Trisodium Nitrilotriacetate

(3rd Priority List)

CAS-No.: 5064-31-3

EINECS-No.: 225-768-6

Strategy For Limiting Risks

Human Health

Draft of 16.09.2008

The rapporteur for trisodium nitrilotriacetate is the Federal Institute for Occupational Safety and Health.

Contact point:

Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA)

Anmeldestelle Chemikalien / Zulassungsstelle Biozide

(Federal Institute for Occupational Safety and Health

Division for Chemicals and Biocides Regulation)

Friedrich-Henkel-Weg 1-25

44149 Dortmund (Germany)

fax: +49(231)9071-2679

e-mail: chemg@baua.bund.de

CONTENT

0 Summary

There are five producers and/or importers of trisodium nitrilotriacetate (NTA) in the EU. According to the data supplied by the producers and importers, 36090 t/a (calculated as Na_3NTA) are produced, 6040 t/a are imported and 10090 t/a exported outside of the EU, thus 32040 t/a are consumed within Europe. According to CEFIC (2001), 26642 t/a were marketed in 2000, the difference to the producers data might be explained by exports or imports of trisodium nitrilotriacetate containing formulations.

Today the original synthesis of NTA from ammonia and chloroacetic acid has only historical significance. The oxidation of triethanolamine is likewise of no industrial importance. The one-stage alkaline and two-stage acid processes now in use are based on the cyanomethylate ion of ammonia (or ammonium sulphate) with formaldehyde and sodium cyanide (or hydrogen cyanide).

NTA is an aminocarboxylic acid with three functional groups which donate electrons. These 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.

NTA and its sodium salt are used to soften water and to remove traces of alkaline earth and heavy metals. They are often included in detergent and cleaner formulations for household or industrial use.

Trisodium nitrilotriacetate is not included in Annex I of the Directive 67/548/EEC, but voluntarily labelled by industry with Xn, R22-40, S36/37-45 (GESTIS, 2008).

In March 2006 the EU-Working group on classification and labelling of dangerous substances under Directive 67/548/EEC agreed upon the following classification:

Carc, Cat. 3, R40; Xn, R22; Xi, R36

Concentration Limits:
$C \geq 25$ %: Xn; R22-36-40
$20 \leq$ % $C < 25$ %: Xn; R36-40
$5 \leq$ % $C < 20$ %: Xn; R40

The agreed classification will be included in the 31. Adaption to Technical Progress (ATP).

Trisodium nitrilotriacetate will have to be labelled with

Xn, R22-36-40, S (2-)26-36/37-46

Workers

It has been concluded from the risk assessment that there is a 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 (with a critical exposure level of 2.85 mg/kg/day for both endpoints) has to be reduced for scenario 2 (use of Na_3NTA in formulation process without PPE) and 3 (high pressure cleaning without PPE). Inhalation exposure (with a critical exposure level of 2 mg/m^3 for both endpoints) has to be reduced for scenario 1 (production of NTA) and 2b (use of Na_3NTA in formulation process without LEV).

The risk reduction strategy recommends the following measures:

- to establish at community level an occupational exposure limit value for NTA according to Directive 98/24/EEC

- to apply the following revised classification and labelling of NTA in the forefront of a future Adaption to Technical Progress of Directive 67/548/EEC:

  Carc, Cat. 3, R40; Xn, R22; Xi, R36
  Concentration Limits:
  C ≥ 25 %: Xn; R22-36-40
  20 ≤ % C < 25 %: Xn; R36-40
  5 ≤ % C < 20 %: Xn; R40

- to transfer the classification into the Inventory according to Article 114 of Regulation (EC) 1907/2006

1 Background

In the framework of EU Regulation 793/93 on the evaluation and control of the risks of existing substances data are gathered, priority substances are selected, their risks are assessed and, if necessary, strategies for limiting the risks are developed. The risk assessments cover the risks to man exposed directly at the workplace or as a consumer and indirectly through the environment and the risks to the environment. Trisodium nitrilotriacetate is a substance on the third priority list (Regulation (EC) No. 143/97 of the Commission of 28 January 1997).

Trisodium nitrilotriacetate (Na3NTA) is a colourless crystalline powder at room temperature and normal pressure. The Melting point is 410 °C with decomposition above 200 °C, the Relative density is 1.77 at 20 °C, water solubility is about 640 g/l at 20 °C, the Partition coefficient is -2.62.

Production

The following companies are producer and/or importers of NTA:

- 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)

According to the data supplied by the producers and importers for this report, 36090 t/a (calculated as Na_3NTA) are produced, 6040 t/a are imported and 10090 t/a exported outside of the EU, thus 32040 t/a are consumed within Europe. According to CEFIC (2001), 26642 t/a were marketed in 2000, the difference to the producers data might be explained by exports or imports of NTA containing formulations.

Processing / Application (Categories of use, Amounts)

Today the original synthesis of NTA from ammonia and chloroacetic acid has only historical significance. The oxidation of triethanolamine is likewise of no industrial importance. The one-stage alkaline and two-stage acid processes now in use are based on the cyanomethylate ion of ammonia (or ammonium sulphate) with formaldehyde and sodium cyanide (or hydrogen cyanide).

The alkaline process was long the established method for NTA production. Trisodium nitrilotriacetate is synthesized as follows:

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

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

The reaction can be carried out batch wise or continuously, but the continuous process is more economical. The resulting solution is sold directly as a 40-wt% solution, or used in the production of Na_3NTA in powder form, or acidified to pH 1 - 2 to yield the acid (H_3NTA).

Acid Process: The significant yield of by-products in the alkaline process has led in recent years 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; corrosion can also be a problem. In the first stage, ammonia is reacted with formaldehyde to give hexamethylenetetramine, which is then reacted with hydrogen cyanide in sulphuric acid solution to yield triscyanomethyl amine. The solid triscyanomethyl amine is sparingly soluble in the acidic solution and is filtered off, washed, and saponified with NaOH to give Na_3NTA. The resulting solution has a far lower by-product content than the solution from the alkaline method. It is also sold as 40 % product or used in the production of Na_3NTA or H_3NTA (see above).

The NTA amounts (calculated as Na_3NTA) marketed in the Western European countries are given in the following table. The figures are derived from sales information of the producers. A direct correlation to the consumption volume is therefore not precise, however the figures may be regarded as an approximation for the European consumption. Imports and exports of Na_3NTA containing formulations are not considered.

Table 1.1: Na_3NTA Sales in European Countries (CEFIC, 2000)

Country	**Sales [t] in 1999**
Germany	3396
Belgium / Luxembourg	1814
The Netherlands	2055
France	1838
Italy	825
UK	7274
Ireland / Denmark	561
Spain / Portugal / Greece	5108
Finland	Not published
Norway	0
Sweden	1734
Austria	Not published
Switzerland	631
Total West. Europe	**26756**

Use Pattern

NTA is an aminocarboxylic acid with three functional groups which donate electrons. These 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.

NTA and its sodium salt are used to soften water and to remove traces of alkaline earth and heavy metals. They are often included in detergent and cleaner formulations for household or industrial use.

The application volumes (calculated as Na_3NTA) were (CEFIC, 2000; CEFIC 2001):

Table 1.2: Use pattern of Na_3NTA (CEFIC, 2000; CEFIC 2001)

	IC/UC *	**Germany (1999)**	**Western Europe (2000)**
Marketed amount		**3396 t**	**26642 t**
Textile cleaning, household and industrial	5 / 11 13 / 11	238 t (7%)	973 (3.7%)
Cleaning agents	6 / 9	2207 (65%)	17905 (67.2%)
Others	15 / 0	951 (28%)	7764 (29.1%)

* industrial category / use category

2 The Risk Assessment

2.1 Workers

2.1.1 Introductory remarks

For occupational risk assessment of trisodium nitrilotriacetate the MOS approach as outlined in the revised TGD is applied. This occupational risk assessment is based upon the toxicological profile of trisodium nitrilotriacetate and the occupational exposure assessment. The threshold levels identified in the hazard assessment are taken forward to this occupational risk assessment.

This introductory remark specifies the route-specific information on absorption, applies these absorption data to transform the external occupational exposure levels to the corresponding internal body burden, and gives a short introduction to the MOS approach used.

Systemic availability for different routes of exposure

For the majority of toxicological endpoints trisodium nitrilotriacetate data originate from oral studies. Since workers are exposed either by inhalation or by skin contact, route-to-route transformation is essential for the occupational risk assessment.

Experimental data with rats show a median value for oral absorption of about 50%. With reference to the chapter on toxicokinetics a value of 100% for oral absorption in rats is discussed. However, a value of 50% for oral absorption in the rat is taken, sticking on the agreement of the last member state discussion (TCNES II ´07), knowing, that this approach leads to lower critical exposure levels and thus is more conservative. 20% is taken for the oral absorption of humans.

There are no data known concerning absorption after inhalation. Considerations about the chemical structure and physico-chemical data (molecular weight, water solubility, partition coefficient and ionisation state) result in a default value 20% absorption after inhalation.

Experimental in vitro data show very low absorption percentages after application of radiolabeled NTA on human skin. At the low dose dilution (1% NTA), absorption percentages ranged between 0.042 and 0.472 % within the five different samples. For higher NTA concentrations in solution, a higher absorption rate of 10 % (default based on physico-chemical properties due to the lack of meaningful experimental data) is taken for risk characterization, knowing that this very conservative approach might take the human variability adequately into account.

In table 2.1.A the exposure levels are summarised and the route-specific and total internal body burdens are identified.

Table 2.1.A: Trisodium nitrilotriacetate exposure levels which are relevant for occupational risk assessment and internal body burden.

Exposure scenario			Inhalation		Dermal contact		Internal body burden		
							Inhalation[1]	Dermal[2]	Combined
			mg/m³	mg/kg/d	mg/p/d	mg/kg/d	mg/kg/d		
1a	Production of Na_3NTA	dust	3.9[3]	0.56	42[4]	0.6	0.11	0.06	0.17
1b		liquid			8.4[4]	0.12		0.01	0.12
2a	Use of Na_3NTA in formulation process (up to 40%)	dust	0.62[7]	0.09	3,000[6]	42.8	0.02	4.28	4.3
			6.25[8]	0.89			0.18		4.46
2b		liquid	negl.	negl.	4,600[6]	65.7	negl.	6.57	6.6
3a	High pressure cleaning (diluted solutions, < 2% NTA)	droplet aerosols	0.3[9]	0.04	252[5]	3.6	0.01	0.36	0.37
3b		liquid			19[5]	0.27		0.03	0.04

[1]based on the assumption of 20% inhalative absorption; breathing volume of 10 m^3 per shift
[2]based on the assumption of 10% systemic availability of trisodium nitrilotriacetate after dermal contact
[3]measurement data
[4]EASE-estimation (90% protection by suitable gloves)
[5]EASE-estimation without gloves
[6]determined by analogy (calculation without gloves)
[7]EASE with LEV
[8]EASE without LEV
[9] analogy, 4 hours per day, without LEV, without PPE

MOS Approach

The MOS approach for human risk characterisation is described in detail in chapter 4 of the revised TGD. The following chapter contains a short introduction to the MOS approach used. The basic principle of the MOS approach is a comparison of scenario-specific MOS values (the relationship between the experimental NOAEL respectively the adjusted starting point and the exposure level) with a reference MOS (product of various assessment factors).

MOS calculation and the adequate starting point

Basically, MOS values are calculated as quotient of a relevant NOAEL from experimental animal testing or human studies and actual workplace exposure levels. In specific situations, the MOS approach requires converting the original NOAEL into an adequate starting point or corrected NOAEL previously to MOS calculation in order to be directly comparable to the exposure assessment. If the route of application in animal or human studies is different from the actual occupational exposure, the dose units of the experimental data should be converted to the dose unit of the exposure data.

For occupational risk assessment, the corrected inhalatory NOAEC accounts for the difference of the standard respiratory volume (6.7 m³) and the respiratory volume for light activity (10 m³).

MOS values are calculated for different routes of exposure and for different toxicological endpoints. The routes of exposure specifically considered in occupational risk assessment are inhalation exposure and dermal contact.

In addition, for risk assessment of combined exposure (inhalation exposure and dermal contact) an adequate internal NOAEL is derived from external NOAELs and specific information on route-specific absorption. For MOS calculation, the adjusted internal starting point is divided by the internal body burden. Depending on route-specific exposure and absorption, inhalation exposure and/or dermal exposure may contribute to the internal body burden. With respect to the possible outcome of an assessment for combined risks, interest focuses on scenarios with conclusion ii at both exposure routes. Based on theoretical considerations, combined exposure will not increase the most critical route-specific risk component more than twice.

Reference MOS

The MOS values calculated have to be compared with a reference MOS. The reference MOS is an overall assessment factor, which is obtained by multiplication of individual assessment factors. The Technical Guidance Document emphasises several aspects which are involved in the extrapolation of experimental data to the human situation. For these assessment factors, default values are recommended. It is important to point out that any relevant substance-specific data and information may overrule the defined default values.

Interspecies extrapolation on the one hand is based on allometric scaling. For remaining interspecies differences the revised TGD proposes an additional factor of 2.5.

For workers, an adjustment factor for intraspecies differences of 5 is recommended. Based on an evaluation of empirical data by Schneider et al. (2004) it is anticipated that a factor of 5 will be sufficient to protect the major part of the worker population (about 95%).

For chemical substances it is usually expected that the experimental NOAEL will decrease with increasing duration of application. Furthermore, other and more serious adverse effects may appear with prolonged exposure duration. For duration adjustment, a default factor of 6 is proposed for extrapolation from a subacute to chronic exposure. The duration adjustment factor is lower (a factor of 2) for the transition from subchronic experimental exposure to chronic exposure.

The TGD defines two further adjustment factors (uncertainty in route-to-route extrapolation and dose-response relationship including severity of effect). In specific cases these factors may be different from one.

Adjustment factors for trisodium nitrilotriacetate

For trisodium nitrilotriacetate the oral NOAELs (usually from rat studies) were transformed into the adequate starting points for dermal contact and inhalation exposure. Because of experimental data oral absorption of the rat is assumed to be 50%. By default a 10% dermal and 20% inhalative absorption has been taken. For occupational risk assessment, the corrected inhalatory NOAEC accounts for the difference of the standard respiratory volume (6.7 m³) and the respiratory volume for light activity (10 m³).

For interspecies extrapolation for the rat the allometric scaling factor of 4 and the factor of 2.5 for remaining differences are applied. For intraspecies extrapolation, the default factor of 5 was used.

Because relevant long-term studies are available, for systemic effects no duration adjustment was necessary. With respect to local effects a reduced duration adjustment factor of 2 was taken, because no significant change of the NOAEC from a short term study compared with a 4 week study was reported.

Comparison of MOS and reference MOS

The MOS values for different toxicological endpoints and different exposure scenarios are compared with the substance- and endpoint-specific reference MOS. MOS values clearly above the reference MOS do not lead to concern, whereas MOS values that are clearly below the reference MOS are cause for concern. There may be various risk-related aspects which are not covered by default assessment factors. These additional qualitative aspects should be carefully considered when performing a risk assessment and should have adequate influence on finding of conclusions.

Critical Exposure Levels

In a parallel procedure, which gives identical but more direct results, the adjusted toxicological starting point is directly divided by the reference MOS. As a result, an exposure level (in mg/m³ or mg/kg/d) is identified, which may serve as a direct trigger for decisions when compared with the occupational exposure levels. In the context of this risk assessment report this trigger value is called "critical exposure level". Concern will be expressed for scenarios with occupational exposure levels higher than the relevant "critical exposure level".

2.1.2 Occupational Risk Assessment

Acute toxicity

The lowest oral LD50 values of 1,300-1,470 mg/kg are described for female rats. From a reprotoxicity study at rats a NOAEL of 450 mg/kg/day is reported. The minimum dermal lethal dose of trisodium nitrilotriacetate for rabbits is more than 10,000 mg/kg.

A repeated inhalation study from EPA (1980) on rats and guinea pigs showed no adverse effects at an exposure level of 210 mg/m^3 trisodium nitrilotriacetate for a time period of 4 weeks (no histopathology was done).

To assess the acute risks after trisodium nitrilotriacetate exposure the NOAEL from the reprotoxicity study is taken (450 mg/kg/day); taking also into account that compared to the NOAEL for repeated dose toxicity (see below) this NOAEL is plausible and careful enough.

Internal starting point

The calculation of the internal starting point has to account for a factor of 1/2 for 50% oral absorption for the rat. This gives an internal value of 225 mg/kg/day (450 x ½).

Inhalative exposure

Assuming 20% absorption by inhalation, the internal starting point has to be multiplied with 5 to get the external inhalation dose. This results in a value of 1,125 mg/kg/day (225 mg/kg/day x 5). The inhalation dose of 1,125 mg/kg/day is divided by a factor of 0.38 m^3/kg (rat breathing volume during 8 hours) and is multiplied by a factor of 6.7/10 for activity-driven differences of respiratory volumes in workers. This results in an inhalative starting point of 1,985 mg/m^3 (1,125 x 1/0.38 x 6.7/10).

For the identification of the reference MOS the interspecies factor of 2.5 for remaining differences is multiplied with an intraspecies factor of 5 which results in a reference MOS of 12.5 (2.5 x 5). The corresponding critical exposure level calculates to 159 mg/m^3 (1,985 / 12.5).

The highest inhalative exposure value of 6.25 mg/m^3 results from scenario 2a (use of Na_3NTA in formulation process, without LEV). Comparing this value with the critical exposure level of 159 mg/m^3 there is no is no reason for concern (see table 2.1.B).

Conclusion: ii

Dermal exposure

The internal starting point of 225 mg/kg/day is multiplied by the factor of 10 to account for 10% dermal absorption. This results in a value of 2,250 mg/kg/day (225 x 10) for the adequate dermal starting point.

For the calculation of the reference MOS an interspecies factor of 4 x 2.5 (rat) is taken. For intraspecies differences no further factor is used, because the dermal absorption percentage of 10%, taken from the experimental data is a very conservative approach which took the human variability into account. This results in a reference MOS of 10 (4 x 2.5) the corresponding critical exposure level calculates to 225 mg/kg/day (2250 / 10). There is no concern with respect to dermal acute toxicity (see table 2.1.B).

Conclusion: ii

Combined exposure

The internal starting point of 225 mg/kg/day is divided through the reference MOS of 10 (the reference MOS for internal and dermal exposure is identical). The corresponding critical exposure level calculates to 22.5 mg/kg/day (225 / 10).

There is no concern with respect to acute toxicity after combined exposure of trisodium nitrilotriacetate.

Conclusion: ii

Table 2.1.B: Estimation of MOS values for acute toxicity of trisodium nitrilotriacetate

			Inhalation			Dermal			Combined		
Starting point for MOS calculation			1,985 mg/m^3			2,250 mg/kg/day			225 mg/kg/day		
Reference MOS			12.5			10			10		
Critical exposure level			159 mg/m^3			225 mg/kg/day (external)			22.5 mg/kg/day (internal)		
			Exposure (mg/m^3)	MOS	Conclusions	Exposure (mg/kg/d)	MOS	Conclusions	Internal body burden (mg/kg/d)	MOS	Conclusions
1a	Production of Na_3NTA	dust	3.9	509	ii	0.6	3,750	ii	0.17	1,324	ii
1b		liquid				0.12	18,750	ii	0.12	1,875	ii
2a	Use of Na_3NTA in formulation process (up to 40%)	Dust, with LEV	0.62	3,200	ii	42.8	53	ii	4.3	52	ii
		Dust, without LEV	6.25	318	ii				4.46	50	ii
2b		liquid	negl.	-	ii	65.7	34	ii	6.6	34	ii
3a	High pressure cleaning (diluted solutions, < 2% NTA)	droplet aerosols	0.3	6,620	ii	3.6	625	ii	0.37	608	ii
3b		liquid				0.27	8,330	ii	0.04	5,625	ii

Irritation/Corrosivity

Skin

There are no human data on skin irritation. Experimental data (Draize test, rabbit, 25%-solution, 24-hour exposure) only indicate mild acute skin irritation. Trisodium nitrilotriacetate is not considered to be a skin irritating substance.

Conclusion: ii

Eyes

Moderate eye irritation was observed in a Draize test, which was not reversible within the study duration (Monsanto Company, unpublished report, 1968). Since the study was terminated on day 7, the reversibility of eye irritation on day 21 could not be assessed as required by standard protocols. However, due to the nature of the effects, irreversibility is not expected. Another study indicated recovery from moderate irritation following application of a 38% trisodium nitrilotriacetate solution (BASF, 1982), but this study does not allow to

conclude effects of the pure substance. Based on the limited data available, the current classification of R36 - Irritating to eyes - is confirmed.

For those trisodium nitrilotriacetate preparations which are classified and labelled as irritating to the eyes, conclusion ii is proposed on the grounds that control measures exist which can minimise exposure and risk of irritation, thereby reducing concern. However, these controls must be implemented and complied with to reduce the risk of irritation to the eyes.

Conclusion: ii

Inhalative irritation

There is no evidence for respiratory tract irritation in humans. In a rat inhalation study (6 h/d, 4 d) excessive concentrations of 2,000 mg/m³ trisodium nitrilotriacetate were irritative to the mucosa of the respiratory tract including the nose and the eyes. At 200 mg/m³ no adverse effects were reported (EPA, 1980). With reference to the highest occupational exposure levels of about 5 mg/m³ (shift average), a concern for acute respiratory tract irritation cannot be recognized, since significant reactions only occurred at highest concentrations.

Conclusion: ii

Sensitisation

Skin

Available data on skin sensitisation (Buehler test, human patch tests) do not show a skin sensitising potential, but these data are not considered sufficiently reliable in order to properly assess the skin sensitising potential of trisodium nitrilotriacetate. The performance of a Local Lymph Node Assay (LLNA, preferred) or a Magnusson Kligman Test could be considered. However, based on a “weight of evidence approach” based on QSAR considerations and negative findings for 3 structurally related substances (EU “new substances” notifications), further testing may be waived Overall, it can be concluded that there is no evidence to conclude a skin sensitising potential for NTA and additional testing may be waived.

Conclusion: ii

Respiratory sensitisation

No information on the sensitising potential of the substance at the respiratory tract is available. For the time being a valid study to investigate respiratory sensitisation in experimental animals cannot be recommended. However, trisodium nitrilotriacetate is not suspected to be a potent respiratory sensitiser in humans according to the fact that during all the years of use no notice of specific case reports has been given. There is no indication of concern with respect to respiratory sensitisation at the workplace.

Conclusion: ii

Repeated dose toxicity

Inhalation (local effects)

Inhalation studies on rats showed that excessive trisodium nitrilotriacetate concentrations of 2,000 mg/m³ (6 h/d, 4 d) were irritative to the mucosa of the respiratory tract including the nose and the eyes, whereas at 200 mg/m³ no adverse effects were reported. Prolongation of

inhalation exposure to a period of 4 weeks resulted in dyspnoe in rats and guinea pigs at trisodium nitrilotriacetate concentration of 340 mg/m³, the corresponding NOAEC for local effects in both species was 210 mg/m³. Histopathology data were absent. The experimental NOAEC of 210 mg/m^3 is taken to assess occupational risks after repeated inhalation.

The NOAEC is multiplied by a factor of 6.7/10 (activity-driven differences of respiratory volumes in workers) and a factor of 6/8 (differences between experimental exposure duration and occupational shift length of 8 h). This results in a value of 105 mg/m^3 as inhalation starting point (210 mg/m^3 x 6.7/10 x 6/8).

For the identification of the reference MOS the interspecies factor of 2.5 for remaining differences is multiplied with an intraspecies factor of 5. A reduced default factor to adjust for possible differences of thresholds for short-term and chronic exposure of 2 is used, because no difference between the NOAECs of the short-term study and the 4 week study was reported.

This gives altogether a reference MOS of 25 (2.5 x 5 x 2). The critical exposure level regarding local effects after repeated exposure is identified as 4.2 mg/m^3 (105 / 25).

Concern results for scenario 2a: Use of Na_3NTA in formulation process (up to 40%, dust, without LEV). The other scenarios are out of concern (see table 2.1.C).

Conclusion: iii

Table 2.1.C: MOS values for local effects of trisodium nitrilotriacetate after repeated inhalation

Starting point for MOS calculation		105 mg/m^3		
Reference MOS		25		
Critical exposure level		4.2 mg/m^3		
		Exposure (mg/m^3)	MOS	Conclusions
1. Production of Na_3NTA		3.9	27	ii
2a Use of Na_3NTA in formulation process (up to 40%), dust	with LEV	0.62	170	ii
	without LEV	6.25	17	iii
2b Use of Na_3NTA in formulation process (up to 40%), liquid		negl.	-	ii
3. High pressure cleaning (diluted solutions, < 2% NTA)		0.3	350	ii

Dermal contact (local effects)

Two ml/kg/day of a 2.5% aqueous solution of trisodium nitrilotriacetate (≈50 mg/kg/day) was applied to the clipped and abraded backs (no data on cm² of skin area) of 6 rabbits for a period of 91 days (65 treatments) (Nixon, 1971). No adverse effects were observed. However, the data reported were incompliant to standard test design.

Since in a Draize test with rabbits a 25% trisodium nitrilotriacetate-solution resulted in mild acute skin irritation after 24 hours, it cannot be excluded that repeated exposure to formulations with more than 25% trisodium nitrilotriacetate might result in slight irritation to the skin. Risk reduction is necessary, because after repeated exposure of trisodium nitrilotriacetate systemic effects are described and extrapolation leads to a low critical exposure level (see below). Therefore no further repeated dose toxicity study, regarding the dermal local effects is warranted.

Conclusion: ii

Systemic effects (RDT) by inhalation, dermal contact, combined exposure

No human data are available. Animal studies after repeated oral intake of trisodium nitrilotriacetate show, that the mainly affected organ system is the urinary tract with lesions at several organs: the kidneys, ureters and urinary bladder. Target tissues are the epithelium of the proximal convoluted tubels of the cortex region and the transitional cell epithelium of the renal pelvis, the ureters and the urinary bladder.

For the assessment of repeated dose toxicity an oral 24-month carcinogenicity rat study with trisodium nitrilotriacetate is used (NCI, 1977). In this study trisodium nitrilotriacetate was tested at diet concentrations of 0, 200, 2,000, and 20,000 ppm (app. 0, 9, 92, 921 mg nitrilotriacetate/kg/day.) Increased numbers of dysplasias in the urinary bladder and transitional cell hyperplasias were seen in the renal pelvis, the ureter and in the urinary bladder of males and females at all dose groups. At the high dose level body weight was significantly reduced and the mean survival rate for males was significantly lower. Additionally hydronephrosis was evident at the high dose level in most of the animals. Based on the findings of mortality increase and renal hydronephrosis at the high dose level, a NOAEL for toxic lesions could be estimated to 2,000 ppm (92 mg/kg/day). However, at this dose preneoplastic lesions in rats were increased since hyperplasias were observed at lower doses than cytotoxicity. The hyperplasias are interpreted as the relevant toxic effect and serve as basis for the assessment of repeated dose toxicity.

It is preferred to use a BMD value, calculated for the increase of hyperplasias. The BMDL10 regarding the hyperplasias was 5.7 mg/kg/day, when the Gamma Multi-Hit model was applied. This value serves as basis for the risk assessment of repeated dose toxicity (and later on for carcinogenicity).

Internal starting point

The calculation of the internal starting point has to account for a factor of 1/2 for 50% oral absorption for the rat, resulting from experimental data. The BMDL of 5.7 mg/kg/day will be transformed to an internal starting point of 2.85 mg/kg/day (5.7 x ½).

Inhalative exposure

Assuming a 20% absorption by inhalation, the internal starting point has to be multiplied by 5 to get the inhalatory dose. This results in a value of 14.3 mg/kg/day (2.85 mg/kg/day x 5). The inhalatory dose of 14.3 mg/kg/day is divided by a factor of 0.38 m^3/kg (rat breathing volume during 8 hours) and is multiplied by a factor of 6.7/10 for activity-driven differences of respiratory volumes in workers. This results in an inhalative starting point of 25 mg/m^3 (14.3 x 1/0.38 x 6.7/10).

For the identification of the reference MOS the interspecies factor of 2.5 for remaining differences is multiplied with an intraspecies factor of 5. This gives altogether a reference MOS of 12.5 (2.5 x 5). The corresponding critical exposure level calculates to 2 mg/m^3 (25 / 12.5).

Based on this calculation, scenario 1 (Production of Na_3NTA) and scenario 2a (use of Na_3NTA in formulation process, dust without LEV) reach concern (see table 2.1.D).

Conclusion: iii

Dermal exposure

The internal starting point of 2.85 mg/kg/day is multiplied by the factor of 10 to account for a 10% dermal absorption. This results in a value of 28.5 mg/kg/day (2.85 x 10) for the adequate dermal starting point.

For the calculation of the reference MOS an interspecies factor of 4 x 2.5 (rat) is taken. For intraspecies differences no further factor is used, because the dermal absorption percentage of

10%, taken from the experimental data is a very conservative approach which took the human variability into account. This results in a reference MOS of 10 (4 x 2.5) the corresponding critical exposure level calculates to 2.85 mg/kg/day (28.5 / 10).

Conclusion iii is expressed for scenarios 2a and 2b (use of Na_3NTA in formulation process, dust resp. liquid) and scenario 3a (high pressure cleaning with droplet aerosols). Particularly the concern for scenario 2a and 2b is pronounced, because the critical exposure level is exceeded by a factor of 15-25 (42.8 and 65.7 mg/kg/day exposure versus the critical exposure level of 2.85 mg/kg/day, see table 2.1.D).

Conclusion: iii

Combined exposure

The internal starting point of 2.85 mg/kg/day is divided through the reference MOS of 10 (the reference MOS for internal and dermal exposure is identical). The corresponding critical exposure level calculates to 0.285 mg/kg/day (2.85 / 10).

Nearly all scenarios reach concern except scenario 3b (high pressure cleaning, diluted solutions, < 2% NTA of liquids). This conclusion already results at least from a single route of exposure (inhalation and/or dermal), therefore no scenario has a specific concern regarding combined exposure.

Conclusion: iii

Mutagenicity

From the whole amount of data on mammalian somatic cells in vitro and in vivo, there is no plausible evidence for in vivo mutagenicity of NTA and its sodium salts. There is no reason for concern.

Conclusion: ii

Carcinogenicity

Carcinogenicity of inhalation, dermal, and combined exposure

There are several oral studies with administration of trisodium nitrilotriacetate via the diet or the drinking water available. These studies showed that long-term treatment with trisodium nitrilotriacetate was associated with tumor development in the urinary tract. Occupational risk assessment will rely on the results of the 24 months-study in rats with application of trisodium nitrilotriacetate in the diet. The study was also taken for the risk assessment of repeated dose toxicity (see above). F344 rats in groups of 24 males and 24 females were fed with diet concentrations of 0, 200, 2,000, and 20,000 ppm trisodium nitrilotriacetate (app. 0, 9, 92, 921 mg/kg/day). At all doses increased numbers of transitional cell hyperplasia of the urinary tract were seen with a significant increase at the middle and high dose group. Additionally one tumor (papilloma of the bladder) was found in a mid dose female, and several tumors at different stages were seen at multiple localisations (kidney, ureter, urinary bladder) at the high dose level.

Based on the actual knowledge a direct genotoxic mechanism of trisodium nitrilotriacetate carcinogenesis could not be demonstrated. For carcinogenic risk assessment it is assumed that carcinogenicity is mediated by a non-genotoxic (epigenetic) mechanism.

Based on the available data (see chapter on hazard assessment) the substance-induced development of hyperplasia (in the urinary bladder of the female rat) is taken as a primary adverse effect, finally resulting in the development of tumors. Thus the risk assessment for carcinogenicity starts with the same BMDL10 value of 5.7 mg/kg/day which was used for the assessment of repeated dose toxicity. The formal assessment factors and conclusions on carcinogenicity are therefore identical to the values for repeated dose toxicity. The calculations are shown in the chapter above and in table 2.1.D.

There is need for risk reduction after inhalation exposure for scenario 1 (Production of Na_3NTA) and scenario 2b (use of Na_3NTA in formulation process without LEV), and for dermal exposure of the scenarios 2a and 2b (use of Na_3NTA in formulation process, dust resp. liquid) and scenario 3a (high pressure cleaning with droplet aerosols). Especially the dermal exposure resulting from scenarios 2a and 2b has to be reduced, because exposure exceeds by a factor of about 40-60 compared with the critical exposure level.

Conclusion: iii

Table 2.1.D: MOS values for RDT and cancer risks by trisodium nitrilotriacetate

			Inhalation			Dermal			Combined		
Starting point for MOS calculation			25 mg/m^3			28.5 mg/kg/day			2.85 mg/kg/day		
Reference MOS			12.5			10			10		
Critical exposure level			2 mg/m^3			2.85 mg/kg/day (external)			0.285 mg/kg/day (internal)		
			Exposure (mg/m^3)	MOS	Conclusions	Exposure (mg/kg/d)	MOS	Conclusions	Internal body burden (mg/kg/d)	MOS	Conclusions
1a	Production of Na_3NTA	dust	3.9	6.4	iii	0.6	48	ii	0.17	17	iii[(1)]
1b		liquid				0.12	238	ii	0.12	24	iii[(1)]
2a	Use of Na_3NTA in formulation process (up to 40%)	Dust, with LEV	0.62	40	ii	42.8	0.7	iii	4.3	0.6	iii[(1)]
		Dust, without LEV	6.25	4	iii				4.46	0.6	iii[(1)]
2b		liquid	negl.	-	ii	65.7	0.4	iii	6.6	0.4	iii[(1)]
3a	High pressure cleaning (diluted solutions, < 2% NTA)	droplet aerosols	0.3	83	ii	3.6	8	iii	0.37	7.7	iii[(1)]
3b		liquid				0.27	148	ii	0.04	71	ii

[(1)]conclusion iii already results from inhalative and/or dermal exposure, therefore no specific concern regarding combined exposure is expressed

Reproductive toxicity

Fertility impairment and developmental effects by inhalation, dermal and combined exposure

Trisodium nitrilotriacetate did not adversely affect reproductive performance and capability through two successive generations in rats at dietary levels of approximately 450 mg/kg/day, whereas some mild toxicity (not further specified) had been reported. In addition, any specific teratogenic potential and/or impairment of embryo/fetal development are not indicated from the same data. Therefore no MOS calculation is performed for this endpoint. There is no reason for concern.

Conclusion: ii

2.1.3 Summary of occupational risk assessment

Table 2.1.E indicates the toxicological endpoints of concern for trisodium nitrilotriacetate. The most critical endpoints are repeated dose toxicity and carcinogenicity after inhalation and dermal contact and local effects after repeated inhalation.

Table 2.1.E: Endpoint-specific overall conclusions

Toxicological endpoints		General conclusion	Exposure Scenarios
Acute toxicity	inhalation	ii	
	dermal	ii	
	combined	ii	
Irritation/ Corrosivity	dermal	ii	
	eye	ii	
	acute respiratory tract	ii	
Sensitisation	skin	ii	
	respiratory	ii	
Repeated dose toxicity	inhalation, local	iii	2a
	inhalation, systemic	iii	1, 2a[(2)]
	dermal, local	ii	
	dermal, systemic	iii	2, 3a
	combined, systemic	iii	1, 2, 3a
Mutagenicity		ii	
Carcinogenicity	inhalation	iii	1, 2a
	dermal	iii	2, 3a
	combined	iii	1[(1)], 2[(1)], 3a[(1)]
Reproductive toxicity	inhalation	ii	
	dermal	ii	
	combined	ii	

[(1)]conclusion iii already results from inhalative and/or dermal exposure, therefore no specific concern for the combined exposure scenario is indicated

[(2)]without LEV

Risk estimation is mainly based on oral studies. There are no data known concerning absorption after inhalation or dermal application. Because of the chemical structure and physico-chemical data 20% absorption is assumed as default value for absorption via the inhalative exposure, and 10% for dermal absorption. These values were taken forward to risk characterisation.

The most critical toxicological endpoint is the systemic toxicity after repeated exposure respective carcinogenicity. For the risk assessment the increase of hyperplasias served as

combined starting point of both endpoints, assuming that carcinogenicity is mediated by a non-genotoxic (thresholded) mechanism. The collective starting point was calculated by using a Benchmark dose computation. The formal assessment factors and conclusions on carcinogenicity were identical for both endpoints. Thus an identical critical exposure level for both endpoints was identified.

Besides scenario 3b (high pressure cleaning (diluted solutions, <2% NTA) for liquids), all scenarios reach concern. Especially dermal exposure (with a critical exposure level of 2.85 mg/kg/day) has to be reduced for scenario 2 and 3, and inhalation exposure (with a critical exposure level of 2 mg/m^3) has to be reduced for scenario 1 and 2b.

Tables 2.1.F (inhalation) and 2.1.G (dermal contact) try to visualize the risk profile of trisodium nitrilotriacetate. According to the specific arrangement of exposure scenarios you will find the relatively high risks at the left upper corner, the relatively low risks at the bottom of the right corner. This table may help to reach consistent conclusions for different endpoints and scenarios.

Table 2.1.F: Ranking of occupational risks (inhalation) for trisodium nitrilotriacetate

Exposure scenario	Exposure (mg/m^3)	Carcinogenicity	Repeated dose toxicity (systemic)	Repeated dose toxicity (local)	Acute toxicity
		Critical exposure level in mg/m^3			
		2 mg/m^3	2 mg/m^3	4.2 mg/m^3	159 mg/m^3
a. Use of Na_3NTA in formulation process (up to 40%), dust without LEV	6.25	iii	iii	iii	ii
1.Production of NTA	3.9	iii	iii	ii	ii
2a.Use of Na_3NTA in formulation process (up to 40%), dust with LEV	0.62	ii	ii	ii	ii
3.High pressure cleaning (diluted solutions, <2% NTA)	0.3	ii	ii	ii	ii
2b. Use of Na_3NTA in formulation process, liquid (up to 40%)	negl.	ii	ii	ii	ii

Table 2.1.G: Ranking of occupational risks (dermal contact) for trisodium nitrilotriacetate

Exposure scenario	Exposure (mg/kg/d)	Carcinogenicity	Repeated dose toxicity (systemic)	Acute toxicity
		Critical exposure level in mg/kg/d		
		2.85	2.85	225
2b.Use of Na_3NTA in formulation process (up to 40%), liquid	65.7	iii	iii	ii
2a.Use of Na_3NTA in formulation process (up to 40%), dust	42.8	iii	iii	ii
3a.High pressure cleaning (diluted solutions, <2% NTA), droplet aerosols	3.6	iii	iii	ii
1a.Production of NTA, dust	0.6	ii	ii	ii
3b.High pressure cleaning (diluted solutions, <2% NTA)	0.27	ii	ii	ii
1b.Production of NTA, liquid	0.12	ii	ii	ii

2.2 Consumers

3 Current Risk Reduction Measures

Classification and labelling

Trisodium nitrilotriacetate is not included in Annex I of the Directive 67/548/EEC, but voluntarily labelled by industry with Xn, R22-40, S36/37-45 (GESTIS, 2008).

In March 2006 the EU-Working group on classification and labelling of dangerous substances under Directive 67/548/EEC agreed upon the following classification:

Carc. Cat. 3; R40

Xn; R22

Xi; R36

Concentration Limits:

C ≥ 25 %: Xn; R22-36-40

20 ≤ % C < 25 %: Xn; R36-40

5 ≤ % C < 20 %: Xn; R40

The agreed classification will be included in the 31. Adaption to Technical Progress (ATP).

Trisodium nitrilotriacetate will have to be labelled with

Xn, R22-36-40, S(2-)26-36/37-46

Abbreviations:

Carcinogenic, Cat. 3	Carcinogenic, Category 3
Xn	Harmful
Xi	Irritant
R 22	Harmful if swallowed
R 36	Irritating to eyes
R 40	Limited evidence of a carcinogenic effect
S (2-)	Keep out of the reach of children.
S 26	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice.
S 36/37	Wear suitable protective clothing and gloves.
S 45	In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible).
S 46	If swallowed, seek medical advice immediately and show this container or label.

3.1 Workers

As a result of its classification as a hazardous substance Trisodium nitrilotriacetate is subject to general regulations concerning its supply and handling.

Safety data sheets

In accordance with Regulation (EC) No 1907/2006 of the European Parliament and of the council of 18 December 2006, corrected in May 07 and amended in November 07 (Regulation (EG) Nr. 1354/2007) anyone placing Trisodium nitrilotriacetate on the market has to provide a safety data sheet for the professional user.

The information system for hazardous substances and preparations in the form of labelling and the safety data sheets is considered sufficient in principle to provide the user with appropriate information for the selection of suitable occupational safety measures.

Occupational safety and health regulations

Regarding the production and use of Trisodium nitrilotriacetate the following directives are primarily applicable as general regulations for occupational safety and health at the European level:

- 98/24/EC on the protection of workers from the risks related to exposure to chemical agents at work
- 89/656/EEC on the use of personal protective equipment

Only limited knowledge is available about the extent to which the EU Member States have in each case transposed these basic requirements into national law.

Occupational exposure Limits

There are no occupational exposure limit values for Trisodium nitrilotriacetate in the EU.

Personal Protection Equipment (PPE) against dermal and eye exposure

According to community legislation workers have to be provided with suitable PPE if their health is at risk due to exposure against chemicals. PPE that protects against the risks of Trisodium nitrilotriacetate is available. The Type of filter and the material of gloves, material thickness and breakthrough time have to be specified in the Safety Data Sheet.

Are existing controls sufficient to limit occupational risks?

It has been concluded from the risk assessment that there is a need for limiting the risks due to repeated dose toxicity and carcinogenicity which are the effects with the lowest critical exposure levels.

Dermal exposure:

Dermal exposure (with a critical exposure level of 2.85 mg/kg/day for both endpoints) has risen concern in scenario 2 "use of Na_3NTA in formulation process without PPE" and scenario 3 "high pressure cleaning without PPE".

Dermal exposure in scenario 2 "use of Na_3NTA in formulation process without PPE" has been assessed by default values and under the assumption that PPE is not used. Default values cover a range from worst case exposures to typical values. For the use of powders this range covers 3 000 – 900mg/p/day, for liquids 4600-164 mg/p/day. For risk assessment the higher values were taken forward in order to rise awareness. For the same reason exposure was assessed for the unprotected worker.

Workplace legislation covers a range of organisational, technical and personal protection measures that will be able to control the risks identified in the risk assessment. If a company follows good practice the exposures should not be higher than the typical values. The typical exposure levels assumed for use of liquids give no reason for concern. Exposure is 2.34 mg/kg/day (which is lower than CEL), even if PPE (gloves) would not used. If powders are used in formulation processes, typical exposures that could be achieved under the general conditions of good practice are still considerably higher (typical exposure 12.8 mg/kg/day) than the critical exposure level. In Addition to general good practice personal protection (gloves, efficacy supposed to be 90%) is necessary to reduce predicted exposures to a tolerable level (typical exposure and PPE result in 1,28mg/kg/day). Taking into account, that the risks of the substance, recommendations for handling and use and recommendations for appropriate PPE have to be communicated by labelling and Safety Data Sheet, additional measures to those foreseen in workplace legislation are not considered necessary to reduce the risks of dermal exposure in scenario 2.

The third scenario that has risen concern for dermal exposure was and scenario 3 "high pressure cleaning without PPE". Dermal exposures for this scenario were assessed by the EASE model resulting in an exposure range from 1.2 - 3,6mg/kg/day. For risk assessment the higher values were taken forward in order to rise awareness. For the same reason exposure was assessed for the unprotected worker. These worst case assumptions result in a merely slight upper deviation from the critical exposure limit. In addition, it has to be taken into account, that the critical exposure limit for dermal exposure has been derived under the conservative approach of 10% absorption through the skin. For the specific concentration range of 0,1-2% of NTA, which is typical for high pressure cleaning solutions, experimental in vitro data have shown distinctly lower absorption percentages through human skin (0.042 and 0.472 %). As a result of this closer analysis of data, additional measures to reduce the risk of dermal exposure during high pressure cleaning are not proposed.

Inhalative exposure

Inhalation exposure (with a critical exposure level of 2 mg/m^3 for repeated dose toxicity and carcinogenicity) has risen concern in scenario 1"production of NTA" and 2b"use of Na_3NTA

in formulation process without LEV". Additional measures to relieve this concern are discussed in Chapter 4 and 5.

3.2 Consumers

Trisodium nitrilotriacetate is not currently regulated under Council Directive 76/769/EEC (Restrictions on the marketing and use of dangerous substances) or under any other Community legislation.

4 Possible Further Risk Reduction Measures

4.1 Workers

The following further Risk Reduction Measure is considered to be probably effective:

- Occupational Exposure Limit

The option is assessed in section 5.

4.2 Consumers

5 Assessment of Possible Further Risk Reduction Measures

The TGD requires that possible further risk reduction options be examined against the following criteria

- effectiveness
- practicality
- economic impact
- monitorability.

5.1 Workers

Occupational Exposure Limit

Exposure reduction by technical and organisational measures and personal protection are foreseen in workplace legislation

In order to make such exposure reduction obligatory in the framework of worker protection legislation and enforceable in all scenarios, it is recommended to establish an occupational exposure limit for NTA.

This OEL should take into account the risk assessment (critical exposure level of 2 mg/m3 for the most critical effects). The OEL will also trigger that personal protective equipment is provided if workplace concentrations exceed the OEL in specific and non-routine-situations.

Within the framework of workplace legislation an occupational exposure limit is an enforceable and effective means to make exposure control obligatory. If this OEL takes into account the risk assessment, it can also be considered to be an effective means for health

protection in the workplace. It can be monitored by existing techniques of workplace measurement.

Data used for risk assessment comprised exposures higher than a possible OEL of 2 mg/m^3 in scenario 1 (production of NTA) and 2b (use of Na_3NTA in formulation process without LEV). For Risk assessment the higher exposures were taken forward to rise awareness: in scenario 1 the 95th percentile of measurements (3,9 mg/m^3) was used for risk assessment. Measured data however show a range from 0.02 – 5.6 mg/m^3 with a mean value of 1.3 mg/m^3. So it is plausible to suppose that in practice it will be practical to keep workplace air concentrations below 2 mg/m^3 .

Scenario 2b ran in concern only because of absence of LEV – which is not considered to be state of the art when handling dusty hazardous substances. So overall, the proposed OEL can be regarded as a practical measure that will not result in undue efforts for industry.

Marketing and Use Restrictions

Not applicable.

5.2 Consumers

6 Further Risk Reduction Measures Recommended

6.1 Workers

The risk reduction strategy recommends the following measures:

- to establish at community level an occupational exposure limit value for NTA according to Directive 98/24/EEC

- to apply the following revised classification and labelling of NTA in the forefront of a future Adaption to Technical Progress of Directive 67/548/EEC:

  Carc, Cat. 3, R40; Xn, R22; Xi, R36
  Concentration Limits:
  C ≥ 25 %: Xn; R22-36-40
  20 ≤ % C < 25 %: Xn; R36-40
  5 ≤ % C < 20 %: Xn; R40

- to transfer the classification into the Inventory according to Article 114 of Regulation (EC) 1907/2006

6.2 Consumers

7 Marketing And Use Restrictions

Not applicable for workers

8 Possible Monitoring Arrangements

9 Organisations consulted