

2. Exposure**2.1 General discussion**

Triethylenetetramine is produced by the reaction of aqueous ammonia with 1,2-dichloroethane. This process yields the entire family of ethyleneamines: ethylenediamine, piperazine, diethylenetriamine, triethylenetetramine, tetraethylenepentamine, pentaethylenhexamine and aminoethylpiperazine. These polyamines are produced as their hydrochloride salts, and must be neutralized, typically with aqueous caustic soda, to obtain the free amines. The by-product salt produced in the neutralisation step is separated and the individual products are isolated by fractional distillation (8).

TETA can be used as an intermediate in a number of production processes (10):

- The reaction with polyisobutenylsuccinic anhydride yields the corresponding polybutenylsuccinimides, which are ashless, dispersant-detergent additives for motor oil.
- Polyamide-epichlorohydrin resins are produced by the reaction of epichlorohydrin with a polyamide, such as those formed by polymerisation of adipic acid and TETA. These are used in the paper industry as wet-strength additives for liner board, toweling, tissue and sanitary applications.
- The ethoxylated products of TETA are curing agents for epoxy resins. The largest application is surface coatings (35%).
- Imidazolines from the condensation of TETA with two moles of fatty acid are cationic surfactants used as fabric softeners, asphalt emulsifiers, oil field corrosion inhibitors, ore flotation agents and epoxy curing agents.
- Reactive polyamides from the polymerisation of dimer acids with TETA are mostly used as curing agents for epoxy surface coatings.

In 1989 - 1991, 1200 - 1500 t/a were produced in Germany. Production capacities as of 1990 for other countries are available as well (8):

Netherlands	ca. 6000 t/a	(2 sites)
USA	> 11000 t/a	(3 sites)
Japan	ca. 1800 t/a	(1 site)

According to the German producer, ca. 40 to 50% are sold in Germany (> 10 clients) and ca. 40 - 50 % are exported; the rest is further processed by the same producer. Import volumes are estimated by the producer at ca. 1500 t/a. The total consumption in Germany amounts to ca. 2200 t/a.

In Germany, triethylenetetramine (TETA) is mainly used as

- intermediate for curing agents for epoxy resins (ca. 1600 t/a)
- direct curing agent for epoxy resins (ca. 160 t/a)
- intermediary for auxiliary agents used in the paper industry, the textile industry and in glues (ca. 330 t/a)
- intermediate for asphalt emulsifiers (ca. 110 t/a)

Ca. 100 t/a are used by the producer as an intermediate. No information is available on the processing at other chemical manufacturers.

In Sweden, the use pattern of TETA is similar to the use pattern described for Germany:

- intermediate for transport, fertilizer and plastics industry (200 - 533 t/a)
- adhesive, binding agent (4 - 6 t/a)
- hardener for plastic (1 - 4 t/a)
- others (max 5 t/a)

The use pattern for other countries is not available.

2.2 Environmental exposure

2.2.1 General/Environmental fate

TETA is completely miscible with water forming an alkaline solution (pH 10 at 10 g/l). The technical product has a vapour pressure of ca. 1 Pa at 20 °C. The calculated Log Pow (unprotonated form) amounts to ca. -1.4 and indicates a low potential for bioaccumulation. There are no measured Koc-values available. For ethylenediamine (CAS Nr. 107-15-3) and diethylenetriamine (CAS Nr. 111-40-0), Koc-values of 4766 and 19111 were measured respectively (1). The high adsorption is most likely due to electrostatic interaction. A comparable Koc can be expected for TETA, which would suggest a high potential for geoaccumulation.

Based on the physical-chemical properties the target compartment of TETA in the environment is the hydrosphere (the estimation of the distribution with a Fugacity model is not opportune due to the protophile behaviour of TETA).

TETA is not readily biodegradable (0% after 20 days, OECD GL 301 D; same result with adapted inoculum). Also, in a test on inherent biodegradability with industrial sludge, TETA was not degraded (0 % DOC removal after 28 days, OECD GL 302 B). TETA has therefore to be regarded as **non biodegradable**. Adsorption onto sewage sludge was not observed.

In a test on hydrolysis, TETA was not found to have undergone hydrolysis after 36 days.

Direct photolysis of TETA in the hydrosphere is not to be expected (molar extinction coefficient < 10 l / (mol·cm) at > 240 nm). The half-life due to photooxidative degradation by OH-radicals in the atmosphere is estimated to be 1.7 hours. As TETA does have a low tendency to pass from water to air, this does not represent a significant removal process from the environment.

Based upon the physical-chemical and biodegradation properties of TETA, no elimination in waste water treatment plants is assumed.

2.2.2 Exposure assessment

a) Local concentrations

Considering the above described use pattern, point releases are to be expected during production and processing.

production

According to the German producer, no continuous releases occur during the production process to waste water. During cleaning operations of the production facility and the distillation column, the releases are estimated by the German producer at ca. 1 g/t related to the production capacity (8). For a production capacity of 5000 t/a (worst case assumption) a release of 5000 g TETA during one day (assuming one cleaning operation per year) can be estimated. Assuming no elimination in the WWTP, 5000 g are released into a river with a flow of 60 m³/s, according to the generic release scenario for production in (3). A **PEC_{local} of 1 µg/l** is calculated.

processing

Many processes involving TETA as intermediate with different release rates are to be expected.

Specific data are available only from one German producer, using ca. 100 t TETA per year for processing with fatty acids: a maximum of 2.4 kg/a are released to the waste water (8).

For a generic estimation, the following worst case situation according to the release scenario for intermediates described in (3) is used.

For a processing site using 1000 t/a of TETA, a release factor of 0.7 % is assumed. Considering no elimination in the WWTP, 7 t/a are released into a river with a flow of 60 m³/s. Assuming release over 300 days per year, a concentration of **PEC_{local} = 4.5 µg/l** is calculated.

b. Regional concentrations

Diffuse release into the environment would occur through the direct use of TETA as a curing agent. Also, the curing agents produced from TETA contain residual concentrations of TETA (approx. 7.9%).

The final extent of conversion of TETA during curing reactions is not known. On the other hand, the conversion of diethylenetriamine was determined to be 60 to 80 % (2) (related to the total NH-functions). As TETA presents 6 NH-functions, a molecular conversion rate of > 90% can be assumed.

About 160 t/a of TETA are used directly as curing agent. With a conversion factor of 90%, ca. 16 t are available as free molecules in the resins. On the worst case assumption, that 10% are released through migration from the matrix (3), a maximum of 1.6 t/a are released into the environment through this path.

About 1600 t/a are processed to yield curing agents containing an average of 7.9% free TETA. For a rough estimate, it is assumed that TETA reacts with the same amount of chemicals so that 3200 t of curing agents with ca. 250 t of free TETA result. Of these, max. 10% (see above) remain unreacted in the curing process and 10 % of these may be released through migration, i.e. a maximum of 2.5 t/a.

For the calculation of the regional PEC the use of a fugacity model is not opportune due to the ionic nature of TETA. The regional concentration can be estimated in a first approach with the following formula (9):

$$PEC_{\text{regional}} = \frac{EMIS}{FLOW + V \cdot k}$$

with: EMIS: emission into surface water = $1.6 + 2.5 = 4.1$ t/a
 FLOW: flow through the water compartment
 V: Volume of water compartment
 k: first order biodegradation rate constant

The default values described in (3) will be used for the calculation:

- a small but densely populated area is considered: 200x200 km with 20 million inhabitants;
- with an area fraction of water of 0.02 and a mixing depth of 3 m, $V = 2.4 \cdot 10^9$ m³
- with an average residence time of the water of 40 days, $FLOW = 6 \cdot 10^7$ m³/d
- TETA being non-biodegradable, $k = 0$

=> **PEC_{regional} = 0.18 µg/l**

2.3 Consumer exposure

Where epoxy resins are cured in do-it-yourself applications (e.g. in coatings, adhesives, and epoxy-fiber composites), consumers may come into contact with TETA or TETA-derived curing agents, either when mixing the ingredients, or when grinding and polishing the solidified product whereby unreacted TETA may be set free.

2.4 Occupational exposure

The production unit simultaneously produces ethylenediamine, diethylenetriamine, triethylenetetramine and other substances from ammonia and 1,2-dichloroethane.

To date, exposure to triethylenetetramine (TETA) has not been measured directly. Instead, exposure is estimated on the basis of measurements of ethylenediamine (according to TRGS 402) - the end product with the lowest boiling point.

The MAK-value of 25 mg/m³ for ethylenediamine is consistently met. All measurements indicate that exposure is below 1 mg/m³.

Substance	Boiling Point	Vapour Pressure
Ethylenediamine	116.5 °C	12.1 hPa
TETA	approx. 280 °C	< 0.1 hPa

Due to ethylenediamine's significantly lower boiling point and its greater vapour pressure (by a factor of 100) it can be concluded with certainty that the concentration of TETA in the air during synthesis and processing does not exceed 0.1 mg/m³.

Exposure is, therefore, clearly below the actual occupational exposure limit of 6 mg/m³ in Sweden.

3. Toxicity

3.1 Human Toxicity

a) Acute Toxicity

Triethylene tetramine is of low acute toxicity on oral administration (LD₅₀ rat > 2000 mg/kg bw) and moderate toxicity on dermal application (LD₅₀ rabbit 550-805 mg/kg bw). Exposure to saturated vapour was tolerated without impairment whereas the exposure to aerosol leads to reversible irritations of the mucous membranes in the respiratory tract. According to EC Directive 67/584/EEC triethylene tetramine is labelled as harmful in contact with skin (R 21).

Conclusion:

Moderate acute toxicity

Priority setting: low priority or concern

b) Repeated Dose Toxicity

In a subacute study (rat, oral, up to 2980 mg/kg bw) retarded body weight gain and elevated liver and kidney weights were observed in the highest dose groups. From this study, a NOAEL of 500 mg/kg was derived.

In a subacute study, undiluted test substance was rubbed into the skin of pregnant and non-pregnant guinea pigs (4 mg/guinea pig and day = ca. 9 mg/kg bw) daily for 55 days. In the course of the experiment the death of test animals (2/9) as well as of the control animals (6/11) occurred (11). In another study, dermal application to pregnant and non-pregnant guinea pigs (4 mg/animal = ca. 9 mg/kg bw) daily for the first 10 days and every second day for next 45 days resulted in reduced weight gain, and from the 5th day of treatment in inflammatory alterations at the application site with subsequent erosions. In the course of the experiment 7/11 pregnant and 7/11 non-pregnant animals died (12). It is unclear whether the death of the animals is due to the strong irritant and/or the skin sensitization potential of the test substance.

In an additional study F344 rats and B6C3F1 mice received triethylenetetramine dihydrochloride in the drinking water at concentrations of 0, 120, 600, 3000 ppm (target concentration) for up to 92 days. Each dose group were fed either cereal based (NIH-31) or purified (AIN-76A) diet both containing nutritionally adequate levels of copper. An additional control group of rats and mice received a Cu-deficient AIN-76A diet. Signs of triethylenetetramine dihydrochloride toxicity were noted only in B6C3F1 mice fed AIN-76A diet given 3000 ppm triethylenetetramine dihydrochloride. These toxic signs included inflammation of the lung interstitium, hemapoetic cell proliferation of the spleen, liver periportal fatty infiltration, kidney weight reduction, reduced renal cytoplasmatic vacuolization and body weight gain reduction. From this study a NOAEL of 600 ppm for mice was derived. According to the authors, the signs observed in F344 rats appear to be related to copper deficiency (13).

Lifelong dermal application to mice (1.2 mg/mouse and application) caused no skin tumours or any tumours.

In a former inhalation study with rats, mice, guinea pig and rabbit (aerosol: 0.4 ml in 0.5 ml ethanol in a 400 l chamber, 10 d), no irritations or other toxic effects were observed.

Conclusion:

Signs of impairment only in mice following subchronic oral dosing of 3000 ppm triethylenetetramine dihydrochloride. NOAEL: 600 ppm [92 (male), 99 (female) mg/kg bw].

Priority setting low priority or concern

c) Reproductive/Developmental Toxicity

In rabbits, triethylene tetramine does not cause embryotoxic and teratogenic effects, even at maternally toxic dose levels (4).

In rats, there are several studies concerning developmental toxicity. The oral treatment of rats with 75, 375 and 750 mg/kg resulted in no effects on dams and fetuses, except slight increased fetal body weight (5). After oral treatment of rats with 830 or 1670 mg/kg bw only in the highest dose group increased fetal abnormalities in 27/44 fetus (69,2 %) were recorded, when simultaneously the copper content of the feed was reduced. Copper-supplementation in the feed reduced significant the fetal abnormalities of the highest dose group to 3/51 (6,5 % fetus. These findings suggest that the developmental toxicity is produced as a secondary consequence of the chelating properties of triethylene tetramine (6).

In chapter 3.1.b) 2 studies on pregnant guinea pigs dermally treated with 4 mg/animal = ca. 9 mg/kg bw daily for 55 days or daily for 10 days and every second day for the next 45 days, respectively, were described (11, 12). Beside the clear mortality rate and the local effects, necrotic changes of the placenta and miscarriage or mortification of the fetuses and stillbirth of malformed fetuses were observed. Due to the clear maternal toxicity and due to the lack of dose-response relationship the reported studies are not suitable to evaluate developmental toxicity.

There are no data on effects on fertility with triethylene tetramine. In the subchronic toxicity studies with mice and rats, which were described in chapter 3.1.b, the reproductive organs are examined. In mice, there were no treatment related effects on the reproductive organs. According to the authors the only finding which may be attributable to trien-2HCl occurred in AIN-76A-fed female rats. There was a significant dose-related trend toward an increased prevalence of uterine dilatation (13). There are no changes of the vagina and the ovaries. Therefore dilatation of uterus in isolation cannot be regarded as hormonal effects. Thus, this finding is not suitable to evaluate any reproductive toxicity. In addition, oral treatment of rats with the analogue diethylene triamine caused no adverse effects respective mating index, fertility index and number of live and dead pups.

Triethylene tetramine is used in the therapy of Wilson's disease. While taking 400 to 800 mg triethylene tetramine 3 times a day for about 120 months, there have been six pregnancies in four female patients. There were no miscarriages and no fetal abnormalities. All six children developed normally (7).

Conclusion:

From experiences with humans (substance given as a drug) there is no reason to assume that the substance reveals effects on reproduction.

Priority setting: low priority or concern

d) Genetic Toxicity

The results of the genetic toxicity testing are not uniform. In vitro, triethylene tetramine has clear genotoxic activity in the Ames-test and in mammalian cytogenetic tests. Whereas in vivo, triethylene tetramine is not clastogenic in the mouse micronucleus test following intraperitoneal injections of 130 to 600 mg/kg bw. The study was conducted in accordance with GLP standards. In addition, there is a further micronucleus test using oral application (14) which yielded a negative result as well. In this study, mice received once 1500, 3000 and 6000 mg/kg bw. These doses are within the range of and/or greater than the LD50 value for mice, which is cited in the basic data set: LD50(mice) = 1600 mg/kg bw (15). The test design and test performance was carried out according to W. Schmid and coworkers who developed the test (see references).

Following 1500 and 3000 mg/kg bw the percentage of erythrocytes containing micronuclei corresponds with the percentage of those in the concurrent solvent control. Following 6000 mg/kg bw a decrease in erythrocytes containing micronuclei was noted and was thus lower than those in the concurrent solvent control.

Triethylene tetramine revealed no mutagenic activity in the SLRL test in *Drosophila melanogaster*.

Conclusion:

As triethylene tetramine revealed no mutagenic activity in relevant in-vivo tests there is no reason to assume genotoxicity.

Priority setting: low priority or concern

e) Sensitization

The sensitization potency of triethylene tetramine was investigated in the Guinea Pig Maximization Test (GPMT) and in the Mouse Ear Swelling Test (MEST).

One of the GPMTs (16) used triethylene tetramine as a commercial product (no further information on purity of the substance). The method used was in accordance with the original description of the GPMT by Magnusson and Kligman (20, 21). Control animals received vehicle only. Induction concentration was 0.5 % in water and challenge concentration was 2 %. 12/15 animals (80 %) showed positive reactions 24 hours after removal of the patch. In the second GPM test, carried out according to OECD Guideline 406, purified TETA (purity: 99.5 %) was used and the applied concentrations were for induction 0.5 % and for challenge 2 % as well. As positive control served dinitrochlorobenzene. 9/10 animals (90 %) showed positive reactions (17). As additional test, the MEST was performed with 10 mice (17). The concentration of the purified TETA (purity: 99.5%) for the induction procedure was 10 % and the challenge concentration was 2.5 %. Oxazolone served as positive control. In 4/10 mice positive reactions were seen.

Cross reactions between triethylene tetramine, ethylenediamine and diethylenetriamine were also observed in guinea pigs (18).

Numerous reports concern the sensitizing potential of triethylene tetramine in humans (18).

In Poland, 20 - 51.2 % out of 20 - 447 examined workers exposed to epoxy resins reacted positive to triethylene tetramine (19). At another factory dermatitis was observed in 126 out of 422 workers. Skin tests were carried out on 99 patients. A positive reaction was observed in 55.1 % of these cases (18). In an examination of 20 workers exposed to casting resins and triethylene tetramine 5 showed positive reaction to triethylene tetramine whereas in another group of 23 epoxy resin-workers, suffering from dermatitis, none

reacted positive on a patch test with triethylene tetramine (18). In a control group of 112 persons 2 persons (1.5 %) gave positive patch test results (18).

Cross reactions between triethylene tetramine, diethylenetriamine and ethylenediamine were also reported (18).

Conclusion:

Triethylene tetramine induces skin sensitization in guinea pigs, mice and man. According to EC Directive 67/584/EEC triethelyene tetramine is labelled: R 43 = may cause sensitization by skin contact.

3.2 Ecotoxicity

3.2.1 Aquatic organisms

a) Toxicity to fish

<i>Poecilia reticulata</i>	96h-LC ₅₀	570 mg/l
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Other test results with *Leuciscus idus* and *Pimephales promelas*, which could not be validated, are in the same order of magnitude.

b) Toxicity to invertebrates

<i>Daphnia magna</i> (several tests)	48h-EC ₅₀	31.1 - 33.9 mg/l
Effect: immobilisation	21d-EC ₅₀	> 3.2 - < 10 mg/l
	21d-NOEC	1 mg/l

(immobilisation of parental organisms was the most sensitive effect parameter)

Furthermore, concentrations of 293 - 7313 mg/l had no teratogenic effects on sea-urchin (*Paracentrotus lividus*) eggs. The larvae were most sensitive and showed delay of development at 293 mg/l

c) Toxicity to algae

<i>Scenedesmus subspicatus</i>	72h-E _B C ₅₀	2.5 mg/l
	72h-E _B C ₁₀	0.67 mg/l
	72h-E _μ C ₅₀	>= 100 mg/l
	72h-E _μ C ₁₀	0.95 mg/l

Effect: growth inhibition (B = biomass; μ = growth rate)

Due to the intensive growth of the algae the pH in the control and in the concentrations up to 1 mg/l increased within 72 h to 10.2 - 10.3.

<i>Selenastrum capricornutum</i>	72h-EC ₅₀	20 mg/l
Effect: growth inhibition (biomass)	72h-NOEC	< 2.5 mg/l

<i>Selenastrum capricornutum</i>	96h-EC ₅₀	3,7 mg/l
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Effect: growth inhibition (biomass)

A further test with *Chlorella pyrenoidosa* was considered to be non valid.

d) Toxicity to microorganisms

Pseudomonas fluorescens 24h-EC₀ 500 mg/l

Effect: growth inhibition (biomass)

e) Derivation of PNEC

Algae are clearly the most sensitive species to TETA. According to the EU-Technical Guidance Document (3), the value of the safety factor is **F = 50** (long term tests have been performed for two trophic levels and with the organisms which were the most sensitive in the acute tests).

With the lowest aquatic effect concentration of 0.67 mg/l:

$$\text{PNEC} = \frac{670}{50} = 13.4 \mu\text{g/l}$$

3.2.2 Terrestrial organisms

Acute oral toxicity to the redwinged blackbird (*Agelaius phoeniceus*) was determined to be 18h-LD₅₀ > 101 mg/kg bw.

4. Initial Assessment

4.1 Human toxicity

4.1.1 Identification of critical toxic effects

Triethylene tetramine is a severe irritant to skin and eyes and induces skin sensitizations. Triethylene tetramine is of moderate acute toxicity: LD50(oral, rat) > 2000 mg/kg bw, LD50(dermal, rabbit) = 550 - 805 mg/kg bw. Acute exposure to saturated vapour via inhalation was tolerated without impairment.

Following repeated oral dosing via drinking water only in mice but not in rats at concentration of 3000 ppm there were signs of impairment. The NOAEL is 600 ppm [92 mg/kg bw (oral, 90 days)]. Lifelong dermal application to mice (1.2 mg/mouse) did not result in tumour formation.

There are differing results of the genetic toxicity for triethylene tetramine. The positive results of the in vitro tests may be the result of a direct genetic action as well as a result of an interference with essential metal ions. Due to this uncertainty of the in vitro tests, the genetic toxicity of triethylene tetramine has to be assessed on the basis of in vivo tests. The in vivo micronucleus tests (i.p. and oral) and the SLRL test showed negative results.

There are no data on reproductive toxicity (fertility assessment). The analogue diethylene triamine had no effects on reproduction. Triethylene tetramine shows developmental toxicity in animal studies if the chelating property of the substance is effective. The NOEL is 830 mg/kg bw (oral).

Experience with female patients suffering from Wilson's disease demonstrated that no miscarriages and no fetal abnormalities occur during treatment with triethylene tetramine.

4.1.2 Comparison of Exposure and Critical effects

Workplace

There are no measurements of the concentration of triethylene tetramine in the air at the workplace. To estimate the exposition at the workplace adequately the results of the concentration measurements of the product with the lowest boiling point has to be applied: ethylene diamine (see chapter 4.2). All results of these measurements are below 1 mg/m³ (TLV: 25 mg/m³). Because of the higher boiling point and the lower vapour pressure of triethylene tetramine it can be assumed that the concentration in the air at the workplace is below or equal than 0.1 mg/m³.

The EHE (Estimated Human Exposure) can be calculated according to the following equation:

$$\text{EHE} = \frac{\text{respiratory rate (10 m}^3\text{)} * \text{exposition (mg/m}^3\text{)}}{\text{body weight (70 kg)}}$$

exposition < 1 mg/m³

EHE < 0.143 mg/kg bw

exposition < 0.1 mg/m³

EHE < 0.0143 mg/kg bw

Thus the estimated human exposure is far below the NOAEL described in animal experiments of 92 mg/kg bw for subacute toxicity and a NOAEL of 850 mg/kg bw for teratogenicity. The safety margin based on the lowest NOAEL is between:

$$\frac{92 \text{ mg/kg bw}}{< 0.143 \text{ mg/kg bw}} > 643.4 \quad \text{and} \quad \frac{92 \text{ mg/kg bw}}{< 0.0143 \text{ mg/kg bw}} > 6434$$

and thus does not suggest a particular risk.

Isolated cases of exposure through skin contact cannot be ruled out. However, the risk is to be assumed very low.

Consumer area

Data on consumer exposure are not available. However, it cannot be excluded that products containing triethylene tetramine give off small amounts of the substance. Due to the low toxicity in animal experiments it can be assumed that the probability of acute poisoning is very low. In addition, the application of triethylene tetramine as drug excluded high toxicity to humans. Also multiple administration of TETA to animals did cause neither significant systemic effects nor the formation of tumours.

Exposure via the environment

Data are not available on exposure of the general population. Exposure of the population via the hydrosphere is considered to be minimal, even assuming the concentration in drinking water to be equal to the regional predicted concentration in surface waters (0.18 µg/l). With 2 l drinking water/person/day, the daily dose would be 0.005 µg/kg bw/day. Compared to the exposure at the working place the exposure through the environment is negligible.

4.2 Assessment of environmental hazards

In the following table, the PEC/PNEC ratios for the different exposure scenarios are presented:

Scenario	PEC _{local} + PEC _{regional} [µg/l]	PEC/PNEC
production (site)	1 + 0.18	0.08
processing (site)	4.5 + 0.18	0.35

A PEC/PNEC < 1 in all scenarios, a low potential risk to the aquatic compartment is at present to be expected.

A significant exposure to the **terrestrial** compartment could not be identified. Further work is presently not necessary for an assessment of risks to this compartment.

5. Conclusions and Recommendations

An environmental hazard assessment of triethylenetetramine was possible with the available data and showed that the compound was presently of low concern to the environment. No further work is recommended.

On the basis of the known facts and properties, triethylene tetramine may represent a hazard for human health. The chemical is a severe irritant to skin and eyes and induces skin sensitization. The substance is classified and labelled accordingly within the EU: R 34 = causes burns; R 43 = may cause sensitization by skin contact.

From experience with humans (substance given as a drug) there is no reason to assume that the substance reveals further toxic effects. Besides appropriate classification and labelling no further work is recommended.