEC-values were from tests with metal enriched media (European Commission, 2005 and REACH registration data).
In these tests the higher NOEC values indicated that NTA was forming complexes with the metals in the media making them less bioavailable. The test results with algae are not applied in the calculation of the PNEC since these results, in the risk assessment report, were evaluated to be caused by nutrient deficiency (European Commission, 2005).

Regarding sediments organisms there are neither monitoring data, nor toxicity tests with benthic organisms available. The Na_3NTA concentration could be modelled using the equilibrium partitioning method (European Commission, 2005).

TABLE 5-2:
RESULTS FROM AQUATIC (FRESHWATER) TOXICITY TESTING WITH NA_3NTA (EUROPEAN COMMISSION, 2005) AND (REACH REGISTRATION DATA, 2013). VALUE IN BOLD IS APPLIED IN THE AQUATIC RISK ASSESSMENT.

	Organism	Duration [h]	Endpoint	Endpoint [mg/L]
Acute	*Fish -Oncorhynchus mykiss*	96	Flow through lethality test	LC_{50} = 98
	Crustacean -Daphnia magna	24	Immobilization test	EC_{50} = 79
	Algae - Nacicula seminulum	96	Static - biomass	E_bC_{50} = 133
Chronic	*Fish - Oncorhynchus mykiss*	27 d	Embyo-larval test	EC_1 = 20.2
	Fish- Lepomis macrochirus	28 d	Flow through lethality test	LC_{10} = 96
	Fish - Pimephales promelas	224	Generation cycle test Endpoints: survival, spawning activity, and	NOEC =54

	Organism	Duration [h]	Endpoint	Endpoint [mg/L]
			egg hatchability at the highest tested concentration: 53.9 mg/L	
	Crustacean- Gammarus Pseudolimnaeus	21 weeks	Generation cycle test	**NOEC = 9.3**
	Algae *(Selenastrum capricornutum, Scenedesmus subspicatus and Chlorella vulgaris)*	120 h	Static- cell concentration	NOEC = 5

5.3.2 Predicted No Effect Concentration for aquatic organisms ($PNEC_{aquatic}$)

Long-term tests are available for fish, crustaceans and algae. The most sensitive endpoint reported as an EC_{50}- or an NOEC-value is applied in the calculation of the Predicted No Effect Concentration (PNEC) dividing the selected endpoint with an assessment factor (AF). The effect on algae is believed to be caused by nutrient deficiency, and therefore the most sensitive endpoint was found for the amphipod *Gammarus pseudolimnaeus* with a long term (21 weeks) NOEC of 9.3 mg/L. Acute and chronic toxicity data are available for the three trophic levels fish, crustacean and algae. According to the guideline, an assessment factor of 10 has to be used (ECHA, 2008). Therefore, a $PNEC_{aquatic}$ of 0.93 mg/L is determined for freshwater in the risk assessment report (European Commission, 2005 and REACH registration data, 2013).

5.3.3 Effects on microorganisms

A test on cell multiplication inhibition with different protozoa was performed. The lowest effect on microorganisms was in a test with protozoa where a 72-h EC5 > 540 mg/L H_3NTA was reported (European Commission, 2005).

5.3.4 Predicted No Effect Concentration ($PNEC_{STP}$) – microorganisms

A $PNEC_{STP}$ > 540 mg NTA/L was calculated dividing the EC5 > 540 mg NTA/L derived for microorganisms with an assessment factor of 1 (European Commission, 2005).

5.3.5 Effect on terrestrial organisms

No data are reported on terrestrial toxicity in the EU RAR and REACH registration data. Studies are not conducted since exposure of the terrestrial compartment is not likely due to the use (complexing agent and cleaning agents) and subsequent disposal of Na_3NTA via waste water (European Commission, 2005 and REACH registration data, 2013).

5.3.6 Effect in the atmosphere

Because there are no fumigation tests available, an effects assessment for this compartment cannot be performed in the risk assessment report (European Commission, 2005). Due to the low vapour pressure the substance is however not anticipated to evaporate ($P = 1*10^{-7}$ Pa 25 °C) (REACH Registration data, 2013).

5.3.7 Combination effects

No data on combination effects have been retrieved within this report. However, as previously mentioned a complexation agent like NTA may carry different kinds of metals which can be released when NTA is degraded, making the metals available to aquatic organisms. The presence of NTA may therefore influence the toxicity of metals towards aquatic organisms.

5.3.8 Bioaccumulation

Table 5.4 shows experimental BCF values obtained after exposure of aquatic organisms to a Na_3NTA concentration of 400 µg/l. Values obtained were between 1 and 20 L/kg. According to the ECHA Guidance Document R.11 on PBT assessment (ECHA, 2012), a substance fulfills the criteria for bioaccumulation if the BCF is > 2000 L/kg. Moreover, the very low Log P (octanol/water) at -2.6 indicates a very low potential for bioaccumulation. This supports the conclusion that biomagnification via the food chain is highly unlikely (European Commission, 2005).

TABLE 5-3
RESULTS FROM BIOACCUMULATION STUDIES WITH NA_3NTA

Species	BCF (L/kg)	Equilibrium after (h)
Fish (*Brachidanio rerio*)	1-3	96
Guppy *(Lebistes reticulatis)*	Male: 1-2 Female: 6	72-96
Goldfish (Carassius auratus)	1-2	72-96
Snail *(Lymnea stagnalis)*	8 ≥ 20	3-7 days ≤ 72 days
Notoneda *species*	2-4	48
Tubificidae	5-10	5 days
Frog larvae *(Rana temporaria)*	5-10	96 hours
Frog *(Rana temporaria)*	<1	-
Crayfish *(Procambarus)*	1	4 hours

"-": no data

5.3.9 PBT and vPvB assessment

The PBT (Persistent, Bioaccumulative and Toxic) and vPvB (very Persistent and very Bioaccumulative) criteria as stated in REACH Annex IIIV are shown in Table 5.12 below.

Based on these criteria it can be concluded that since NTA is readily biodegradable and the longest half-life = 20 days is reported for sediment, NTA does not fulfill the requirement for persistent (P) and very persistent (vP).

Also NTA has a Log P_{ow} of -2.6, and a low potential for bioaccumulation is confirmed by experimentally determined BCF values at 1-6 in fish. NTA can therefore not be considered as bioaccumulative (B) and very bioaccumulative (vB).

Finally the toxicity to aquatic organisms does not fulfill the 'T' criteria for PBT at < 0.01 mg/L.

The conclusion is that NTA does not fulfill the P, B and T criteria for PBT substances and the vP and vB criteria for vPvB substances according to REACH Annex XIII (ECHA, 2012; European Commission, 2005).

TABLE 5-4
PBT AND VPVB CRITERIA ACCORDING TO REACH ANNEX VIII (ECHA 2012)

Criteria	PBT-criteria	vPvB-criteria
Persistence	T1/2 > 60 days in marine water, or T1/2 > 40 days in fresh- or estuarine water, or T1/2 > 180 days in marine sediment, or T1/2 > 120 days in fresh- or estuarine sediment, or T1/2 > 120 days in soil.	T1/2 > 60 days in marine, fresh- or estuarine water, or T1/2 > 180 days in marine, fresh- or estuarine sediment, or T1/2 > 180 days in soil.
Bioaccumulation	BCF > 2,000 L/kg	BCF > 5,000 L/kg
Toxicity	NOEC or EC10 (long-term) < 0.01 mg/L for marine or freshwater organisms, or - substance meets the criteria for classification as carcinogenic (category 1A or 1B), germ cell mutagenic (category 1 or 1B), or toxic for reproduction (category 1A, 1B or 2) according to the CLP Regulation, or - there is other evidence of chronic toxicity, as identified by the substance meeting the criteria for classification: specific target organ toxicity after repeated exposure (STOT RE category 1 or 2) according to the CLP Regulation	Not applicable

5.4 Environmental exposure

5.4.1 Sources of release

During the production, formulation and use of Na_3NTA releases may occur via waste water into the aquatic compartments. According to data from the producers, the total yearly release into the aquatic compartments amounts to 24.1 tonnes/year (European Commission, 2005). Moreover, NTA will be released into the water environment as a result of its use as a complexing agent in cleaning agents etc. which will be released with waste water. Due to the use and disposal described above, release via solid waste is not expected.

Estimation of the PEC_{local}

Estimated predicted environmental concentrations (PEC_{local}) from the production, formulation and use of Na_3NTA, as specified in the European Commission (2005), are summarised in the tables below (Table 5.5-5.6).

Table 5.5 shows the results from the calculation of the estimated predicted environmental concentrations (PEC) of NA_3NTA from production.

TABLE 5.5
ESTIMATED PREDICTED ENVIRONEMENTAL CONCENTRATION (PEC_{LOCAL}) IN THE AQUATIC ENVIRONMENT FROM FOUR PRODUCTION SITES OF Na_3NTA (EUROPEAN COMMISSION, 2005)

Site	PEC_{local}	Release
B	<5.1 µg/L	<370 g/year
C	5.6 µg/L	7.6 tonnes/year
D	<450 µg/L	10.8 tonnes/year
E	14 µg/L	5.7 tonnes/year

Table 5.6 shows the results from the calculation of the estimated predicted environmental concentration (PEC) of NA_3NTA from formulation and use in cleaning agents and in cleaning of textiles. In the calculations it was assumed that all releases are to waste water, and a total use volume of 17,905 tonnes/year was applied for cleaning agents (industrial use) and 973 tonnes/year was applied for textile cleaning (both household and industrial use) which corresponded to the amount used in 2000. Based on the calculations, the PEC from cleaning agents was 49 µg/L for both formulation and use, and from cleaning agents the PEC was 20 µg/L and 500 µg/L for formulation and use, respectively.

TABLE 5.6
ESTIMATED PREDICTED ENVIRONMENTAL CONCENTRATION (PEC) IN THE AQUATIC ENVIRONMENT FROM *FORMULATION AND USE* OF NA_3NTA (EUROPEAN COMMISSION, 2005)

	Formulation	Use
Cleaning agents	49 µg/L	49 µg/L
Textile cleaning	20 µg/L	500 µg/L

Similar calculations have not been performed for soil, sediment, air and sewage treatment plants (STP).

Estimation of $PEC_{regional}$ and $PEC_{continental}$

For the regional exposure assessment it is assumed that the total European Na_3NTA consumption volume (26,642 tonnes in 2000) is released into the waste water. Furthermore, 10% of the European releases are taken for the regional and 90% for the continental scenario. Table 5.7 below shows the release amounts and the resulting PECs based on calculations by EUSES.

TABLE 5.7
CALCULATED $PEC_{REGIONAL}$ AND $PEC_{CONTINENTAL}$ (STP = SEWAGE TREATMENT PLANT) (EUROPEAN COMMISSION, 2005)

Parameter	Regional	Continental
Release into waste water [tonnes/year]	2,664	23,978
Release into STPs (70%) [tonnes/year]	1,865	16,785
Release via STP effluents [tonnes/year]	93	893
Direct release into hydrosphere (30%) [tonnes/year]	799	7,193
Total release into hydrosphere [tonnes/year]	892	8,032
$PEC_{aquatic}$ [µg/L]	4.2	0.48
PEC_{air} [µg/m³]	$9.4 * 10^{-16}$	$1.1*10^{-16}$
$PEC_{agricultural\ soil}$ [µg/kg dw]	$6.9*10^{-10}$	$7.9*10^{-11}$
$PEC_{industrial\ soil}$ [µg/kg dw]	$2.6* 10^{-9}$	$3.0*10^{-10}$
$PEC_{natural\ soil}$ [µg/kg dw]	$2.6* 10^{-9}$	$3.0*10^{-10}$
$PEC_{sediment}$ [µg/kg dw]	4,2	0.48

STP: Sewage Treatment Plant

5.4.2 Monitoring data

In Tables 5.8-5.11 below results from environmental monitoring are reported.

Sewage treatment plants

Monitoring data from sewage treatment plants (STP) (Table 5.8) confirm a removal of NTA in the STP where the concentration in the influent is higher than in the effluent. The concentration in the effluent is also quite constant and for most sites below 100 µg/L (except UK where concentrations are as high as 740 µg/L). The EU report does not give any information on the number of measurements.

Previously, concentrations in waste water sludge mainly from Central and Northern Europe as well as Northern America were reported in the range 10-50 mg/kg dry weight (Danish EPA, 1995).

TABLE 5.8
NTA CONCENTRATIONS IN IN- AND OUTFLOW OF STREAMS FROM SEWAGE TREATMENT PLANTS (EUROPEAN COMMISSION, 2005)

Location	Year		Concentration NTA (µg/L)
Zurich, Glatt	Winter 1984	Influent	40-380
		Effluent	3-30
	Winter 1987	Influent	330-1,490
		Effluent	5-50
Hessen	1987	Influent	100-300
		Effluent	<2—26
Bielefeld-Heepen	1987	Influent	63-68
		Effluent	8-16
UK (10 plants)	1982	Effluent	<2-740

Surface water
Monitoring data from Germany, UK and Austria are available for surface water.
NTA is continuously monitored in German surface waters. In the following Table 5.9, measurements from 1997/98 are presented, the results are sorted in concentration ranges, the 90%ile values are considered. From a total of 2,283 measurements, the highest detected concentration was 100 µg/L H_3NTA (= 135 µg/L Na_3NTA). However, most sites (65) have concentrations in the range of 1-10 µg/L. This figure corresponds well with the estimated regional $PEC_{aquatic}$ = 4.2 µg/L concentration in Table 5.7.

TABLE 5.9
H3NTA CONCENTRATIONS GERMAN SURFACE WATER 1997/98 (EUROPEAN COMMISSION, 2005)

90%ile concentration [µg/L]	Number of sites
0-1	2
1-10	65
10-100	17
Total	**84**

Samplings of surface waters in the UK were carried out in April and May 1992 (Table 5.10). And sampling sites are classified as class 1-3 polluted, where class 3 is the highest degree of pollution (not further defined in the EU RAR). In Class 3 rivers, the mean and medium concentrations were 16 µg/L and 10 µg/L, respectively. There were no identifiable differences between the means for the Class 1 or Class 2 rivers for which both the overall mean and the medians were less than 2 µg/L (European Commission, 2005).

TABLE 5.10
RESULTS FROM A UK SURVEY: NTA CONCENTRATIONS SURFACE WATER 1992 (EUROPEAN COMMISSION, 2005)

Location	Mean measured concentration [µg/L]	Median measured concentration [µg/L]
Class 3 river (highly polluted)	16	10
Class 1 and 2	<2	<2

In Austria the measured concentration of NTA in surface water was below the limit of detection (<2 µg/L) in 78 of 85 samplings of surface water collected (Table 5.11). In six sample places, a maximum value between 6 and 10 µg/L was measured. In one case (sample from a channel near Vienna), the medium and highest values were 42 and 231 µg/L, respectively (European Commission, 2005). This shows that the Austrian measurements in most cases are below or in the same range as the estimated value $PEC_{aquatic}$ =4.2 µg/L.

TABLE 5.11
NTA CONCENTRATIONS MEASSURED IN AUSTRIAN SURFACE WATER. THE SURVEY INCLUDED A TOTAL OF 85 LOCATIONS (EUROPEAN COMMISSION, 2005)

Number of location	Mean measured NTA concentration [µg/L]	Highest measured NTA concentration [µg/L]
78	<2	<2
6	-	6-10
1	42	231

During a monitoring campaign in 10 Swiss rivers performed in 1990, the yearly average NTA concentrations were in the range of 0.8 – 10 µg/L, which is close to the estimated value $PEC_{aquatic}$ =4.2 µg/L. Measurements in 5 lakes near drinking water works performed in 1993 resulted in a maximum concentration of 0.5 µg/L (European Commission, 2005).

When comparing the calculated $PEC_{aquatic}$ (Table 5.7) with the monitoring data in Tables 5.8 – 5.11, it can be seen that the available monitoring data are lower than the PEC. This can be explained by the more conservative approach which is applied when applying the default values for calculating the PEC which are incorporated in the EUSES program.

NTA and heavy metal interaction
Raw sewages always contain a more or less high amount of heavy metals. In general, heavy metals are strongly adsorbed onto sewage sludge thus being removed from the water phase. Complexation agents like NTA may carry the metals in the soluble phase. If the complexation agent is degraded the metal ions become adsorbed to the sludge and will be removed from the water phase. If, however, the complexation agent is not degraded, the metal ions are kept in a soluble chemical complex leading to increased metal concentrations in the effluent.

From studies on the influence of NTA on heavy metal concentrations in waste water treatment plants, it can be concluded that increased heavy metal releases into the aquatic environment can occur with high NTA loads, if the metals are forming a complex with NTA, or when NTA degradation is disturbed (European Commission, 2005).

Sediment
No monitoring data for sediments are available (European Commission, 2005).

Atmosphere
Na_3NTA and NTA have very low vapour pressures (calculated values at 1*10-7 Pa 25 °C and 9.54*10-7 Pa at 25 °C, respectively, (Table 1.2 and 1.3)) and are not expected to evaporate from an aqueous solution (European Commission, 2005).

5.5 Environmental risk characterisation

The scientific literature on environmental fate and toxic effects mostly refers to Na_3NTA regarding the amounts and concentrations. Thus, for the environmental risk assessment all production and use volumes applied were also as Na_3NTA equivalents.

Applying the assessment factor method, a $PNEC_{aquatic}$ of 0.93 mg/l and a $PNEC_{STP}$> 540 mg/l was determined.

The risk is expressed by the calculation of a risk characterisation ratio (RCR):

RCR = PEC/PNEC,

Where a RCR above 1 indicates a risk to the compartment and a RCR below 1 indicates that no risk is expected.

5.5.1 Aquatic compartments

In the following table (Table 5.13), the results for all calculated exposure scenarios are listed:

TABLE 5.13
RISK CHARACTERISATION FOR THE AQUATIC COMPARTMENT (95 % REMOVAL IN SEWAGE TREATMENT PLANTS (STP))

Scenario	$PEC_{local\ aquatic}$ (µg/L)	$RCR_{aquatic}$	$C_{effl.}$ (mg/L)	$C_{effl.}/PNEC_{STP}$ ($RCR_{STP.}$)
Producer A	Only import			
Producer B	<5.1	<0.005	No STP	
Producer C	5.6	0.006	0.054	<0.0001
Producer D	<450	<0.48	No STP	
Producer E	14	0.015	1.1	<0.002
Textile cleaning, formulation	20	0.022	0.16	<0.0003
Textile cleaning, use	500	0.54	5.0	<0.0009
Cleaning agents, formulation	49	0.053	0.45	<0.0008
Cleaning agents, use	49	0.053	0.45	<0.0008

The available studies on biodegradation reveal that NTA is removed in municipal treatment plants with rates generally above 95% under normal operation conditions. Also some studies, but not all, showed a lower removal during winter (<50%).

For the exposure calculations in this assessment, a removal of 95% was used. Based on this removal, all calculated RCRs were below 1 indicating that no risk is anticipated (Table 5.3). Assuming a worst case approach (i.e. a removal rate of 50%), only the PEC/PNEC ratio of the scenario for the use in textile cleaning will be > 1 (2.0) i.e. indicating that a risk cannot be excluded. Taking into account that this scenario is nearly completely based on default values, it is concluded that even with a lower biodegradation there is no risk to the aquatic compartment (European Commission, 2005).

Regarding sediments there are neither monitoring data, nor available toxicity tests with benthic organisms available. Because of the low partitioning coefficients (Log P_{ow} = -2.62), no accumulation in sediments is expected (please refer to section 5.2 on adsorption/desorption). Thus a risk assessment of this sub-compartment is not necessary (European Commission, 2005).

5.5.2 Influence on the distribution of heavy metals

The influence of NTA on the distribution of heavy metals was examined. It was concluded that significant remobilisation processes, i.e. metal release, are only expected in extreme cases, i.e. when high NTA amounts are released. This would lead to increased concentrations of the metals with high conditional complex-formation constants. With the concentrations estimated in this risk assessment, those effects are not expected (European Commission, 2005).

5.5.3 Atmosphere

No relevant releases into the atmosphere are expected (based on calculated vapour pressure: P = $1*10^{-7}$ Pa 25 °C); therefore a risk characterisation for this compartment is not relevant (European Commission, 2005, REACH Registration data, 2013).

5.5.4 Terrestrial compartment

No relevant releases into soils are expected; therefore a risk characterisation for the terrestrial compartment is not considered necessary in the risk assessment report (European Commission, 2005).

Also a high removal rate in sewage treatment plants is observed (>95%) and participation to sludge is not expected (log Pow =-2.6). Therefore, further transfer from sludge to agricultural soil is not expected (European Commission, 2005). A concentration in waste water sludge mainly from Central and Northern Europe as well as Northern America has been reported in the range 10-50 mg/kg dry weight (Danish EPA, 1995). However, because the substance is readily biodegradable, it will most likely be removed after mixing of the sludge in the aerobe zone.

5.6 Summary and conclusions

In the EU RAR, the environmental risk was assessed for the aquatic, terrestrial and atmospheric compartments. Toxicity data were available for the aquatic compartment and for microorganisms representing the microflora in sewage treatment plants.

The calculated risk characterisation ratios for all life-cycle steps, routes of exposure and environmental targets did not indicate a risk for the environment (RCR < 1). The calculations were performed for the main uses: textile cleaning and cleaning agent (formulation and use). Other uses will result in relatively lower releases and entail less corresponding lower risks to the environment.

The conclusion of no concern is strengthened by the general trend of a reduced production and use of Na_3NTA leading over time to an overall reduction of the releases and exposure of the environmental compartments. The EU RAR concludes that there is no need for further information and/or testing, and for risk reduction measures beyond those which are being applied already (European Commission, 2005).

The available monitoring data from European freshwater environments in general correspond well with the predicted regional concentration $PEC_{aquatic}$= 4.2 µg/L.

Based on the criteria for PBT and vPvB, it was concluded that since Na_3NTA is readily biodegradable and since the longest half-life = 20 days, reported for sediment, NTA does not fulfill the requirement for persistent (P) and very persistent (vP).

Also Na_3NTA has a Log P_{ow} of -2.6, and a low potential for bioaccumulation (BCF values at 1-6 in fish). Na_3NTA can therefore not be considered as bioaccumulative (B) and very bioaccumulative (vB).

Finally, the toxicity to aquatic organisms did not fulfill the 'T' criteria for PBT at < 0.01 mg/L.

Overall, it can be concluded that the available information confirm the conclusion of the European Risk Assessment (Environment) from 2005 on 'no risk' in the environmental compartments.

6. Human health effects and exposure

A Risk Assessment covering human health effects and exposure has been carried out by the Commission. In 2008 the environmental risk assessment report was published (European Commission, 2008) with Germany as the Rapporteur. Information retrieved from this report is included in the sections below. The main conclusions from the EU Risk Assessment regarding the human health were:

Workers: There is a need for limiting the risks; and risk reduction measures, which are already being applied, shall be taken into account. More specifically, the conclusion refers the need for limiting the risks due to repeated dose toxicity and carcinogenicity which are the effects with the lowest critical exposure levels. Especially dermal exposure has to be reduced by use of Na3NTA in the formulation process without Personal Protection Equipment (PPE) and by high pressure cleaning without PPE. Inhalation exposure has to be reduced in the production of NTA and for the use of Na3NTA in the formulation process without Local Exhaust Ventilation (LEV) (European Commission, 2008).

Regarding consumers: There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already (European Commission, 2008).

Regarding man exposed indirectly via the environment: There is at present no need for further information and/or testing and for risk reduction measures beyond those which are being applied already (European Commission, 2008).

The Risk Assessment report was followed by a so called EU Risk reduction strategy (European Commission, 2008a). The strategy recommended to establish an occupational exposure limit for NTA and to apply the proposed classification from the EU-working group on classification and labelling of dangerous substances. A harmonized classification according to these recommendations has now been established for Na_3NTA, but there is currently no community OEL for the substance.

6.1 Human health hazard

Since there are no available studies of direct effects from human exposure to NTA in the work environment or after consumer use, the human risk assessment and classification in the EU have mainly been based on animal studies and *in vitro* tests.

According to the CLP Regulation (EC No 1272/2008) NTA is harmful if swallowed (Acute Tox. 4), causes serious eye irritation (Eye Irr., 2) and is suspected of causing cancer (Carc. 2).

Due to NTA's recent classification as a suspected carcinogen the EU Scientific Committee on Consumer Safety (SCCS) (2010) assessed the risk to consumers through exposure from cosmetics. They considered studies of different sodium salts of NTA and with different degree of hydration. The assessment thus included administration of both trisodium nitrilotriacetate (Na_3NTA), trisodium nitrilotriacetate monohydrate ($Na_3NTA.H_2O$), of other salts such as disodium nitrilotriacetate monohydrate ($Na_2NTA.H_2O$), and of nitrilotriacetic acid (H_3NTA) as relevant information, because these compounds are dissociated under physiological conditions into the sodium cations and the respective anionic species of nitrilotriacetic acid depending on the actual pH in solution.

6.1.1 Hazard identification

6.1.1.1 Toxicokinetics and metabolism

In an unpublished industry study the absorption in the gastro-intestinal tract after administration of non-labelled Na_3NTA to rats by gavage was measured to about 50% of the dose. The urinary excretion half-life was determined as 5-6 hrs (European Commission, 2008).

In rats, a single dose of ^{14}C-labeled NTA in solution was almost completely absorbed and thereafter rapidly excreted unchanged in the urine (Michael & Wakim, 1971). Within 1 hr about 31% of the oral dose was identified in the urine, and after 72 hrs. 95% of the dose had been eliminated by the urine and 2% with faeces. The rest accumulated mainly in the blood (serum), kidneys, and bone (tibia). After repeated dosing, more NTA accumulated in the bone and less was excreted in the urine. Large species differences were observed concerning urinary and faecal excretion. After a single oral administration of ^{14}C-labelled NTA, respectively, 23%, 69% and 14% of the dose was excreted in the urine in rabbit, dog and monkey after 72 hrs. The amounts excreted through faeces were 33%, 5%, and 65%, respectively. The data indicate that the absorption in rabbits is less or slower. A considerable 80% excretion in the urine of dogs found in another study confirmed the high excretion in that animal species, and that the blood concentration peaked after about 1 hour (Budny, 1972).

In mice, the absorption and excretion of NTA were rather similar to that in the rats (Chu *et al.* 1978). About 99% of the doses were eliminated unchanged after 24 hours, 96% in the urine and 3% in faeces.

In a study with 8 human volunteers receiving 10 mg ^{14}C-labelled NTA orally, the blood NTA level peaked at 6.5 ng/g serum after about 2 hours (Budny & Arnold, 1973). After 120 hours the faeces contained 77% of the radioactivity and 12% was recovered in the urine. Of that, 87% was excreted during the first 24 hours. Less than 0.1% was recovered as CO_2 in the expired air. In contradiction to the animal experiments the humans were exposed to NTA after fasting for 10 hours. That might have interfered with the absorption of NTA in the gastro-intestinal tract.

In Table 6.1 the results of the various studies are shown. The large species differences in absorption and excretion make it questionable directly to extrapolate toxicity from animal experiments to humans.

TABLE 6.1
ELIMINATION OF ORALLY ADMINISTERED ^{14}C-LABELED NTA AND SALTS IN VARIOUS SPECIES

Species	Dose (mg/kg b.w.)	% excreted in		Measured time after administration (hours)	Reference
		Urine	Feces		
Mouse	180	96	3	24	Chu *et al.* 1978
Rat	10	95	3	72	Michael & Wakim, 1971
Dog	50	69	5	72	Michael & Wakim, 1971
Rabbit	50	23	33	72	Michael & Wakim, 1971
Monkey	50	14	65	72	Michael & Wakim, 1971

Dog	20	80	3	72	Budny, 1972
Human	0.1-0.2	12	77	120	Budny & Arnold, 1973

Based on the animal studies SCCS (2010) found it appropriate to choose 50% as a default value for absorption of NTA after oral administration. However, since human data pointed to a lower absorption rate, a value of 20% was proposed and used for risk characterisation purposes.

Good data on skin absorption and uptake through the airways are missing. In an unpublished report, skin penetration of ^{14}C-labeled Na_3NTA through human skin has been studied in an *in vitro* test with prepared human skin. Test substance preparations corresponding to a high (40% NTA) and low (1% NTA) aqueous dilution were applied for an exposure time of 5 min. At the high dose only 0.001% was absorbed after 5 min., whereas up to 0.5% was absorbed of the low dose. Based on this single, unpublished study, using a very short exposure time, the European Commission (2008) selected for further risk characterisation as a worst-case assumption 1% absorption rate for the low dose and 10% for the high dose, where there is also a risk of damage to the skin and enhanced absorption. This assessment did not take into account that e.g. when consumers are exposed to NTA during use of cleaning products, their skin may be defatted and damaged.

6.1.1.2 Acute oral toxicity

The acute toxicities of NTA and its salts have been investigated in solution in some older and mostly unpublished studies with various experimental animals, mainly rats. The oral administration of the salts was in 20-80% solutions/suspensions. For rats the oral LD_{50} ranged from 1.10-5.34 g/kg b. w., for mice from 0.68-3.16 g/kg b. w., in monkeys 0.75 g/kg b. w. and for dogs >5 g/kg bw,b. w. (European Commission, 2008; Olsen & Jensen, 1989).

In conclusion, the acute oral toxicities of NTA and its sodium salts were low but sufficient for a hazard classification as harmful. However, the relevance and quality of some of the studies may be questionable.

6.1.1.3 Effects on the skin and mucous membranes

Since NTA is an acid and Na_3NTA is alkaline, skin irritation or corrosion are to be expected from contact with the solutions according to the proposed EU classification mentioned earlier.

There are no case reports on skin irritation or allergy, and trisodium NTA induced no skin sensitisation in the Draize test with 66 volunteers (Nixon, 1971).

Only unpublished inadequate industry studies of the effect of NTA and its salts on the skin of rabbits exist. A Draize test using a 25% aqueous solution of nitrilotriacetic acid trisodium salt monohydrate showed mild skin irritation with a slight to well-defined erythema and slight edema which reversed within 5 days. The aqueous solution (no information on the amount used) was applied to the clipped intact skin of 3 albino rabbits.

In a related study by the same company (Monsanto), doses of between 1,000-10,000 mg trisodium NTA hydrate/kg body weight as a 25% aqueous solution were applied to the intact skin of rabbits. At the highest doses activity and appetite were reduced and mild weakness appeared for 2-3 days. Therefore, 10,000 mg trisodium NTA hydrate/kg body weight was considered a minimum lethal dose (European Commission, 2008).

Installation in the eye of rabbits of 3 ml of a detergent product containing 11-35% Na_3NTA caused only a mild eye irritation and no permanent damage (Nixon, 1971).

Mild and moderate eye irritation, respectively, was detected in Draize tests using solutions of nitrilotriacetic acid trisodium salt monohydrate by two different company (BASF, Monsanto) studies (European Commission, 2008).

The NOAEL for local effects on the intact or abraded skin was considered to be 2.5% NTA in 2 mL solution (50 mg/kg bw/day) (SCCS, 2010).

6.1.1.4 Effects on the airways

In a pulmonary screening test with mice exposed to NTA containing aerosols for 5 minutes, slight sensory irritation was seen at a concentration of 0.22 mg/L (220 mg/m^3). At 1.09-1.41 mg/L, the irritation was moderate and at 7.6 mg/L, the irritation was serious. No deaths were observed. In a $^{4h}LC_{50}$ study with 10 white albino rats inhaling NTA powder at a concentration of 5 mg/L, there was some sign of adverse effects but all animals recovered after cessation of exposure. In a repeated inhalation study, male rats were exposed to micronised NTA in 6 hours a day for 4 days followed by a 14-day observation period. At the highest concentration of 2 mg/L, all rats had respiratory, nasal and eye irritation (European Commission, 2008).

6.1.1.5 Effects on internal organs

The NTA concentration in the urine may reach 200 times the blood concentration. The critical targets for NTA are organs of the urinary tract with lesions at several sites: in the kidneys, ureters and urinary bladder. High doses may cause enlarged and discoloured kidneys with severe tubular hyperplasia, vacuolisation and calcification of tubules with formation of insoluble CaNaNTA. Males are more susceptible than females, possibly because of lower pH values in male urine.

In rats exposed by gavage to NTA as its acid for 3 weeks, the NOAEL was 150 mg/kg bw/day. The LOAEL for the adverse effects on the kidneys after 30 days of exposure to rats was 0.73 mmol/kg bw/day (approximately 187 mg/kg bw/day). The lowest NOAEL for renal toxicity was 0.03% NTA in the diet (19 mg/kg bw/day) in a 2-year study by Nixon *et al.* (1972). Nevertheless, SCCS and European Commission 2008 used a NOAEL of 92 mg/kg bw/day for non-cancer endpoint after oral administration (see Chapter 6.4).

6.1.1.6 Effect on reproduction

In a two-generation feeding study with rats receiving 0.1% and 0.5% Na_3NTA in the feed continuously throughout two generations no effects on fertility, lactation or offspring were observed. In a teratology study, pregnant rabbits were daily exposed to up to 250 mg NTA in water administered via gavage during day 7-16 of gestation without any significant adverse effect (Nolen *et al.* 1971).

In another teratology study pregnant mice were exposed to 14C-labelled NTA intravenously, respectively orally, and the distribution of radioactivity at different time-intervals was studied with whole-body autoradiography. The results from the autoradiographic study revealed a strong accumulation of radioactivity in the skeleton present up to at least 48 h (the longest time-interval studied). There was also a strong accumulation of radioactivity in the fetal skeleton thus indicating transplacental transfer. No teratogenicity was detected in another group of mice exposed to 0.2% NTA via drinking water during gestation days 6 to 18 (Tjalve, 1972).

6.1.1.7 Mutagenicity/Genotoxicity

Nitrilotriacetic acid and its sodium salts have been tested in a large number of mutagenicity/ genotoxicity tests both *in vitro* and *in vivo*. In most instances no - or very little - activity was determined (IARC, 1999). For example, no mutagenic activities were detected in the common *in vitro* tests with bacteria and fungi, but the applied test concentration of NTA, for example for *Escherichia coli,* was 15 times higher than a toxic dose for that strain.

However, *in vivo* high doses of NTA as acid caused aneuploidy in germ cells from *Drosophila melanogaster* and from a mouse strain.

The trisodium NTA salt caused significant

- chromosome aberrations in rat kangaroo kidney cells *in vitro*,
- gene mutations at very low dose (≥ 10^{-5} M) in human EUE cells *in vitro*,
- micronucleus formation in Chinese hamster lung cells *in vitro*,[4]
- induced micronuclei and chromosome aberrations in plant cells.

In the SCCS 2010 opinion it is concluded:
"No data were available on the genotoxic and related effects of NTA **in humans**. NTA was mostly not genotoxic in mammalian cells *in vitro* or mutagenic to bacteria. NTA was not genotoxic in experimental systems *in vivo*, except that H3NTA induced aneuploidy in mouse germ cells. NTA is not considered to be mutagenic/genotoxic."

However, the SCCS seems to have a discrepancy in comparison to the original papers regarding evaluation of the three tests: "genotoxicity in human EUE cells, the micronucleus formation in Chinese hamster lung cells, and aneuploidy in germ cells from *Drosophila melanogaster*", as negative in their conclusions, which partly are based on incorrect reading of their own tables (from IARC, 1999).

SCCS did not include a rather recent French paper by Nesslany *et al.* (2008) confirming the lack of mutagenicity of NTA in bacteria tests, but showed a strong increase in micronuclei formation in mouse lymphoma cells by NTA without metabolic activation. Tested with an excess of Ca^{2+} there was no effect. Also observed was an unexpected high potency by NTA for increasing DNA damage in an *in vivo* assay in rat kidney. That result was not influenced by Ca^{2+}.

Possibly, genotoxicity occurs only at concentrations which deplete the cells of essential divalent trace elements (Olsen & Jensen, 1989).

In conclusion, the SCCS opinion on this endpoint could be further discussed.

6.1.1.8 Carcinogenicity

No study of cancer in humans related to NTA has been identified, but several long-term animal experiments with mice and rats have been undertaken with administration of NTA via drinking water and feed.

In an old study from the U.S. National Cancer Institute (NCI), groups of B6C3F1 mice of both sexes received, respectively, the maximum tolerated dose (MTD = 15000 ppm = 1.5%) and ½MTD of nitrilotriacetic acid in the diet for 18 months. After three months' observation time, animals of each sex had dose-related increased incidences of renal tumors, mostly adenocarcinomas, and this was most significant for high-dosed male mice (24 animals out of 44). The control animals had no tumors. In a similar study with Na_3NTA hydrate in the feed, the MTD was three times lower (the salt more toxic to mice than the acid), and no urinary tract tumors were observed. However, a dose-related increase in the incidence of hematopoietic tumors in male mice was determined in the exposed animals.

The same NCI report (1977) also contains the results of similar feeding studies with Fisher 344 rats exposed to NTA as the acid at MTD (15000 ppm) and ½MTD (7500 ppm). In male rats exposed to the acid, a dose-related increased incidence of urinary tract tumors, mainly tubular-cell adenomas and carcinomas, was observed. In exposed female rats, an increased incidence of transitional and

[4] In the SCCS 2010 reference this test is wrongly considered negative in the text but correctly marked positive in the table 1!

squamous-cell carcinomas of the urinary bladder, pheochromocytomas of the adrenal gland, and liver tumors were observed. No increase in tumor incidences was observed after similar exposures to the trisodium salt hydrate for 18 months. However, after 24 months' exposure to 20000 ppm (2% = 921 mg/kg bw/day) of this salt, kidney and urinary-tract tumors were observed in both males and females given the highest dose. In male rats were observed tubular-cell adenomas and adenocarcinomas of the kidney, transitional-cell carcinomas developed in the renal pelvis and in the ureter, with metastases mainly in the lungs. In the females were also observed tubular-cell adenomas and adenocarcinomas of the kidney, transitional-cell carcinomas in the ureter and in the urinary bladder, with metastases mainly in the lungs. A NOAEL of 92 mg/kg bw/day was derived from the study.

In a famous study (Goyer *et al.* 1981), rats of both sexes were exposed to 0.1% Na_3NTA monohydrate in the drinking water for 2 years. In the exposed group of 183 rats, 25 with renal adenomas and 4with renal adenocarcinomas were observed. For comparison, only 5 rats of 186 of the controls had renal adenomas. Based on this study, the dose causing tumours in 16% of the animals (TD_{16}) was calculated to around 150 mg/kg bw/day, corresponding to a middle-potent carcinogen (Olsen & Jensen, 1989).

The International Agency for Research of Cancer (IARC) has evaluated NTA in 1989 and 1998. The later conclusion was that there was inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of nitrilotriacetic acid and its salts. The overall evaluation was that nitrilotriacetic acid and its salts were possibly carcinogenic to humans (Group 2B).

In the later 12th National Toxicology Program (NTP) Report on Carcinogens (2011) it was concluded: *"Nitrilotriacetic acid is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals."*

6.1.1.9 Mechanisms and interactions

NTA is a metal ion chelating agent, and urinary calcium and zinc concentrations were increased in urine of rats and mice with high urinary NTA levels.
Anderson *et al.* (1985) and Nesslany *et al.* (2008) postulated that the chronic toxicity and carcinogenicity of NTA could be a consequence of changes in Zn^{2+} and Ca^{2+} concentrations and distribution in the kidneys, and that would suggest a cancer threshold dose.

Both the extent and the severity of renal tubular cell toxicity associated with constant systemic loads of NTA were shown to depend on the availability of zinc in the circulation. However, the disposition of copper, iron and manganese was not appreciably influenced by oral NTA administration (up to 2 % Na_3NTA or 1.5 % H_3NTA in diet to rats) (European Commission, 2008). Specifically, NTA decreases the toxicity of cadmium chloride, by increasing the excretion of cadmium, and change the body distribution.

An example of interactions is that low concentrations ($5x10^{-3}$ M) of NTA are causing gene mutations in rat embryo cells infected by RLV virus (Traul *et al.*, 1981).

Animal experiments have indicated that NTA both can promote and inhibit the effects of some liver and urinary tract carcinogens of the *N*-nitroso-type.

6.2 Human exposure

6.2.1 Direct exposure

Around 67 % of the total European consumption of trisodium nitrilotriacetate are applied in cleaning agents for household and industrial use, 29 % of the marketed amount are used in other industrial categories for example in uses as water softener, about 3.7 % are used for the textile cleaning in industry and household (European Commission , 2008). That means that there is a potential for direct human exposures at consumer uses and occupational settings.

Trisodium nitrilotriacetate hydrate is a white crystalline powder (non-volatile salt) but is mainly handled in the form of aqueous preparations, which depending on pH may contain covalent and more volatile non-dissociated nitrilotriacetic acid. Inhalation exposures to vapours during the handling of solutions are assumed to be negligible, but formation of droplet aerosols containing NTA, e.g. during use of aerosol spray cans or high-pressure application of aqueous preparations, may lead to significant exposures. With regard to the handling of powdery Na_3NTA, exposures to dust in the production of the substance and its further processing to aqueous solutions during charging activities and filling activities are mainly to be expected (European Commission, 2008).

6.2.1.1 Consumer exposure

According to German data, Na_3NTA is used in all-purpose cleaners (up to 15 %), oven cleaners (up to 6 %), floor cleaners and polish (up to 20 %), machine dishwashing products (up to 7.5 %), glass cleaners (up to 8 %), bathroom cleaners (up to 7.5 %), hand dishwashing products (up to 0.8 %), laundry products (up to 3 %), and carpet cleaners (up to 3.5 %) (European Commission, 2008). In addition, Na_3NTA is used in car care product, including insect remover sprays (30%). It is also used in cosmetics (up to 5%) (SCCS, 2010). These uses will mainly result in consumer exposure of the skin by powder or liquids and inhalation of dust and aerosols.

When using cleaning agents, the consumer will often use protective gloves and decrease the skin exposure. Use of NTA and its salts in cosmetics is prohibited in the EU. Non-compliance may entail a risk to the user (see calculations later).

The European Commission (2008) has made some exposure scenarios. At exposure to dust from dishwashing powder containing 7.5% Na_3NTA, the external exposure accounted for 3.4 x 10-4 µg/kg bw/event of washing – a negligible exposure.

According to a Dutch eco-label study cited by European Commission (2008), the use of cleaning spray cans (bathroom-, oven- or glass cleaner) with up to 8% Na_3NTA in confined spaces may result in aerosol exposure concentrations of around 4 mg/m^3. The same study models the dermal exposure to a liquid cleaner and floor polish in a household. The amount of Na_3NTA that could potentially be taken up per day accounted for 0.059 mg/kg bw/day.

The increased self-service at car washing stations, use of spray cans with NTA and hobby cleaning with the use of high-pressure equipment may increase the non-professional exposures considerably but there are no available data. The European Commission (2008) reported a potential dermal uptake of 0.69 mg NTA/kg body weight/day from consumer use of high-pressure washers.

Residues of NTA in washed textiles or dinnerware are very low, and the respective skin and oral exposures will be negligible and an order of magnitude lower, respectively 1.7 and 0.05 µg/kg bw/day European Commission 2008).

6.2.1.2 Occupational exposure

Workers can be exposed to Na_3NTA by inhalation of dust and aerosols or by skin contact of solids and liquids at concentrations until 40% at the production of NTA, use in formulation processes and use of these formulations in business (e.g. cleaning).

Exposure to trisodium nitrilotriacetate (Na_3NTA) is possible at sampling, cleaning/maintenance, and during filling of the substance in powder form in sacks and big-bags and also by handling the liquid product at production facilities. Exposure associated with transporting the chemical would result from loading, unloading, coupling, uncoupling and drumming operations.

In an older reference from the USA, it was estimated that about 2,600 workers were exposed to NTA salts during production and formulation of detergents. At production and in loading areas airborne levels were respectively 0.033 mg/m^3 and 0.82 mg/m^3 (IARC, 1990).

A few workplace measurements showed 8h-TWAs between 0.02 and 5.6 mg/m^3 at sack fillings (European Commission, 2008). No official Occupational Exposure Limit (OEL) has been established at Community level in the EU. The European Commission (2008) recommended that for the assessment of risks of inhalation exposure to powdered trisodium nitrilotriacetate at workplaces with local exhaust ventilation a level of exposure ranging from 2 to 5 mg/m^3 and a 95th percentile of 3.9 mg/m^3 should be used. If local exhaust ventilation was not established levels of inhalation exposure ranging 5-50 mg/m^3 were estimated.

For the dermal exposure it is relevant that Na_3NTA is produced in two forms: an aqueous solution with a concentration of up to 40% and as powder. Dermal exposures are possible during the drumming of the 40 % aqueous solutions and during bagging of trisodium nitrilotriacetate in powder form but no measurements are available. Gloves and eye protection are required for minimizing the exposure but unintended contamination during the handling of used gloves or use of wrong or damaged gloves may happen. It should be noted that production of Na_3NTA does not take place in Denmark.

The European Commission (2008) made a model estimation of the level of skin exposure to 0.1 – 1 mg/cm^2/day. For Na_3NTA as powder the dermal exposure levels were estimated to 4.2-42 mg/person/day. For the 40% solution a dermal exposure of 8.4 mg/person/day was estimated subject to suitable gloves was worn. The exposure to the eyes was supposed to be largely avoided using eye protection.

The occupational exposures to NTA by professional use of washing- and cleaning products are not well studied and difficult to model. European Commission (2008) discusses a German case study where workplace measurements were conducted during high-pressure cleaning of cars in a washing bay. Linear alkyl benzene sulfonate (LAS) was measured as a surrogate for estimating the exposure to NTA. The LAS content was 0.7% and the Na_3NTA 2%. Of 20 measurements with sampling time of 210 minutes 18 were below the detection limit (0.17 mg/m^3). The study assumed the 8h-TWA of NTA to 0.3 mg/m^3. However, the detection limit for LAS was too high and too close to the two measured levels.

At high-pressure cleaning both inhalation and skin exposure are to be expected. The estimated work exposure concentration for inhalation was surprisingly low at 0.6 mg/m3. On the other hand a high dermal exposure of between 84 and 252 mg/person/day was estimated by modeling. This exposure is more than ten times the normal exposure by professional cleaning (European Commission, 2008).

6.2.2 Indirect exposure

Since crystalline Na_3NTA is highly water soluble, the major sinks are related to the aquatic environment. Indirect exposures via environment are mainly via drinking water. In Denmark drinking water is mostly based on ground water, which is less likely to contain NTA compared to surface waters.

6.2.2.1 Ambient air
The salt Na_3NTA has no significant vapor pressure therefore any air pollution of NTA may only be by particles containing NTA. Such situations may occur occasionally around factories producing and using Na_3NTA without insufficient exhaust air cleaning systems.

6.2.2.2 Drinking water
NTA has been measured in ground water at a concentration of 0.3-1.3 µg/L and in river water in Germany and Switzerland in concentrations of 3-55 µg/L (European Commission, 2008).

In drinking water produced by filtering river water containing up to 9.1 µg NTA/L, the NTA level was less than the detection limit of 1 µg/L, which was rather high compared to the results above. Based on these limited data the drinking water intakes of NTA may be insignificant (European Commission, 2008).

Historically, after introduction of NTA in detergents in the USA the mean NTA concentrations increased 4 times in river waters (from 2 to 8 µg/L) and in drinking water (from 1 to 4 µg/L) (IARC, 1990).

6.2.2.3 Food
Because NTA does not accumulate in biota and food chains, any potential food exposure will mainly be from minor residues of cleaning agents in finished food.

6.2.2.4 Indoor climate
During cleaning processes, especially in confined spaces for instance cleaning an oven with a spray, considerable exposure levels for the cleaner may be generated (see above) but ventilation will quickly dilute the concentrations.

6.3 Bio-monitoring data
No available data.

6.4 Human health impact
NTA has been used in a variety of product groups, and the risk of these uses has been addressed in the context of the SCCS (2010), EU Risk Assessment Reports (2005, 2008, 2008a) as well as in the REACH registration dossier. The main conclusions from the EU Risk Assessment Reports are referred in the introduction paragraphs to Section 6 of this report.

Cosmetics
Use of Na_3NTA in cosmetic products is prohibited in the EU. The safe use of Na_3NTA in cosmetics was evaluated by SCCS (2010) by calculating the Margin of Safety (MOS) which should be at least 100 to demonstrate safe use. The daily Na_3NTA exposure was estimated to 17.8 g/day, and with skin absorption of 10% the maximum daily absorption through the skin was calculated to 89 mg Na_3NTA and the systemic exposure dose (SED) to 1.48 mg/kg. Based on a NOAEL for carcinogenicity of 92 mg/kg bw/day and an oral absorption in rat considered to be 50 %, the SCCS concluded that the Margin of Safety (MOS) was 31 and thus too small.

There is a lower NOAEL for renal toxicity after exposure in the diet (19 mg/kg bw/day) in a 2-year study, which could have been used, giving a 4 times lower margin of safety. This change would only lower the MOS and therefore not change the conclusion that there is no safe use of NTA in cosmetics.

6.5 Summary of health effects
The available studies have shown that absorption of Na_3NTA/H_3NTA after oral administration seems to be rather rapid and extensive but it varies between animal species and seems to be lowest

for humans. For assessment of human exposure oral absorption of 20% has been used by EU agencies. Skin absorption is much smaller and probably less than 1% of the dose. The blood levels will peak after a few hours. The elimination half-life is relatively short and most will be eliminated from the body in three days. In monkeys, rabbits and humans most are excreted in the feces whereas mice, rats and dogs excrete almost all with the urine. The differences in toxicokinetics among animal species are important to take into account when extrapolating animal data to humans.

The acute oral toxicities of NTA and its sodium salts were low but sufficient for a classification as harmful. However, the relevance and quality of some of the studies may be questionable. NTA and its salts are mildly irritating to skin, eyes and airways.

The critical targets for NTA toxicity are organs of the urinary tract with lesions in the kidneys, ureters and urinary bladder. The lowest NOAEL for renal toxicity was 0.03% NTA in diet (19 mg/kg bw/day) in a 2-year rat study. In a two-generation feeding study with rats receiving 0.1% and 0.5% Na_3NTA in the feed continuously throughout two generations no effects on fertility, lactation or offspring were observed. Intravenously exposure to ^{14}C-labelled NTA showed strong accumulation of radioactivity in the maternal skeleton and in the fetal skeleton showing that NTA can pass the placenta. In mice the sodium salt was more toxic than the acid.

Na_3NTA has shown some *in vitro* genotoxicity in various cell system, but no data are available on the genotoxic and related effects of NTA in humans. Probably, genotoxicity occurs only at concentrations which deplete the cells of essential divalent trace elements.

In mice and rats, NTA and/or its salts induce increased incidence of especially various tumors mainly in the kidneys and urinary tract. In one study with rats a NOAEL of 92 mg/kg bw/day was derived for tumor induction. In 1998 IARC concluded that there was inadequate evidence in humans and sufficient evidence in experimental animals for the carcinogenicity of nitrilotriacetic acid and its salts. The overall evaluation was that nitrilotriacetic acid and its salts were possibly carcinogenic to humans (Group 2B). In the 12th NTP Report on Carcinogens from 2011 Nitrilotriacetic acid was reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

Since NTA is widely used in cleaning agents for household and industrial use, there is a potential for direct exposures of both consumers and workers. Workers may be exposed to dust during production and formulation of detergents and consumers may be exposed to dust from dish-washing powder. Use of aerosol spray cans or high-pressure application of aqueous preparations containing NTA may lead to significant inhalations.

Indirect exposures via drinking water, ambient air, food and others are insignificant. There is no available bio-monitoring data.

The EU Scientific Committee for Consumer Safety has estimated a Margin of Safety for NTA in cosmetics of 31, which was considered too low and therefore NTA has been banned in cosmetics in the EU.

The EU Risk Assessment Report and the related Risk Reduction Strategy (European Commission 2008 and 2008a) concluded that there is a risk to workers by dermal exposure and/or by inhalation during production and formulation stages of NTA as well as by use of NTA containing products for high pressure cleaning without PPE. A Community OEL was recommended but has not yet been established. Furthermore, it was recommended to establish the harmonised classification, which is currently in force.

7. Information on alternatives

7.1 Identification of possible alternatives

According to A.I.S.E (pers. communication) it is difficult to discuss alternatives as this is seen as confidential business information. An internet search was therefore performed in order to retrieve information on possible alternatives to NTA.

It must be emphasised that in order to evaluate if a substance is a *suitable alternative* to another, several factors have to be investigated, and these factors have to be investigated on a case by case basis and in collaboration with industry, which has the right expertise and know how. This will include considerations of:

- Technical suitability:
  - are the alternatives just as effective as NTA when it comes to their function as complex binders, do they do the job?
  - are the alternatives stable in the final product and during its application?
- Economic suitability:
  - are the identified alternatives economically suitable?
- Hazards and risks of possible alternatives:
  - does the alternatives lead to an overall reduced risk to humans and the environment
  - are there any implications in terms of increased energy consumption or resource issues related to the shift to the alternatives, e.g. increased CO2 emissions or potential depletion of non-renewable resources.

Table 7.1 presents a list of possible alternative groups of substance to NTA. They were presented in a report from the Danish EPA (2009) concerning possible alternatives to phosphate, and are assumed alternatives to NTA fulfilling the same technical function in detergent products. The list is more or less identical to the list of identified substances for substitution of phosphate in laundry detergents and automatic dishwashing products developed by the Swedish Chemical Agency (2006). In Table 7.1 the CAS numbers of example substances have been added, e.g. reported in HERA reports (HERA, 2013), together with their corresponding classifications.

The classification of NTA and the alternatives mentioned in Table 7.1 are suitable considering an overall reduced risk to humans and the environment. Several of the substances included in the table are as NTA classified as irritant (e.g. H302; H319). From a risk point of view it is, however, the classification as Carc 2 (Suspected of causing cancer (H351)) which is the driver for a substitution, and it is noted that none of the proposed alternatives have such classification.

Consequently it is likely to be the specific technical and/ or economic suitability of the alternatives that will determine the choice. It needs to be noted that such evaluation of alternatives has to be made on a case-by-case basis.

TABLE 7.1
SUBSTANCES CONSIDERED AS POSSIBLE ALTERNATIVES TO NTA. INCLUDING NOTIFIED /HARMONISED CLASSIFICATION AND GHS HAZARD STATEMENT. BASED ON CAS NUMBERS REPORTED IN HERA REPORT (HERA, 2013)

Substance	CAS	Classification	GHS Hazard statement
Zeolites	308081-08-5	H315	Causes skin irritation
		H319	Causes serious eye irritation
		H335	May cause respiratory irritation
Polycarboxylates/ Polyacrylates#	9003-01-4	H315	Causes skin irritation
		H319	Causes serious eye irritation
		H335	May cause respiratory irritation
		H340	May cause genetic defects
		H412	Harmful to aquatic life with long lasting effects
	52255-49-9	H319	Causes serious eye irritation
Sodium citrate	68-04-2	H302	Causes skin irritation
		H315	Causes skin irritation
		H319	Causes serious eye irritation
		H335	May cause respiratory irritation
Citric acid#	77-92-9	H315	Causes skin irritation
		H318	Causes serious eye damage
		H319	Causes serious eye irritation
		H335	May cause respiratory irritation
	5949-29-1	H315	Causes skin irritation
		H318	Causes serious eye damage
		H319	Causes serious eye irritation
		H335	May cause respiratory irritation
	6132-04-3	H319	Causes serious eye irritation
Sodium carbonate#	497-19-8*	H319	Causes serious eye irritation
Sodium bicarbonate	144-55-8	H319	Causes serious eye irritation
Sodium silicate	15859-24-2	H315	Causes skin irritation
		H319	Causes serious eye irritation
		H335	May cause respiratory irritation

Substance	CAS	Classification	GHS Hazard statement
Phosphonates#	6419-19-8	H290 H314 H315 H318 H319 H412	May be corrosive to metals Causes severe skin burns and eye damage Causes skin irritation Causes serious eye damage Causes serious eye irritation Harmful to aquatic life with long lasting effects
	2809-21-4	H290 H302 H314 H315 H318 H319 H413	May be corrosive to metals Causes skin irritation Causes severe skin burns and eye damage Causes skin irritation Causes serious eye damage Causes serious eye irritation May cause long lasting harmful effects to aquatic life
Sodium tartrate	868-18-8	H302	Harmful if swallowed
Sodium gluconate	527-07-1	H302	Harmful if swallowed
IDS (IminoDiSuccinate)	62782-03-0*	H312 H319	Causes serious eye irritation Causes serious eye irritation
MGDA (Methyl Glycine Diacetic Acid)	164462-16-2 77554-84-8	NA	NA
GLDA (GLutamic acid Diacetic Acid)	51981-21-6	H315 H319	Causes skin irritation Causes serious eye irritation
EDTA (Ethylene Diamine Tetraacetic Acid)	64-02-8*	H302 H318	Harmful if swallowed Causes serious eye damage

NA: CAS number not available

One example of an alternative to NTA is **glutamic acid diacetic acid** (GLDA), which has been introduced as an alternative to both EDTA and NTA. The substance is biodegradable and made from a naturally occurring amino acid. It has high water solubility over a wide range of pH values including at low pH where for example EDTA has a low solubility. It is thermally stable and does not decompose at temperatures >300°C (makes GLDA applicable in hard water boilers and has potential for use in strong alkaline hard surface cleaning agents used in food.). GLDA behaves similarly to NTA in cleaning formulations and is an excellent complex binder.

Also **Sodium gluconate** may be an alternative. Sodium gluconate is non-corrosive, non-toxic (i.e. no classification required) and readily biodegradable (98% after 2 days). It is an excellent chelator, especially in alkaline and concentrated alkaline solutions. It forms stable chelates with calcium, iron, copper, aluminium and other heavy metals, surpassing EDTA, NTA and related compounds (CLP-chemicals, information retrieved august 2013). G**luconates** as well as the **citrates** have properties that make them technically suitable for formulations in cleaning products (Jungbunzlauer, 2009). Based on the classification of the examples mentioned in Table 7.1 they also seem as suitable from a risk reduction point of view.

7.2 Summary and conclusions

NTA was introduced as an alternative to phosphate in detergents and all-purpose cleaners in order to avoid eutrophication problems in surface waters after release with waste water. Because of the classification as a Carc. 2 substance, suitable alternatives have been considered and introduced. Some substances which are considered alternatives to phosphates are most likely also suitable alternatives to NTA. Substances include zeolites, polycarboxylates, sodium citrate, citric acid, phosphonate and EDTA. These substances are not like Na_3NTA classified for carcinogen endpoints and are from a human health point of view less hazardous than Na_3NTA. It need be noted that EDTA is not readily biodegradable and can as Na_3NTA interact and mobilise metals in the wastewater treatment systems and environment.

A more detail analysis of alternatives need consider in more details the technical and economic suitability of the individual candidate substance. This will include a description of the specific technical requirements for different uses of the alternatives.

8. Abbreviations and acronyms

ADI	Acceptable daily ntake
BCF	Bioconcentration factor
CEFIC	European Chemical Industry Council
CLP	Classification, Labelling and Packaging Regulation
DOC	Dissolved Organic Carbon
EC_n	Effect concentration where n % of the species tested show the effect
ECHA	European Chemicals Agency
EPA	Environmental Protection Agency
EU	European Union
Kow	Octanol/water partitioning coefficient
Kp	Partial pressure equilibrium constant
LC	Lethal effect concentration
LOUS	List of Undesirable Substances (of the Danish EPA)
NOAEL	No observable adverse effect level
NOEC	No observable effect concentration
OECD	Organisation for Economic Co-operation and Development
OEL	Occupational Exposure Limit
PEC	Predicted environmental concentration
PNEC	Predicted no effect concentration
REACH	Registration, Evaluation, Authorisation and Restriction of Chemicals
STP	Sewage treatment plant
ThOD	Theoretical Oxygen Demand
ThCO2	Theoretical CO_2

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Annex 1: Background information to chapter 3 on legal framework

The following annex provides some background information on subjects addressed in Chapter 3. The intention is that the reader less familiar with the legal context may read this concurrently with chapter 3.

EU and Danish legislation

Chemicals are regulated via EU and national legislations, the latter often being a national transposition of EU directives.

There are four main EU legal instruments:

- Regulations (DK: Forordninger) are binding in their entirety and directly applicable in all EU Member States.
- Directives (DK: Direktiver) are binding for the EU Member States as to the results to be achieved. Directives have to be transposed (DK: gennemført) into the national legal framework within a given timeframe. Directives leave margin for manoeuvring as to the form and means of implementation. However, there are great differences in the space for manoeuvring between directives. For example, several directives regulating chemicals previously were rather specific and often transposed more or less word-by-word into national legislation. Consequently and to further strengthen a level playing field within the internal market, the new chemicals policy (REACH) and the new legislation for classification and labelling (CLP) were implemented as Regulations. In Denmark, Directives are most frequently transposed as laws (DK: love) and statutory orders (DK: bekendtgørelser).

- The European Commission has the right and the duty to suggest new legislation in the form of regulations and directives. New or recast directives and regulations often have transitional periods for the various provisions set-out in the legal text. In the following, we will generally list the latest piece of EU legal text, even if the provisions identified are not yet fully implemented. On the other hand, we will include currently valid Danish legislation, e.g. the implementation of the cosmetics directive) even if this will be replaced with the new Cosmetic Regulation.

- Decisions are fully binding on those to whom they are addressed. Decisions are EU laws relating to specific cases. They can come from the EU Council (sometimes jointly with the European Parliament) or the European Commission. In relation to EU chemicals policy, decisions are e.g. used in relation to inclusion of substances in REACH Annex XVII (restrictions). This takes place via a so-called comitology procedure involving Member State representatives. Decisions are also used under the EU ecolabelling Regulation in relation to establishing ecolabel criteria for specific product groups.

- Recommendations and opinions are non-binding, declaratory instruments.

In conformity with the transposed EU directives, Danish legislation regulates to some extent chemicals via various general or sector specific legislation, most frequently via statutory orders (DK: bekendtgørelser).

Chemicals legislation
REACH and CLP
The REACH Regulation[5] and the CLP Regulation[6] are the overarching pieces of EU chemicals legislation regulating industrial chemicals. The below will briefly summarise the REACH and CLP provisions and give an overview of 'pipeline' procedures, i.e. procedures which may (or may not) result in an eventual inclusion under one of the REACH procedures.

(Pre-)Registration
All manufacturers and importers of chemical substance > 1 tonne/year have to register their chemicals with the European Chemicals Agency (ECHA). Pre-registered chemicals benefit from tonnage and property dependent staggered dead-lines:

- 30 November 2010: Registration of substances manufactured or imported at 1000 tonnes or more per year, carcinogenic, mutagenic or toxic to reproduction substances above 1 tonne per year, and substances dangerous to aquatic organisms or the environment above 100 tonnes per year.
- 31 May 2013: Registration of substances manufactured or imported at 100-1000 tonnes per year.
- 31 May 2018: Registration of substances manufactured or imported at 1-100 tonnes per year.

Evaluation
A selected number of registrations will be evaluated by ECHA and the EU Member States. Evaluation covers assessment of the compliance of individual dossiers (dossier evaluation) and substance evaluations involving information from all registrations of a given substance to see if further EU action is needed on that substance, for example as a restriction (substance evaluation).

Authorisation
Authorisation aims at substituting or limiting the manufacturing, import and use of substances of very high concern (SVHC). For substances included in REACH annex XIV, industry has to cease use of those substances within a given deadline (sunset date) or apply for authorisation for certain specified uses within an application date.

Restriction
If the authorities assess that that there is a risk to be addressed at the EU level, limitations of the manufacturing and use of a chemical substance (or substance group) may be implemented. Restrictions are listed in REACH annex XVII, which has also taken over the restrictions from the previous legislation (Directive 76/769/EEC).

Classification and Labelling
The CLP Regulation implements the United Nations Global Harmonised System (GHS) for classification and labelling of substances and mixtures of substances into EU legislation. It further specifies rules for packaging of chemicals.

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[5] Regulation (EC) No 1907/2006 concerning the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH)

[6] Regulation (EC) No 1272/2008 on classification, labelling and packaging of substances and mixtures

Two classification and labelling provisions are:
1. **Harmonised classification and labelling** for a number of chemical substances. These classifications are agreed at the EU level and can be found in CLP Annex VI. In addition to newly agreed harmonised classifications, the annex has taken over the harmonised classifications in Annex I of the previous Dangerous Substances Directive (67/548/EEC); classifications which have been 'translated' according to the new classification rules.

2. **Classification and labelling inventory**. All manufacturers and importers of chemicals substances are obliged to classify and label their substances. If no harmonised classification is available, a self-classification shall be done based on available information according to the classification criteria in the CLP regulation. As a new requirement, these self-classifications should be notified to ECHA, which in turn will publish the classification and labelling inventory based on all notifications received. There is no tonnage trigger for this obligation. For the purpose of this report, self-classifications are summarised in Appendix 2 to the main report.

Ongoing activities - pipeline
In addition to listing substances already addressed by the provisions of REACH (pre-registrations, registrations, substances included in various annexes of REACH and CLP, etc.), the ECHA web-site also provides the opportunity for searching for substances in the pipeline in relation to certain REACH and CLP provisions. These will be briefly summarised below:

Community Rolling Action Plan (CoRAP)
The EU member states have the right and duty to conduct REACH substance evaluations. In order to coordinate this work among Member States and inform the relevant stakeholders of upcoming substance evaluations, a Community Rolling Action Plan (CoRAP) is developed and published, indicating by who and when a given substance is expected to be evaluated.

Authorisation process; Candidate list, Authorisation list, Annex XIV
Before a substance is included in REACH Annex XIV and thus being subject to Authorisation, it has to go through the following steps:

1. It has to be identified as a SVHC leading to inclusion in the candidate list[7]
2. It has to be prioritised and recommended for inclusion in ANNEX XIV (These can be found as Annex XIV recommendation lists on the ECHA web-site)
3. It has to be included in REACH Annex XIV following a comitology procedure decision (substances on Annex XIV appear on the Authorisation list on the ECHA web-site).

The candidate list (substances agreed to possess SVHC properties) and the Authorisation list are published on the ECHA web-site.

Registry of intentions
When EU Member States and ECHA (when required by the European Commission) prepare a proposal for:

- a harmonised classification and labelling,
- an identification of a substance as SVHC, or
- a restriction.

This is done as a REACH Annex XV proposal.

[7] It should be noted that the candidate list is also used in relation to articles imported to, produced in or distributed in the EU. Certain supply chain information is triggered if the articles contain more than 0.1% (w/w) (REACH Article 7.2 ff).

The 'registry of intentions' gives an overview of intensions in relation to Annex XV dossiers divided into:

- current intentions for submitting an Annex XV dossier,
- dossiers submitted, and
- withdrawn intentions and withdrawn submissions

for the three types of Annex XV dossiers.

International agreements

OSPAR Convention

OSPAR is the mechanism by which fifteen Governments of the western coasts and catchments of Europe, together with the European Community, cooperate to protect the marine environment of the North-East Atlantic.

Work to implement the OSPAR Convention and its strategies is taken forward through the adoption of decisions, which are legally binding on the Contracting Parties, recommendations and other agreements. Decisions and recommendations set out actions to be taken by the Contracting Parties. These measures are complemented by other agreements setting out:

- issues of importance
- agreed programmes of monitoring, information collection or other work which the Contracting Parties commit to carry out.
- guidelines or guidance setting out the way that any programme or measure should be implemented
- actions to be taken by the OSPAR Commission on behalf of the Contracting Parties.

HELCOM - Helsinki Convention

The Helsinki Commission, or HELCOM, works to protect the marine environment of the Baltic Sea from all sources of pollution through intergovernmental co-operation between Denmark, Estonia, the European Community, Finland, Germany, Latvia, Lithuania, Poland, Russia and Sweden. HELCOM is the governing body of the "Convention on the Protection of the Marine Environment of the Baltic Sea Area" - more usually known as the Helsinki Convention.

In pursuing this objective and vision the countries have jointly pooled their efforts in HELCOM, which is works as:

- an environmental policy maker for the Baltic Sea area by developing common environmental objectives and actions;
- an environmental focal point providing information about (i) the state of/trends in the marine environment; (ii) the efficiency of measures to protect it and (iii) common initiatives and positions which can form the basis for decision-making in other international fora;
- a body for developing, according to the specific needs of the Baltic Sea, Recommendations of its own and Recommendations supplementary to measures imposed by other international organisations;
- a supervisory body dedicated to ensuring that HELCOM environmental standards are fully implemented by all parties throughout the Baltic Sea and its catchment area; and
- a co-ordinating body, ascertaining multilateral response in case of major maritime incidents.

Stockholm Convention on Persistent Organic Pollutants (POPs)
The Stockholm Convention on Persistent Organic Pollutants is a global treaty to protect human health and the environment from chemicals that remain intact in the environment for long periods, become widely distributed geographically, accumulate in the fatty tissue of humans and wildlife, and have adverse effects to human health or to the environment. The Convention is administered by the United Nations Environment Programme and is based in Geneva, Switzerland.

Rotterdam Convention
The objectives of the Rotterdam Convention are:
- to promote shared responsibility and cooperative efforts among Parties in the international trade of certain hazardous chemicals in order to protect human health and the environment from potential harm;
- to contribute to the environmentally sound use of those hazardous chemicals, by facilitating information exchange about their characteristics, by providing for a national decision-making process on their import and export and by disseminating these decisions to Parties.
- The Convention creates legally binding obligations for the implementation of the Prior Informed Consent (PIC) procedure. It built on the voluntary PIC procedure, initiated by UNEP and FAO in 1989 and ceased on 24 February 2006.

The Convention covers pesticides and industrial chemicals that have been banned or severely restricted for health or environmental reasons by Parties and which have been notified by Parties for inclusion in the PIC procedure. One notification from each of two specified regions triggers consideration of addition of a chemical to Annex III of the Convention. Severely hazardous pesticide formulations that present a risk under conditions of use in developing countries or countries with economies in transition may also be proposed for inclusion in Annex III.

Basel Convention
The Basel Convention on the Control of Transboundary Movements of Hazardous Wastes and their Disposal was adopted on 22 March 1989 by the Conference of Plenipotentiaries in Basel, Switzerland, in response to a public outcry following the discovery, in the 1980s, in Africa and other parts of the developing world of deposits of toxic wastes imported from abroad.

The overarching objective of the Basel Convention is to protect human health and the environment against the adverse effects of hazardous wastes. Its scope of application covers a wide range of wastes defined as "hazardous wastes" based on their origin and/or composition and their characteristics, as well as two types of wastes defined as "other wastes" - household waste and incinerator ash.

The provisions of the Convention center around the following principal aims:

- the reduction of hazardous waste generation and the promotion of environmentally sound management of hazardous wastes, wherever the place of disposal;
- the restriction of transboundary movements of hazardous wastes except where it is perceived to be in accordance with the principles of environmentally sound management; and
- a regulatory system applying to cases where transboundary movements are permissible.

Eco-labels
Eco-label schemes are voluntary schemes where industry can apply for the right to use the eco-label on their products if these fulfil the ecolabelling criteria for that type of product. An EU scheme (the flower) and various national/regional schemes exist. In this project we have focused on the three most common schemes encountered on Danish products.

EU flower
The EU ecolabelling Regulation lays out the general rules and conditions for the EU ecolabel; the flower. Criteria for new product groups are gradually added to the scheme via 'decisions'; e.g. the Commission Decision of 21 June 2007 establishing the ecological criteria for the award of the Community eco-label to soaps, shampoos and hair conditioners.

Nordic Swan
The Nordic Swan is cooperation between Denmark, Iceland, Norway, Sweden and Finland. The Nordic Ecolabelling Board consists of members from each national Ecolabelling Board and decides on Nordic criteria requirements for products and services. In Denmark, the practical implementation of the rules, applications and approval process related to the EU flower and Nordic Swan is hosted by Ecolabelling Denmark "Miljømærkning Danmark" (http://www.ecolabel.dk/). New criteria are applicable in Denmark when they are published on the Ecolabelling Denmark's website (according to Statutory Order no. 447 of 23/04/2010).

Blue Angel (Blauer Engel)
The Blue Angel is a national German eco-label. More information can be found on: http://www.blauer-engel.de/en.

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