European Union Risk Assessment Report

2,3-EPOXYPROPYLTRIMETHYLAMMONIUM CHLORIDE

CAS No: 3033-77-0

EINECS No: 221-221-0

RISK ASSESSMENT

FINAL APPROVED VERSION

LEGAL NOTICE

Cataloguing data can be found at the end of this publication

Luxembourg: Office for Official Publications of the European Communities, [ECB: year]
ISBN [ECB: insert number here]

Printed in Italy

2,3-EPOXYPROPYLTRIMETHYLAMMONIUM CHLORIDE

CAS No: 3033-77-0

EINECS No: 221-221-0

RISK ASSESSMENT

Final report 2008

Finland

Rapporteur for the risk assessment of 2,3-Epoxypropyltrimethylammonium chloride (EPTAC) is the National Product Control Agency for Welfare and Health, Finland

Contact (human health): National Product Control Agency for Welfare and Health
Chemicals Department
Mr. Marko Kuittinen
e-mail: Marko.Kuittinen@sttv.fi
Fax: +358 (9) 3967 2768

Contact (environment): Finnish Environment Institute
Expert Services Department
Chemicals Division
Mrs Jaana Heiskanen
e-mail:Jaana.K.Heiskanen@ymparisto.fi
Fax: +358 (20) 490 2591

Date of Last Literature Search : **2003**
Review of report by MS Technical Experts finalised: **5/2008**
Final report: **2008**

Foreword

This Draft Risk assessment Report is carried out in accordance with Council Regulation (EEC) 793/93[1] on the evaluation and control of the risks of "existing" substances. "Existing" substances are chemical substances in use within the European Community before September 1981 and listed in the European Inventory of Existing Commercial Chemical Substances. Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of these substances if they are produced or imported into the Community in volumes above 10 tonnes per year.

There are four overall stages in the Regulation for reducing the risks: data collection, priority setting, risk assessment and risk reduction. Data provided by Industry are used by Member States and the Commission services to determine the priority of the substances which need to be assessed. For each substance on a priority list, a Member State volunteers to act as "Rapporteur", undertaking the in-depth Risk Assessment and recommending a strategy to limit the risks of exposure to the substance, if necessary.

The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC) 1488/94[2], which is supported by a technical guidance document[3]. Normally, the "Rapporteur" and individual companies producing, importing and/or using the chemicals work closely together to develop a draft Risk Assessment Report, which is then presented at a Meeting of Member State technical experts for endorsement. The Risk Assessment Report is then peer-reviewed by the Scientific Committee on Health and Environmental Risks (SCHER) which gives its opinion to the European Commission on the quality of the risk assessment.

This Draft Risk Assessment Report is currently under discussion in the Competent Group of Member State experts with the aim of reaching consensus. During the course of these discussions, the scientific interpretation of the underlying scientific information may change, more information may be included and even the conclusions reached in this draft may change. The Competent Group of Member State experts seek as wide a distribution of these drafts as possible, in order to assure as complete and accurate an information basis as possible. The information contained in this Draft Risk Assessment Report does not, therefore, necessarily provide a sufficient basis for decision making regarding the hazards, exposures or the risks associated with the priority substance.

This Draft Risk Assessment Report is the responsibility of the Member State rapporteur. In order to avoid possible misinterpretations or misuse of the findings in this draft, anyone wishing to cite or quote this report is advised to contact the Member State rapporteur beforehand.

[1] O.J. No L 084, 05/04/199 p.0001 – 0075

[2] O.J. No L 161, 29/06/1994 p. 0003 – 0011

[3] Technical Guidance Document, Part I – V, ISBN 92-827-801 [1234]

0 OVERALL RESULTS OF THE RISK ASSESSMENT[4]

CAS Number: 3033-77-0
EINECS Number: 221-221-0
IUPAC Name: 2,3-Epoxypropyltrimethylammonium chloride

Environment

Conclusions for the aquatic compartment (including marine environment):

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to surface water and sediment from cationisation of starch with wet process (Industrial use scenario 1) at local scale for five sites (i.e. sites B4, B9, B10, B23 and B25).

From these five starch cationisation sites, which have risk ratio higher than one, two sites (B4, B25) have monitoring data on EPTAC releases to waste water. The detection limit of EPTAC from waste water effluent (0.7-10 mg/l) is rather high compared to PNEC (0.016 mg/l). Use of lower detection limit might decrease risk from these two sites. For those three sites where no monitoring data is available (B9, B10, B23), releases have been calculated with an actual emission factor from a starch cationisation site with highest release factor (1.32 %). Biodegradation at the WWTP has been assumed to take place at these sites.

The PNEC for water and sediment has been calculated from the chronic NOEC for Daphnia using an assessment factor of 10. Refinement of PNEC is therefore not possible with the dataset currently available.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to fresh water and sediment from production of EPTAC and cationisation of starch with dry process for seven sites (B6, B11, B12, B13, B15, B22 and B28) and with wet process for seven sites (B3, B5, B14, B16, B17, B18 and B21) (Industrial use 1). Conclusion (ii) also applies to paper and board scenario (Industrial use 2), paper recycling (Industrial use 3), AKD formulation (Industrial use 4) and other uses of CHPTAC and EPTAC (Industrial use 5). Conclusion applies also to waste water treatment plants and marine environment from all scenarios.

Conclusions for the atmosphere and terrestrial compartment:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

4 Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion applies to production and all use scenarios.

Human health

Human health (toxicity)

Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to all worker exposure scenarios because of concerns for mutagenicity, carcinogenicity and sensitisation.

Conclusion (iii) also applies in relation to concerns from repeat dose toxicity for sampling and laboratory work during production of EPTAC.

Conclusion (i) There is a need for further information and/or testing.

There is a need to further investigate the reproductive toxicity in a 2-generation fertility test and a developmental toxicity test. However, since EPTAC is a genotoxic carcinogen, this property alone is sufficient to lead to the strictest measures for risk management in work places. Therefore, ***conclusion i on hold*** is drawn for all scenarios .

Consumers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all scenarios since exposure to consumers is considered to be negligible.

Humans exposed via the environment

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account..

Although the modelled exposure figure is likely to be an over estimate, risks can not be excluded as the substance EPTAC is identified as a non-threshold carcinogen thus Conclusion (iii) is drawn for mutagenicity and carcinogenicity. However, the risk assessment indicates that risks are already very low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

Human health (physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all scenarios.

CONTENTS

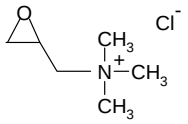
EUSES Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 3033-77-0
EINECS Number: 221- 221-0
IUPAC Name: 2,3-Epoxypropyltrimethylammonium chloride
Molecular formula: $C_6H_{14}NOCl$
Structural formula:



Molecular weight: 151.66
Synonyms: EPTAC, Oxiranemethanaminium, N,N,N-trimethyl chloride, Glycydyltrimethylammonium chloride

For the purpose of this report, the substance 2,3-Epoxypropyltrimethylammonium chloride will be referred to as EPTAC, which has been derived from its IUPAC name.

1.2 PURITY/IMPURITIES, ADDITIVES

The typical concentration of technical EPTAC is 70-75 % water solution. The solubility of the substance limits higher water concentrations. Main impurities are:

Table 1.0: EPTAC impurities

CAS-No:	Name:	Contents:
3327-22-8	3-chlorohydroxypropyltrimethylammonium chloride (CHPTAC)	< 4 %
34004-36-9	2,3-dihydroxypropyltrimethylammonium chloride (diol)	< 3.5 %
55636-09-4	1.3-propanediaminium, 2-hydroxy-N,N,N,N',N',N'-hexamethyl-, dichloride	< 1.5 %
91725-36-9	(3-hydroxypropenyl)trimethylammonium chloride	< 0.2%
106-96-8	Epichlorohydrin	< 10 ppm

In order to prevent or minimize hydrolysis, the commercial EPTAC products contain a small quantity of 3-chlorohydroxypropyltrimethylammonium chloride (max. 4 wt-%, typically 1-2 wt-%). In addition, EPTAC is kept under controlled temperature during storage and transport (Raisio Chemicals, 2004b). For the purpose of this report, the substance 3-chlorohydroxypropyltrimethylammonium chloride will be referred to as CHPTAC, which has been derived from its IUPAC name.

1.3 PHYSICO-CHEMICAL PROPERTIES

Pure EPTAC is at 20 °C and 101.3 kPa a solid substance, which is highly flammable. However, EPTAC is marketed and used as a non-flammable water solution. The physico-chemical analyses were performed in accordance with the EEC-guidelines. The reports contained GLP compliance statements and quality assurance statements. Summary of the physico-chemical data is presented in Table 1.1.

Table 1.1 Summary of physico-chemical properties

Property	Value	Comment
Physical state	solid	
Melting point	118 °C - 126 °C	The temperature range of melting and simultaneous decomposition was between 118 °C and 126 °C. At 118 °C a short melting process started, but this was strongly overlaid by a decomposition process. Method: DSC method, EEC-guideline 92/69/EEC A.1 (CEFIC, 1997d).
Boiling point	-	Boiling point could not be determined because the substance decomposed in the range of the melting point 118 °C and 126 °C. (
Relative density	1.178	At 20 °C for 97.3 % substance. Pycnometer method, EEC-guideline 92/69/EEC A.3 (CEFIC, 1997e).
Vapour pressure	$< 10^{-3}$ Pa	In the temperature range between 22 °C and 80°C. Due to the exothermic decomposition at 120 °C, the upper temperature of the measurement was limited to 80 °C. Test method: Vapour pressure balance, EEC-guideline 92/69/EEC A.4 (CEFIC, 1997a).
Water solubility	852.0 ± 16.7 g/l	At 20 °C. Two factors may have affected the results: 1) one of triplicates was excluded due to a putative handling mistake, 2) a minor proportion of EPTAC was possibly hydrolysed during the test. The pH value of the test solution: pH > 11. Test method: Flask method, EEC-guideline 92/69/EEC A.6 (CEFIC, 1997h).
Partition coefficient n-octanol/water (log value)	Pow < 0.05 or log Pow < -1.3	The partition coefficient (1-octanol/buffered water phase, pH 4 at 25 ± 1 °C. The test substance was not detected in the 1-octanol phase. Therefore, the calculations are based on the detection limit (50 mg/l) and on the concentrations of EPTAC in the water phase. The recoveries were unsatisfactory, possible as a result of partial hydrolysis. The primary results at pH 7 were not reproducible, and could not be used for any evaluation. Test method: Shake flask method, EEC-guideline 92/69 EEC A.8 (CEFIC, 1998c)
Partition coefficient organic carbon-water	Koc 53.8 l/kg	Mesured concentrations of EPTAC from the OECD 303A STP simulation study allowed a Koc of 53.8 to be determined ($K_{p,sludge}$ 26.9 l/kg, assuming an organic carbon content of 50 %), which is equivalent to log Koc = 1.73.
Granulometry	-	-
Conversion factors	-	-
Flash point	138 °C (70%), 155°C (75 %)	(Degussa, 1981b)
Autoflammability	Not self-ignitable	Recording of the self-heating when the temperature was increased up to 400 °C at a rate of 0.5 °C/min, EEC-guideline 92/69/EEC A.16 (CEFIC, 1997f).

Property	Value	Comment
Flammability	Classified as highly flammable.	In a burning rate test, fire in the pile of CHPTAC went out after <45 seconds at a distance of 100 mm. Test method: Burning rate test, EEC-guideline 92/69EEC A.10 (CEFIC, 1997c).*
Explosive properties	No explosive properties	No reactions were observed in tests of thermal or mechanical sensitivity. (In the test of thermal sensitivity, slight damage was found at the bottom of the test tubes in serial two.) Test methods: a test for thermal sensitivity, a test for mechanical sensitivity (shock), and a test for mechanical sensitivity (friction), EEC-guideline 92/69/EEC A.14 (CEFIC, 1997b).
Oxidizing properties	Not likely oxidising	According to Industry statement EPTAC does not have groups which would accelerate the burning rate of a combustible substance. Therefore the study (EEC-guideline 92/69/EEC A.17.) was not performed. Epoxides are generally reactive substances which may have oxidising and corrosive properties.
Viscosity	-	-
Henry's constant	<1.78 · 10-7 Pa m3/mol	Calculated using a vapour pressure of < 0.001 Pa
Surface tension	73 mN/m	Surface tension of an aqueous solution (1 g/l) at 20 °C. CHPTAC is not a surfactant. Method: Ring method. EEC-guideline 92/69/EEC A.5 (CEFIC, 1997g).

* EPTAC is sold only in water solution which is not expected to be flammable.

1.4 CLASSIFICATION

The substance is not at present classified at community level according to the Dir. 67/548/EEC. The manufacturers' classification is:

Classification: Carc. Cat. 2; R45, Muta. Cat. 3;R68, Xn; R 21/22-R48/22, Xi; R41-43;

An agreement was reached on classification by the EU classification and labelling working group. EPTAC is a candidate for the draft proposal of the 31st ATP.

1.4.1 Proposal for Classification on the 31st ATP

Classification: Carc. Cat. 2; R45, Muta Cat 3; R68, Repr. Cat 3; R62, Xn; R21/22-48/22, Xi; R41, R43, R52-53

Labelling: T, R:45-21/22-41-43-48/22-62-68-52/53

S-pharases: S53-45-61

2 GENERAL INFORMATION ON EXPOSURE

2.1 PRODUCTION

2.1.1 Production processes

EPTAC is synthesised from epichlorohydrin, trimethylamine and water. Hydrochloric acid and sodium hydroxide are needed as catalysts. The product is a water solution containing EPTAC 70-75%. Manufacturing process is a closed system, which is operated from a remote control room. According to the producers, this chemical in dry form is not manufactured any more. Also other ways to synthesise EPTAC have been described in the literature.

2.1.2 Production capacity

During 1990-1993 there were two producers of EPTAC within the EU: Degussa AG in Germany and Raisio Chemicals Oy in Finland. The annual production of EPTAC in Europe was over 1000 metric tons per site. In 1998 Degussa ceased its production. In addition to Raisio Chemicals Oy (Finland) there is another company i.e. Sachem Europe (Netherlands), which has started their production of EPTAC in 2002. Due to confidentiality reasons the production volumes for individual producers have not been presented. Taking into account production, import and export volumes, the total volume for consumption was 3866 tons in 1996, 5240 tons in 1999 and 6153 tons in 2001 (CEFIC, 1998d); (CEFIC, 2000a); (QUAS, 2004c). A decrease in EPTAC consumption volumes has been observed in 2002 and 2003. Consumption volumes reached in 2003 a similar level as in 1996 (see table 2.2).

2.2 USES

The main use of EPTAC is for cationisation of starches. Cationised starches are added in paper to give paper better surface quality having to use less starch than without cationising. They are also used in paper making to improve paper strength. According to information from CEFIC 99 % of the volume was used for this purpose and only 1 % for quaternisation of other products such as guar, cellulose derivatives, and proteins in 2001 (Table 2.1) (QUAS, 2004c). Cationised guar gum is used as a retention aid and sizing agent in manufacture of paper and paperboard used for food products. Guar gum is also used as a flocculant in mining industry. Cationised hydroxyethylcellulose is added in hair conditioning and emollient cosmetic creams.

Table 2.1 Uses of EPTAC in 2001 **(QUAS 2004c)**

Use category	Quantity used tons	Percentage of total use
Cationisation of starch	6 082	99
Quaternisation of cellulose, protein, guar and other derivatives	71	1
Total	6 153	100

Industry sent a questionnaire to all known industrial users of EPTAC in 1997 to find out more on uses and exposure. Based on this information there was 11 companies which used EPTAC in the EU in 1997: 9 sites producing cationized starch and two quaternized proteins. The volume covered by these 11 users was 5100 tons which is almost 100 % of the total consumption volume in 1999. In the cationisation of starches amounts of EPTAC used by single plant ranged from 9 to 1387 tons in 1997 (CEFIC, 2000b).

More common chemical for the production of cationic starch is 3-Chloro-2-hydroxypropyl-trimethylammonium chloride (CHPTAC, CAS No. 3327-22-8). Emissions of EPTAC are likely from cationisation with CHPTAC too, since CHPTAC is always transformed to EPTAC before the cationisation of starch and it is the EPTAC which reacts in the reactor with the starch. There was 13 companies using CHPTAC in the EU in 1997: 12 sites producing cationized starch and one quaternised guar. In the cationisation of starches amounts of CHPTAC used by single plant ranged from 23 to 6105 tons in 1997.

On the basis of update carried out in 2004 the total number of EPTAC and CHPTAC users had not increased: in 2001 there were 5 sites using EPTAC, 4 sites using both EPTAC and CHPTAC and 11 sites using CHPTAC for starch cationisation in the EU (QUAS, 2004a). Summed volume of known EPTAC and/or CHPTAC starch cationisation sites covered 94 % of the total volume used for starch cationisation in 2001. In addition some sites had large stocks, which were not consumed in 2001. The total number of known sites using EPTAC or CHPTAC in general was 22 in 2001. Volumes of EPTAC used by single plant ranged from 8.5 tons to 1611 tons and CHPTAC from 2.9 tons to 7947 tons in 2001.

Residual levels of EPTAC (and CHPTAC) have been measured in the cationised starch. According to a survey done by industry in 1998 a range from < 50 to 1400 mg/kg EPTAC was found in the 68 commercial cationic starches available on the European market. A new survey was carried out in 2002, where 95th percentile over 200 samples was 150 mg/kg and 90th percentile was 100 mg/kg (QUAS, 2002). The most recent monitoring programme was initiated by AAC (Accociation des Amidonneries de Cereales de I'U.E) upon request by QUAS in 2003. In this monitoring programme each AAC member was requested to provide 10 samples from different batches of the grades marketed in the largest volumes. Samples were analysed in the IRCOF (Chemistry Research Centre CNRS, INSA – Rouen University in France) by Prof. Conbret with the HPLC/ion exchange/conductimetry detection method. These analyses will replace the data provided earlier as the same analytical method have been used for all samples, samples have been analysed by independent expert and the collection of samples has been organised better (companies that took part in the study represent 75-80 % of the total market of cationic starches) (Oral communication from the representatives of the industry, 29 August 2003). Based on these 58 samples 90th percentile of the EPTAC concentrations was 15.3 mg/kg and the 95th percentile 24.5 mg/kg.

2.3 TRENDS

The total consumption volume of EPTAC (including both import and export) has increased steadily from 3866 tons in 1996 to 6153 tons in 2001 (CEFIC, 1998d); (QUAS, 2004a). A significant decrease in the EPTAC use volumes was observed in 2002 and 2003 (see table 2.2). As the use of CHPTAC leads to releases of EPTAC, consumption of both EPTAC and CHPTAC has been presented in Table 2.2. The total use of EPTAC and CHPTAC has continuously increased between 1996 and 2002.

Table 2.2 Consumption of EPTAC and CHPTAC between 1996 and 2003 (tons/year). CHPTAC volume and total volume is expressed as EPTAC , where the molecular weight difference (CHPTAC: 188 vs. EPTAC: 151) has been taken into account (modified from (QUAS, 2004a)).

	EPTAC	CHPTAC (as EPTAC)	Total (as EPTAC)
1996	3 866	16 835	20 701
1999	5 240	18 543	23 783
2001	6 153	19 031	25 184
2002	5 237	22 455	27 692
2003	3 937	22 097	26 034

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

EPTAC may be released into the environment during its production and industrial use. EPTAC releases have also been monitored from waste water during use of CHPTAC (3-Chloro-2-hydroxypropyl-trimethylammonium chloride) (CAS-3327-22-8). Furthermore releases of EPTAC are likely due to conversion of CHPTAC to EPTAC in the environment. The conversion half-life from CHPTAC to EPTAC is 21 days at pH 7.8 (12 ˚C) according to a laboratory test. Conversion of CHPTAC to EPTAC will be considered at the regional and continental scale in the risk assessment of EPTAC. Conversion in the environment will not be taken into account at local scale.

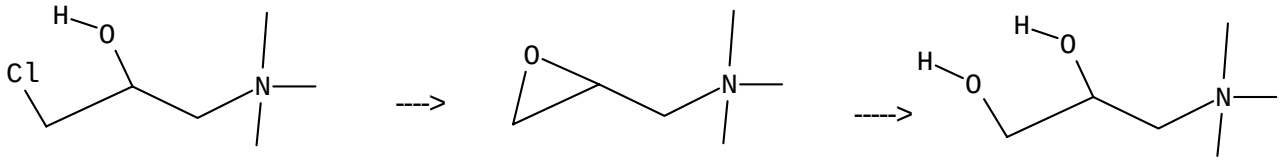
Six exposure scenarios are assessed at the local scale:

1. Production of EPTAC
2. Cationisation of starch with EPTAC and CHPTAC (industrial use scenario 1)
3. Use of starch with residual EPTAC in paper making (industrial use scenario 2)
4. Residual EPTAC and CHPTAC in paper recycling (industrial use scenario 3)
5. Use of starch with residual EPTAC in formulation of Alkyl Ketene Dimer emulsions (AKD-wax) (industrial use scenario 4)
6. Other uses of EPTAC and CHPTAC (industrial use scenario 5).

During cationisation of starch (industrial use scenario 1) direct EPTAC emissions are likely from use of CHPTAC as the cationisation process is carried out in pH > 10 where the CHPTAC will convert to EPTAC. In concentrated aquatic solutions CHPTAC and EPTAC are in principle in equilibrium with each other. During starch cationisation process in very alkaline solutions (pH > 10) the equilibrium balance is strongly, but not entirely, on the side of EPTAC and the reactive form is the EPTAC. Thus the intention in the processes is to convert CHPTAC as much as possible to EPTAC. At the end of cationisation process the starch is neutralised with mineral or organic acid which leads to the conversion of residual EPTAC to the corresponding CHPTAC. To conclude, as the chemical reacting in the cationisation process is EPTAC, there will be direct releases of EPTAC from starch cationisation with CHPTAC and EPTAC. This will be considered at the local scale in the risk assessment of EPTAC.

Conversion of CHPTAC and EPTAC to 2,3-Dihydroxypropyltrimethylammonium-chloride (CAS 34004-36-9) is a competitive reaction during the starch cationisation.For the purpose of this report, the substance 2,3-Dihydroxypropyltrimethylammoniumchloride will be referred to as DIOL., which has been derived from its IUPAC name. DIOL is formed from EPTAC and smaller percentage directly from CHPTAC during the activation of CHPTAC. DIOL is the main by-product yielding up to 15 g/kg modified starch (Hellwig et al., 1992).

Reactions observed are:



CHPTAC EPTAC "DIOL"

In aquatic environment (and in dilute solutions) the same reactions as in cationizing processes are expected to take place, but reactions back to CHPTAC (reactions from right to left) are unlikely. Direct hydrolysis/conversion from CHPTAC to DIOL is possible, but this reaction route is expected to be of minor importance (Hellwig et al., 1992). In a recent hydrolysis test with EPTAC (Raisio Chemicals, 2004) the rate of EPTAC hydrolysis to DIOL was slow, the mean half-life was 177 days at pH 7.8 (12 ˚C). Therefore further conversion to DIOL will not be taken into account in local PEC calculations of EPTAC.

3.1.2 Environmental releases

3.1.2.1 Release from production

Until 1998 there were two producers of EPTAC within the EU, but from 1999 EPTAC was produced by one producer only. In 2002 another company, Sachem Europe (Netherlands) started their production of EPTAC. Due to confidentiality reasons the production volumes for individual produsers, both total and company specific, have not been presented. . Total consumption volume, including production, import and export was 5200 tons in 1999 and 6153 tons in 2001.

EPTAC is produced in a batch process as an aqueous solution up to about 75 %. Due to hazard properties of the starting material epichlorohydrin special care has been taken to keep the process closed. As the synthesis product EPTAC is not washed with water, there are no releases to water or releases are low. Site-specific release information from both existing production plants are presented in Table 3.1.

Table 3.1 Local releases to water from production.

Site	Release to WWTP	Observations
A1	-	Production stopped at this site in 1998.
A2	0	Waste waters recycled back to process
A3	negligible	Waste waters from cleaning of the reactor will be collected to storage vessels, where residual EPTAC will be converted to DIOL. After that waste water is discharged to WWTP.

No emissions to air are expected from production of EPTAC according to TGD.

3.1.2.2 Release from formulation

There is no real formulation step in the production of EPTAC, but different concentrations are derived directly from the production process. Manufacturers of EPTAC produce aqueous solutions of EPTAC at their production plants, which are then sold as such to customers for use. In order to prevent or minimize hydrolysis, the commercial EPTAC products contain a small quantity of CHPTAC (typically 1-2 wt-%). In addition, EPTAC is kept under controlled temperature during storage and transport (Raisio Chemicals, 2004b). Based on the information from the producers no further formulation is carried out for EPTAC.

3.1.2.3 Release from industrial/professional use

3.1.2.3.1 Cationisation of starches (industrial use scenario 1)

In the following section releases of EPTAC from cationisation of starch with EPTAC and CHPTAC are estimated, because releases of both substances are likely using either EPTAC or CHPTAC. In concentrated aquatic solutions CHPTAC and EPTAC are in equilibrium with each other. During cationisation of starch in very alkaline solutions (pH > 10) the equilibrium balance is strongly, but not entirely, on the side of EPTAC. The intention in the process is to convert CHPTAC as much as possible to EPTAC.

At the end of the reaction the cationic starch is generally neutralised with mineral or organic acid to bring the product at the required pH (range 3.0 to 7.0). The acidic pH should lead to the conversion of residual EPTAC to the corresponding CHPTAC. Nevertheless, the reverse reaction is slow and requires relatively high temperature (> 60 ˚C) and strong acidity to be completed. For this reason a mixture of CHPTAC and EPTAC is typically observed in starch as well as in waste water.

Releases to water

EPTAC and CHPTAC are mainly used for cationisation of starches. Cationic starches are added to paper or board to improve dry-strength, printing quality and to improve retention. There were 9 sites using EPTAC and 12 sites using CHPTAC for starch cationisation in the EU in 1996-97. Based on the update for 2001 the number of sites using EPTAC was 5, 4 sites were using both EPTAC and CHPTAC and 11 sites using CHPTAC for starch cationisation in the EU (QUAS, 2004a). EPTAC volume used by these sites was 5941 tons and CHPTAC volume 16 979 tons (as EPTAC) i.e. the total volume was 22 920 tons (as EPTAC) in 2001. In 2001 the total use volume of EPTAC and CHPTAC for starch cationisation was 24 274 tons (as EPTAC), so the known sites cover 94 % of the total volume (QUAS, 2004c). Volumes used by single plants have been higher with CHPTAC: volumes have ranged from 23 to 6105 tons per year as the volumes for EPTAC have ranged from 9 to 1387 tons per year during 1996-97 (CEFIC, 2000b). In 2001 volumes of EPTAC used by single plant ranged from 8.5 tons to 1611 tons (as EPTAC) and CHPTAC from 2.9 tons to 7947 tons (as CHPTAC). All known users use 70 % to 75 % aqueous solution of EPTAC and 50 % to 70 % aqueous solution of CHPTAC.

The cationic starch can be manufactured with two different processes: slurry or dry process. Based on the CEFIC QUAS sector group questionnaire in 1996-97 on EPTAC plants producing cationized starch or proteins there are 5 plants using dry process and 6 using wet/slurry process (QUAS, 2000b). For CHPTAC plants wet/slurry process is mainly used,

but there are CHPTAC sites that use both wet and dry processes. In the slurry process cationic starch is usually filtrated and dried with flash dryer producing waste water. This waste water is usually directed to the WWTP at site or to the municipal WWTP. In the dry process, starch is in powder form to which EPTAC and the catalyst base are introduced. Only low amount of water allows high temperatures to be used in the reaction. Dry cationized starches are typically not washed. The EPTAC process is described as batch process in 9 cases and continuous in 2 cases and when using CHPTAC batch process in 13 cases and continuous in 3 cases (QUAS, 2000b).

Reaction efficiencies in wet and dry cationisation processes differ significantly. Efficiencies can be quite poor especially in wet cationisation from 50 % yield (wheat starch) up to 80 % (potato starch). Unreacted (20-50 %) EPTAC/CHPTAC and DIOL (mainly) are washed to the waste water streams of the cationisation plant. Dry process is more efficient and the yield is ca. 90-95% (Hellwig et al., 1992).

For 9 CHPTAC sites there are measured EPTAC and CHPTAC concentrations available (Table 3.2). EPTAC releases to industrial waste water treatment plants have ranged at these sites from 0.003 t/a to 12.8 t/a, when calculated from the average measured influent concentration. Site-specific emission factors for EPTAC are as follow: 0.0002 %, 0.04 %, 0.06 %, 0.07 %, 0.19 %, 0.70 %, 0.78 %, 1.11 %, and 1.32 %. For EPTAC these sites cover 77 % of the year 2001 total volume used by sites with aquatic releases. An emission factor of 0.7 % to water from processing can be found from the TGD (Table A3.3; Industrial category 3, Chemical Industry: Chemicals used in synthesis, Use category 33: Intermediates).

Table 3.2. Measured releases of EPTAC and CHPTAC from starch cationisation plants to WWTP (calculated from measured average CHPTAC and EPTAC influent concentrations)

Site	Release of EPTAC to industrial WWTP (t/a)	Release of CHPTAC to industrial WWTP (t/a)	Observations
CHPTAC users			
B3	**8.4**	**17.1**	Measured CHPTAC and EPTAC concentrations from influent and effluent available. Volume of 2 WWTPs and receiving water known.
B4	**0.68**	**6.84**	Measured CHPTAC and EPTAC concentrations from influent and effluent available. Volume of WWTP and river flow known.
B5	**0.92(avg) (min. 0.78 , max 1.06**)	**7.28 (avg) (min 5.12 , max 9.44)**	Measured CHPTAC and EPTAC concentrations from influent and effluent available. Volume of 2 WWTPs and receiving water known.
B14	**10.2**	**7.22**	Measured CHPTAC and EPTAC influent and effluent concentrations available. Volume of WWTP and river flow known.
B16	**1.15**	**0.6**	Measured CHPTAC and EPTAC influent and effluent are available. Volume of 2 WWTPs and receiving water known.
B17	**0.003**	**0.113**	Measured CHPTAC and EPTAC influent and effluent concentrations available. Volume of 2 WWTPs and receiving water known.
B18	**0.387**	**0.173**	Measured CHPTAC and EPTAC influent and effluent are available. Volume of 2 WWTPs and receiving water known.
B21	**7.15**	**5.78 (avg) (min.5.57, max.6.02)**	Measured CHPTAC and EPTAC influent and effluent concentration known. Volume of 2 WWTPs and receiving water known.

Site	Release of EPTAC to industrial WWTP (t/a)	Release of CHPTAC to industrial WWTP (t/a)	Observations
B25	**12.81**	**1.42**	Measured CHPTAC and EPTAC concentrations from influent and effluent available. 2 different types of uses at same site. Volume of waste water and cooling water known, dilution to receiving water known.
Total	**41.7**	**46.52**	

For 2 CHPTAC sites and 1 EPTAC site no monitoring data on waste water concentrations is available. For these sites only use volume and the size of WTTP is known. Therefore the highest emission factor of 1.32 % from an existing site and 300 processing days has been used to calculate releases of EPTAC or CHPTAC to water (Table 3.3).

In addition to site-specific exposure estimation presented above, there is a no need to make a generic estimation at a local scale, because the EPTAC + CHPTAC volumes (including both wet and dry processes) used by known sites in 2001 (5 941 + 16 979 = 22 920 t, expressed as EPTAC) covers 94 % of the total volume used for starch cationisation in 2001 (6082 + 18 192 = 24 274 t as EPTAC).

Table 3.3 Calculated local releases of EPTAC from cationisation of starch. Emission factor of 1.32 % has been used to calculate releases.

Site	Release of EPTAC to industrial WWTP (t/a)	Observations
EPTAC users		
B9	6.57	Size of the WWTP known.
B19	-	This site closed at the end of 2002
CHPTAC users		
B10	4.29	Size of the WWTP and river flow known.
B23	24.47	Only volume of effluent and flow of river known.
B26	-	This site closed in 2004
Total	35.33	

For five EPTAC sites and two CHPTAC sites there are no releases to wastewater due to dry process or other process related reasons (Table 3.4). According to Hellwig et. al. (1992) dry process has been more in favour in recent years because there are no effluents from the process and no starch losses exist as a result of washing process. No releases to water have been estimated from plants using dry process.

From site B6 (EPTAC and CHPTAC user) there is no waste water from normal process. Spillages are collected and EPTAC and CHPTAC are converted into DIOL at high pH / long residence time in water. Cleaning water (500 m^3/a) from the site is mixed with high volume of water (200 –300 000 m^3/a) coming from the potato starch plant and sprayed on green fields

(i.e. cultivated areas). Industry states that calculation of local aquatic concentrations is not applicable for these sites. There is no information on the EPTAC or CHPTAC concentrations of the cleaning water and therefore it has not been possible to estimate releases or calculate PECs for this site.

Table 3.4. Justifications on no releases to water based on site-specific information

Site	Justification
EPTAC users	
B6	No waste water from normal process. Cleaning waters are diluted and sprayed on green fields.
B11	Dry process, no emissions to water.
B13	Dry process, no emissions to water.
B15	No waste waters generated. Cleaning waters are re-used in the process.
B22	Dry process, no emissions to water. Industrial and municipal WWTP available.
CHPTAC users	
B12	Waste water is evaporated and concentrated solution is incinerated, partly dry process
B28	Dry process, no emissions to water.

Emissions to air

An emission factor of 0.001 % to air for processing can be found from the TGD for Industrial category 3: Chemical Industry, Chemicals used in synthesis (TGD Table A3.3). Taking into account site-specific use volumes the local emissions to air ranged between 0.011 kg/d and 0.214 kg/d (64.2 kg/a).

Regarding site-specific emission data industry states that there are 4 sites using EPTAC where no emissions to air exist (CEFIC, 2000). In addition there are 6 sites using EPTAC which have measured air emissions. However, site-specific information has been made available to the Rapporteur only for one EPTAC user and one CHPTAC user, where EPTAC emissions are 0.017 kg/a and 0.118 kg/a, respectively.

For CHPTAC there are 11 sites where no emissions to air exist (CEFIC, 2000). In addition there are 3 sites using CHPTAC where CHPTAC emissions are estimated to be 0.308 kg/a, 0.648 kg/a and 1.75 kg/a.

Air emissions estimated according to TGD emission factor results to higher releases and will be used for further calculation side by side with the measured emissions.

3.1.2.3.2 Use of starch with residual EPTAC and CHPTAC in paper making (industrial use scenario 2)

Emissions of EPTAC are also likely from the use of cationised starch in the production of paper and board due to residual levels of EPTAC in the starch. In addition, EPTAC releases may also arise from use of AKD wax (Alkyl Ketene Dimers) which is being formulated with cationic starch. Cationic starch and AKD wax are used in paper making mainly to improve paper strength and printing quality. Starches used to increase the internal strength of paper are added in the beginning (wet end) of the paper/ cardboard machine, whereas starch used to

increase surface strength are added after the wire at the size press as dry end chemicals. For some paper types the cationized starch will be added in both sections of the paper machine.Therefore release estimations from production of three different kind of paper types will be presented:

1) slightly water resistant high grade board for book of small children (wet end use),

2) printing and writing paper (including magazines, excluding newspaper) (wet and dry end use) and

3) food grade board for packaging of dry food like corn flakes or pasta (wet end use).

According to TGD there are no releases to air from this use (Industrial category 12: Pulp, paper and board Industry) and therefore local assessment has not been carried out for this scenario.

Consumption of cationised starch in a paper mill varies from hundreds to thousands tons per year depending on the paper grade manufactured. The total consumption of cationic starch in the EU by paper and board industry is around 550 000 tons per year, representing more than a quarter of the total starch consumption (CEFIC, 2000a). Concentration of EPTAC in the cationized starch as a residue will vary due to type of the starch product and process parameters. In the latest survey from 2003 the EPTAC concentration ranged from 3 to 66 mg/kg in 58 commercial cationic starch available on the European market. For the release calculations value of 90th percentile, 15 mg/kg for EPTAC and 450 mg/kg for CHPTAC, will be used. When taking into account molecular weight difference between CHPTAC and EPTAC (0.81) the CHPTAC residue in starch expressed as EPTAC will be 0.81 x 450 mg/kg = 364.5 mg/kg. This will be used in further calculations.

Before the cationized starches are used in the paper machine, they are typically cooked with a jet-cooker i.e. cooking with steam under a high pressure. Typical cooking temperature is between 120 and 150 °C and the pH varies between 6 - 8. In the jet-cooking simulation made by the industry it was found out that about 45 % of the EPTAC was degraded (not highly dependent on the pH), but that that EPTAC was also formed (11 %) during degradation of CHPTAC (Raisio Chemicals, 1999).

<u>High grade board for books (case 1)</u>

Cationized starch is added to the head box of the paper machine with other wet-end solids. The amount of cationized starch added at this stage may vary from 2-20 kg/ton paper or 0.2-2.5 % of wet end solids. For the local emission estimation 10 kg of cationic starches is dosed per ton of board and in addition it is assumed that also AKD-wax of 0.5 kg/t will be added (contains cationic starches). The amount of residual EPTAC from wet end additive is 150 mg/ton (=10 kg/ton x 15 mg/kg) and from AKD-wax 7.5 mg/ton (=0.5kg/ton x 15 mg/kg). After jet-cooking the amounts will be reduced to 82.5 mg/ton and 4.1 mg/ton, respectively. However, the starch may contain also residual levels of CHPTAC, which will degrade to EPTAC: (11 % x 10 kg/ton x 364.5 mg/ton) + (11 % x 0.5 kg/ton x 364.5 mg/ton) = 421 mg/ton. So the total EPTAC volume is thus 508 mg/ton paper i.e. roughly 0.5 g/ton.

Adsorption of EPTAC to the fibre is poor, maximum 1 % (Raisio Chemicals, 2000), so 99 % of the substance is assumed to maintain in the waste water. However cationic starch once adsorbed also remains fixed on the wet end fibre (Neimo, 1999). EPTAC may also retain to

the paper with the water that remains in the paper after press section of the paper/board machine, but this has not been taken into account in the environmental assessment. Degradation of EPTAC during drying section at the board machine may reduce emissions to water slightly: 5 % degradation/elimination may occur due to longer drying period and higher temperature at the end of the board machine compared to paper machine (Raisio Chemicals, 2000). At the paper machine no remarkable degradation/elimination occur due to short drying time. For the exposure assessment no further adsorption or degradation during drying has been assumed.

Cationized starch is used in paper and board mills with different size. For this calculation an existing board mill which produces 800 000 tons board per year has been chosen. The average number of days in operation for this mill is 350, so it gives a daily production capacity of 2286 tons per day. When we multiply these 2286 tons by the concentration 0.508/ton we get the maximum daily release of 1.161 kg/day to WWTP. This corresponds to 406 kg per year.

Printing and writing paper (case 2)

For some paper types like printing and writing paper cationized starch is added on two sections of the paper machine: at the beginning of the process into the furnish (wet end use) and in the end of the process on the surface of the paper (as surface sizing agent). Printing and writing paper is chosen to represent most probably the highest dosage used in paper mills. For the local emission estimation dosages used are: 7 kg starch /ton paper at the beginning of the process (at the wet end), 1,5 kg/ton as AKD-wax and 40 kg/ton as surface sizing. However, when estimating the releases to water there is no need to take into account the use as surface sizing, since the cationic starch is added to dry paper and thus there are no releases to aquatic environment from surface sizing. The amount of residual EPTAC from wet end additive is 105 mg/ton (7 kg/ton x 15 mg/kg) and from AKD-wax 22.5 mg/ton (1.5 kg/ton x 15 mg/kg). After jet-cooking the summed amount will be reduced to 70.1mg/ton. As starches may contain residual levels of CHPTAC, the amount of EPTAC that is formed during CHPTAC degradation is: from wet end starch 280.7 mg/ton (11 % x 7 kg/ton x 364.5 mg/ton) and from AKD-wax 60.1 mg/ton (11 % x 1.5 kg/ton x 364.5 mg/ton). Total EPTAC volume from wet end usage is thus 411 mg/ton paper i.e. roughly 0.4 g/ton.

Adsorption of EPTAC on fibre is poor, maximum 1 %, so 99 % of the substance is assumed to maintain in the waste water. However, adsorption of cationic starch on the wet end fibre and during surface sizing can be considered to be 100 % (Raisio Chemicals, 2001); (Neimo, 1999). Due to short drying time during drying section at the paper machine no remarkable degradation/elimination has been observed. For the exposure assessment no further adsorption or degradation during drying has been assumed.

For the exposure assessment an existing paper mill which produces 750 000 tons wood free paper per year has been chosen. The average number of days in operation is 350, so it gives a daily production capacity of 2143 tons per day. When we multiply this 2143 tons by the concentration 0.411 g/ton we get the maximum daily release of 0.881 kg/day to WWTP. This corresponds to 308 kg per year.

Food grade board (case 3)

Cationic starch is used in producing triple layer board, which is used in the packaging of dry food, corn flakes, pasta etc. The dosage of cationic starch can be following: for top layer 2

kg/ton, for inner layer 2 kg/ton and for bottom layer 1.5 kg/ton, so the total dosage could be 5.5 kg/ton. This summed dosage can be regarded as a worst case assumption and the actual dosage may be lower when taking into account weighted average of the three layers. However this would require knowledge of the relevant contribution each layer makes to the total mass of the board and such information is not available. In addition the dosage used for this purpose is lower than the dosage used in case 1 or in case 2, so no local estimation has been carried out for this case. It is very likely that this dosage does not cause risk to the environment.

3.1.2.3.3 Residual EPTAC and CHPTAC in paper recycling (industrial use scenario 3)

Releases of EPTAC are possible from paper recycling because of EPTAC impurities in the paper. Therefore a generic scenario for printing and writing paper recycling has been performed according to Emission scenario document (ESD) on pulp, paper and board industry (Environment Agency, draft December 2004). Also recycling scenario from bisphenol-A RAR regarding thermal paper has been applied in preparing this scenario. Printing and writing paper scenario was chosen because of the highest cationic starch dosage used in paper mills. Since there is no monitoring data on EPTAC concentrations from any paper recycling plant default values from ESD have been used to calculate releases.

Based on the paper production capacity by different paper types in EU (CEPI, 2004) and cationic starch dosages used for printing and writing, it is assumed that 95 % of the total consumption of cationic starch (containing EPTAC as impurity) is used in printing and writing paper. This gives a starch consumption value of 522 500 t/y. The total amount of printing and writing paper produced is calculated dividing the cationic starch consumption (522 500 t/y) by the dosage of cationic starch (47 kg/t) resulting 11.1 million tonnes paper per year which contains cationic starch in EU.

According to ESD 10 % of the paper produced is considered to be waste paper, called as broke, which never enters to the commercial use but goes straight from paper producers to recycling. This amount (1.11 million tonnes) will be deducted from 11.1 million tonnes. Default value of 60 % (from ESD) is used for calculation the fraction which goes to recycling from commercial use, which results 5.994 (0.6 x 9.99) million tonnes of recovered paper material. So, in total, the amount of printing and writing paper which goes to recycling stream is 7.104 (1.11 + 5.994) million tonnes of paper in EU. Taking into account the residual level of EPTAC in copy paper, 1232 mg/tonne of paper (Raisio Chemicals, 2001), the total amount of EPTAC which enters to recycling sites each year is 8.75 tonnes in EU.

The total amount of recovered paper used in EU is 42 million tonnes (all types). The estimated number of paper production sites in EU is 1000 and 50 % of them are considered to use recovered materials, hence 500 sites (ESD). The average site uses therefore 84 000 tonnes of recovered material per year. Some sites will use a combination of recovered and new material, but as a worst case it is assumed that only recovered paper is used at the default site. An assumption of 350 operation days per year will be used here in the absence of exact information. This gives a daily use of 240 tonnes of recovered paper material at the site. According to ESD the average production of wastewater is 12 m^3/ tonne of paper which gives daily water use rate of 2 880 m^3 at the average site.

Dividing EPTAC amount which enters to the recycling stream (8.75 t) by the number of recycling sites results the average amount of EPTAC, 17.5 kg/y, which is used per site. Operation days of 350 is used to get daily input to the site which is 0.05 kg/d. As a worst case, for the calculation it is assumed that the paper produced will be higher quality, so deinking step is therefore relevant. Since for highly soluble substances removal rate in deinking process is assumed to be 100 %, deinking will remove 100 % of EPTAC from the paper, hence 0.05 kg/d is emitted to water.

According to TGD there are no releases to air from this use (Industrial category 12: Pulp, paper and board Industry) and therefore local assessment has not been carried out for this scenario.

3.1.2.3.4 Use of starch with residual EPTAC in formulation of AKDs (industrial use scenario 4)

Cationic starches are used in the formulation of Alkyl Ketene Dimer emulsions (AKD-wax) which in turn are used as paper-sizing agents in the manufacture of paper and board. AKDs are used to improve resistance against aqueous based liquids by making the cellulose fibers slightly hydrophobic.

Releases of EPTAC from use of AKDs during paper and board production have been considered at the industrial use scenario 2. An attempt to estimate EPTAC releases from formulation of AKD is presented here.

The total volume of global AKD production was < 50 000 tons in 2001 based on Draft SIDS Initial Assessment Report from 2003. There were eight producers and importers of AKD in the European Union according to IUCLID data base, but there is no information on the total or individual volume produced in the EU. For this calculation the European production of AKD is assumed to be half of the global volume, i.e. 25 000 tons in 2001. Almost all of the produced AKD is reported with the CAS No. 84989-41-3. Typical concentration of cationic starch used in AKD emulsions is around 20 % from the AKD in the emulsion which in turn is varying between 5% and 30% (industry information). Thus the amount of cationic starch varies between 1 % and 6 % in the emulsion.

For the local assessment there is no information available on the volume of formulated AKD at the largest site. As the EU formulation volume is assumed to be 25 000 tons/y, a worst case assumption of the largest site could be 50 % of the volume i.e. 12 500 tons/y. The maximum volume of cationic starches in the formulated AKD at the local site would be 6 % of the 12 500 t/y i.e. 750 t/y. This will be used as starch volume for AKD formulation when actual use volume is not known. This may slightly underestimate the releases. When using an emission factor of 2 % (from TGD), releases of cationic starch to water at local site will be 15 tons/year. As the EPTAC residue in cationic starches is 15.3 mg/kg (90th percentile) this will result an EPTAC release of 0.229 kg/y. If we further divide this with number of operation days (300 days assumed) we get 765 mg/d. This will be used further in PEC local calculations.

An emission factor of 0.25 % to air can be found for formulation from the TGD for Industrial category 12: Pulp, paper and board Industry. As the volume of EPTAC as a residue in the starch is so minor, emissions to air will be negligible and no local air estimation have been carried out for this scenario.

3.1.2.3.5 Other uses of EPTAC and CHPTAC (industrial use scenario 5)

In 2001 less than 100 tonnes (71 tonnes) of EPTAC was used for quaternisation of proteins (and or protein derivatives), guar, cellulose and other derivatives. Industry has provided site-specific data on two sites (B1 and B2) where quaternisation of substances other than starch is being carried out with EPTAC. Concentrations of EPTAC and CHPTAC in waste water at sites have been used to calculate releases (Table 3.5). EPTAC was used fairly seldom, only about 10 days in 2002, which partly explains small releases from these sites.

In addition 1044 tons of CHPTAC was used for chemical synthesis of carnitine salts, quaternisation of guar, proteins (and/or protein derivatives), cellulose (and/or cellulose derivatives) and other derivatives in 2001. Majority of the volume is used by one site (B29), which has provided site-specific information on releases. Based on monitoring data from this site EPTAC releases are 0.45 tons per year (2.25 kg/d x 200 d) (Table 3.5).

Table 3.5 Measured releases of EPTAC and CHPTAC from other uses

Site	Release of EPTAC to WWTP (kg/a)	Release of CHPTAC to WWTP (kg/a)	Observations
B1	**0.01**	**0.16**	Based on influent concentration. Size of WWTP known.
B2	**0.005**	**0.08**	Based on influent concentration. Size of municipal WWTP known.
B29	**450**	**750**	Based on influent concentration. Size of industrial and municipal WWTP and flow of receiving water known.

Emissions to air are negligible for sites B1 and B2 due to low volumes of EPTAC used for these purposes. Therefore emissions to air has not been estimated from these uses. For B29 emission factor of 0.001 % (from TGD) have been used, which results emissions of 9 kg/a (0.0459 kg/d) to air.

3.1.2.4 Regional and continental releases

General discussion

There are direct EPTAC releases to the environment from production and industrial use of EPTAC and CHPTAC. Furthermore releases of EPTAC are likely due to conversion of CHPTAC in the environment. The conversion half-life is 21 days at pH 7.8 (12 ˚C) according to a laboratory test. As the residence time of water at the regional scale is 40 days and 166 days at the continental scale according to EUSES, the conversion of CHPTAC to EPTAC is significant. Therefore in the regional and continental assessment all CHPTAC releases will be converted totally to EPTAC, but taking into account the molecular weight difference by using a conversion factor of 0.81 for CHPTAC.

Production of EPTAC

Based on site specific information there are no releases to water from the two existing producer (Table 3.6).No emissions to air are expected from production of EPTAC according to TGD.

Production of CHPTAC

Based on site-specific information from the CHPTAC producers there are no releases to water from most of the sites. For site A1 releases from cleaning activities are 5.2 kg/year, which makes 0.65 kg CHPTAC/d (which is as EPTAC 0.53 kg/d). This will be taken into account at regional scale (Table 3.6). No emissions to air are expected from production of CHPTAC according to TGD.

Cationisation of starches with EPTAC and CHPTAC (industrial use scenario 1)

For the estimation of releases at regional scale from starch cationisation 10 % of the total volume used for starch cationisation (total EPTAC + CHPTAC volume) in the EU will be used. When comparing this volume, 2 518 t/a, with the highest use volume in 2001 with wet process, 1854 t/a, it can be assumed that more than one site is situated within the region, which is likely as the number of cationisation sites is 20. In order to estimate regional EPTAC releases from direct and converted sources to water there is a need to sum up the emission factors of EPTAC and CHPTAC for sites which have monitoring data available. Summed emission factors are: 0.019 %, 0.054 %, 0.10 %, 0.16 %, 0.38 %, 0.76 %, 1.22 %, 1.83 % and 3.52 %. As a reasonable worst case an average of the two highest release factors, i.e. 2.675 % will be used for the regional assessment. Releases to water at regional scale will be 67 t/a i.e. 223.3 kg/d (Table 3.6).

For the continental assessment it could be possible to estimate releases based on total consumption volume (25 184 t/a) and with the emission factor estimated above (2.67 %). However as there are more realistic local estimations for sites, which cover 90 % of the total volume the assessment has been carried out using local release volumes. Direct EPTAC releases of 158.6 kg/d to municipal WWTP/receiving water have been summed from the local releases (see Tables 3.15 and 3.16). When the conversion of CHPTAC to EPTAC will be considered, the summed local CHPTAC releases, presented as EPTAC, are 0.81 x 230.1 kg/d = 186.4 kg/d (see Tables 3.12 and 3.13 in RAR on CHPTAC). The total EPTAC from direct and converted releases to water at EU scale would be 345.0 kg/d and thus at the continental scale 121.7 kg/d.

Residual EPTAC and CHPTAC in starch used for paper making (industrial use scenario 2)

Consumption of cationic starch in the paper and board industry is around 550 000 tons per year in the EU (CEFIC, 2000). As part of the cationic starch is used for surface sizing, without releases to water, there is a need to calculate the volume of cationic starch from where releases to water exists. Therefore it is assumed that 5 % of the 550 000 tons is used for board making (i.e. 27 500 t) and 95 % for printing and writing production (i.e. 522 500 t). In printing and writing 82.5 % (40 kg/t) is used for surface sizing (without aquatic releases) and 17.5 % (8.5 kg/t) for wet end use (with aquatic releases). When multiplying 17.5 % with 522 500 t we get 91 500 t cationic starch, which cause releases to water. Furthermore we need to add the starch volume used in board production (27 500 t), so the total cationic starch volume will be 119 000 tons per year.

Level of residues, both EPTAC and CHPTAC, in the starch in 58 samples have been analysed by industry in 2003. 90^{th} percentile values, 15.3 mg/kg for EPTAC and 450 mg/kg for CHPTAC, will be used here. Before use on the paper machine cationic starches are typically cooked. During cooking 45 % of the EPTAC concentration is assumed to be degraded, i.e. the concentration in the starch will degrease to 8.4 mg/kg. According to the information from the

industry adsorption of EPTAC to fibers is negligible (max.1 %) and no further degradation during drying has been assumed, so release of 99 percent of the concentration can be assumed. Taking into account the conversion of CHPTAC residue to EPTAC in the environment this will result EPTAC releases of 0.81 x 450 mg/kg = 364.5 mg/kg. When summing direct EPTAC and converted EPTAC results 372.9 mg/kg.

Taking into account the consumption volume of cationic starch (119 000 t/y, which causes aquatic releases) in the EU, total aquatic releases of EPTAC are 44.4 t/y which is 126.9 kg/d . This will be the total EU release volume from paper and board industry to water. For the regional scenario 10 % of the EU releases will be used i.e. 12.7 kg/d (Table 3.6).

No emissions to air are expected from paper production with EPTAC according to TGD.

Residual EPTAC and CHPTAC in paper recycling (industrial use scenario 3)

For the regional and continental calculation it is assumed that 95 % of the cationic starch is used for making printing and writing paper and 5 % for board (high grade and food grade). The volumes of paper, high grade board and food grade board containing cationic starch and entering to recycling are estimated to be 7.1, 0.64 and 1.23 million tonnes per year respectively (for more details see sections 3.1.2.3.3 and 3.1.2.3.2 in EPTAC and CHPTAC RARs). Releases to water are based on predicted concentration of 1232 mg/t (EPTAC) and 1216 mg/t (CHPTAC) in paper, 14 mg/t (EPTAC) and 45 mg/t (CHPTAC) in high grade board and 12 mg/t (EPTAC) and 38 mg/t (CHPTAC) in food grade board (Raisio Chemicals, 2001). For EPTAC this makes 8.77 tonnes and for CHPTAC 8.70 tonnes (converted to EPTAC 7.05 t) per year. Total release will be 15.82 tonnes/year and when divided with 350 days we get 45.2 kg/d. For regional 10 % of the total is assumed i.e. 1.58 tonnes/year (4.5 kg/d).

Residual EPTAC and CHPTAC in starch at formulation of AKDs (industrial use scenario 4)

The total volume of global AKD production was < 50 000 tons in 2001 based on Draft SIDS Initial Assessment Report from 2003. There are 8 producers and importers of AKD in the European Union according to IUCLID data base, but there is no information on the total or individual volume of this production in the EU. For this calculation the European use of AKD is assumed to be half of the total volume, i.e. 25 000 tons in 2001. Almost all of the produced AKD is reported with the CAS No. 84989-41-3. The formulated AKD is further used in the manufacture of paper and board.

Typical concentration of cationic starch used in AKD emulsions is around 20 % from the AKD in the emulsion which in turn is varying between 5% and 30% (industry information). Thus the amount of cationic starch varies between 1 % and 6 % in the emulsion. The maximum volume of cationic starches in the formulated AKD in the EU would be 6 % of the 25 000 t/y i.e. 1500 t/y. This may slightly underestimate the releases as the actual use volume of cationic starch is not known.

From the TGD an emission factor of 2 % to waste water can be found (Table A2.1 in Appendix I of part II). This will result a cationic starch release of 30 t/y. As the EPTAC residue in cationic starches is 15.3 mg/kg (90^{th} percentile) this will result an EPTAC release of 0.459 kg/y. In addition the residual CHPTAC will convert/hydrolyse to EPTAC in the environment and this has to be added. As the CHPTAC residue in the cationic starch is 450 mg/kg (90^{th} percentile) x 0.81 = 364.5 mg/kg, the EPTAC release from CHPTAC residue will be 10.935 kg/y. So the total EPTAC release will be 11.4 kg/year and when assuming 300

operation days we get 0.038 kg/d. This will be the total EU release volume from AKD formulation to water. As the size and the number of production facilities within the EU is unknown, 50 % of the EU releases will be used for the regional scenario (Table 3.6).

Other uses of EPTAC and CHPTAC (industrial use scenario 5)

Use of EPTAC for other purposes (quaternisation of guar etc.) is less than 100 tons (71 tons in 2001). Releases from two known sites are low, 0.012 kg/d total. Use of CHPTAC for chemical synthesis of carnitine salts, quaternisation of guar, proteins (and/or protein derivatives), cellulose (and/or cellulose derivatives) and other derivatives was 1044 tons in 2001. More than 80 % of the volume is used by one site (site B29), which has provided site-specific information on releases. Based on monitoring data from this site summed EPTAC + CHPTAC releases are 3.93 kg/d (EPTAC <1.5 kg/d + 0.81 x 3.0 kg/d). This will be the release volume to the regional scale. Rest of total use volume of EPTAC and CHPTAC (191 t) will be used to calculate releases at the continental scale by using the same release factor as in site B29. This will result 0.82 kg/d (Table 3.6).

The regional and continental release volumes to water from production and industrial uses are summarised in Table 3.6. In the further assessment 80 % of the wastewater is distributed through a sewage treatment plant and 20 % is assumed to be released directly to the environment.

Table 3.6 Summary of regional and continental aquatic EPTAC release estimates

	Regional (kg/d)	Continental (kg/d)	EU total (kg/d)
Production of EPTAC	0	0	0
Production of CHPTAC	0.53	0	0.53
Industrial use 1 (starch cationisation)	223.3	121.7	345.0
Industrial use 2 (paper making)	12.7	114.2	126.9
Industrial use 3 (paper recycling)	4.5	40.7	45.2
Industrial use 4 (AKDs formulation)	0.019	0.019	0.038
Industrial use 5 (other uses of EPTAC and CHPTAC)	3.9	0.82	4.72
Total	244.9	277.4	522.4

Releases to air have been estimated by using the total EPTAC + CHPTAC use volume of 25 184 t in 2001 and an emission factor of 0.001 %. This will result 251.84 kg/year and when dividing with 300 days the total emissions to air will be 0.839 kg/d. As we have one local site which estimated releases are 0.241 kg/d this will be used for the regional assessment and the rest (0.625 kg/d) for the continental assessment.

3.1.3 Environmental fate

3.1.3.1 Degradation in the environment

3.1.3.1.1 Atmospheric degradation

No measured photolytic degradation data is available on EPTAC. A fugacity model EPIWIN v3.2 has been used to estimate degradation rate based on reaction with OH radicals, and the calculated half-life is 8.57 hr. As the substance has low vapour pressure (< 0.001 Pa, tested at 22 – 80°C) and low Henry's law constant, emissions to air are presumably low. Hence no photodegradation has been assumed in the risk assessment.

3.1.3.1.2 Aquatic degradation (incl. sediment)

Abiotic

In the hydrolysis test carried out according to EC test guideline C.7 half-life of approximately 5 days (109 h) was observed at neutral conditions (pH 7) at 25 ˚C (CEFIC, 1998b) (Table 3.7). At pH 4 and pH 9 hydrolysis was slower, 5.5 days (132 h) and 14 days (337 h) respectively. Test temperatures were 35 ˚C and 50 ˚C from where 25 ˚C was extrapolated. If the temperature correction is made according to revised TGD to the measured half-live at 35 ˚C, corrected half-live at 12 ˚C would be 10.5 days (258 h) at pH 7 (Table 3.7). For all pH-values a linear dependence on time of degradation and the natural logarithm of the concentration was obtained, which means, that hydrolysis was pseudo first order.

Table 3.7 Hydrolysis rates of EPTAC (* = measured)

pH	T ½ (35 ˚C)	T ½ (25 ˚C)	T ½ (12 ˚C)
acidic (pH 4)	2.1 days *	5.5 days	13 days
neutral (pH 7)	1.7 days *	5 days	10.5 days
alkaline (pH 9)	5.5 days *	14 days	34.5 days

An additional study was carried out in 2004 to determine the degradation rate of EPTAC at more realistic environmental conditions i.e. at the temperature of 12 °C and pH of 7.8 (Raisio Chemicals, 2004). The substance tested was 73.1 % pure EPTAC, concentrated water solution containing also DIOL (1.8%), CHPTAC (1.2%) and water (23.7%). The concentrations of EPTAC, DIOL and CHPTAC were measured by HPLC.

The test was performed in duplicate and the results differed from each other only slightly. EPTAC half-lives of approximately 170 days (4081 h) and 185 days (4432 h) were received in duplicates. The combined degradation rate was 177 days (4256.5 hours), which is clearly longer than the half-lives at the previous test. Within 49 days EPTAC concentration decreased 17.7 % (replicate A) and 16.0 % (replicate B). It can be observed from both test series that as the EPTAC concentration decreased, concentration of both DIOL and CHPTAC increased. Concentration of DIOL was at the beginning of both test series 15 mg/l and after 49 days 147 mg/l and 151 mg/l. Increase of CHPTAC was much smaller: at the beginning of the test 8.2 mg/l (replicate A) and 7.1 mg/l (replicate B) and after 49 days 14.4 mg/l and 16.6 mg/l respectively.

Table 3.8 Measured hydrolysis rate of EPTAC in 12 ˚C (Raisio Chemicals, 2004).

pH	T ½ (12 ˚C)
7.8	177 days

In the test series A there were two test points (time: 24.5 h and 334.5 h) in which pH exceeded the target pH 7.8 ±0.1. This led to the increase of EPTAC concentration in the test point time 24.5 h (pH 8.12) and also decrease of CHPTAC was observed. In the test series B there was one test point where pH exceeded slightly the target pH 7.8 ±0.1 but no increase of the concentration of EPTAC was observed.

Additional information on hydrolysis rate of EPTAC can be found from a conversion study carried out for CHPTAC where also concentrations of EPTAC and DIOL were measured by HPLC-method. The abiotic degradation of CHPTAC was studied at pH values 7.0, 7.8 and 8.4 at 12 ˚C (Raisio Chemicals, 2004c). The substance tested was 98.7 % pure CHPTAC containing small amounts of DIOL (0.6 %), EPTAC (0.2 %), 2-propanol (0.2 %) and water (0.2 %). In the test conditions CHPTAC reacted with OH-ions, which led to formation of EPTAC. EPTAC was further hydrolysed to DIOL.

At pH 7.0 degradation of CHPTAC was slow and therefore also increase of EPTAC and DIOL was minor compared to pH 7.8 and 8.4. In Table 3.9 some data points have been shown which have been used to calculate half-life for abiotic degradation of EPTAC to DIOL.

Calculation of T ½ has been done as follows (at day 10 as an example): Concentration of DIOL after 10 days is 7.1 mg/l and when comparing this with day 35 and 12.2 mg/l, we get a result that DIOL concentration has increased 5.1 mg/l in 25 days (600.5 hours). For the calculation the average EPTAC concentration is calculated from day 10 (20.0 mg/l) and day 35 (40.6 mg/l), so if we divide DIOL concentration 5.1 mg/l with the average EPTAC concentration of 30.3 mg/l and multiply with 100, the result is 16.8 % EPTAC degradation in 25 days. For the 50 % degradation (T ½), we multiply the 25 days (i.e. 600.5 h) with 2.97 and this results 1783.8 hours i.e. 74 days. The other half-lives at day 18 and 28 are 77 days and 82 days respectively (Table 3.9).

3.9. Conversion of CHPTAC to EPTAC and further to DIOL at pH 7.0

Time	CHPTAC (mg/l)	EPTAC(mg/l)	DIOL(mg/l)	Mass bal. mmol	pH	T ½ (EPTAC)
0	918	2.0	5.7	6.073	6.86	57 days
238.1 h (= 10 d)	894	20.0	7.1	6.108	6.91	74 days
432.1 h (= 18 d)	906	26.6	8.5	6.227	6.97	77 days
673.1 h (= 28 d)	874	35.3	10.6	6.108	6.97	82 days
838.6 h (= 35 d)	858	40.6	12.2	6.061	6.96	

At pH 7.8 degradation of CHPTAC was faster and also the increase of EPTAC and DIOL concentrations were higher than in pH 7.0. EPTAC concentrations were at the beginning of the test 4.5 (replicate A) and 9.7 mg/l (replicate B) and after 35 days 286 and 290 mg/l respectively. Increase of DIOL concentrations was much smaller: at the beginning of the test 7.1 mg/l and after 35 days 43.7 and 43.8 mg/l. The test continued for 35 days, but due to decrease of pH only results till day 10 in test A and till day 7 in test B are comparable with each other due to stable pH (7.8 ± 0.1). In Tables 3.10 and 3.11 some data points have been shown which have been used to calculate half-life for abiotic degradation on EPTAC to

DIOL. Calculation method has been described above (see pH 7.0). EPTAC half-lives ranged from 116 days to 211 days (average 138 days). There is a slight difference between half-lives of test A and B, although concentrations of all three substances are fairly close to each other in both tests. Hydrolysis is slower in pH 7.8 that in pH 7.0.

3.10 Conversion of CHPTAC to EPTAC and further to DIOL at pH 7.8 – replicate A

Time	CHPTAC (mg/l)	EPTAC (mg/l)	DIOL(mg/l)	Mass bal. mmol	pH	T ½ (EPTAC)
0	924	4.5	7.1	6.145	7.77	117 days
23.3 h (= 1 d)	898	29.6	7.1	6.190	7.86	118 days
46.3 h (= 2 d)	845	57.0	7.5	6.082	7.80	141 days
95.3 h (= 4 d)	805	92.6	7.8	6.128	7.76	116 days
170.3 h (= 7 d)	777	140	9.3	6.364	7.74	

3.11 Conversion of CHPTAC to EPTAC and further to DIOL at pH 7.8 – replicate B

Time	CHPTAC (mg/l)	EPTAC (mg/l)	DIOL (mg/l)	Mass bal. mmol	pH	T ½ (EPTAC)
0	942	9.7	7.1	6.307	7.77	136 days
23.0 h (= 1 d)	914	38.1	6.9	6.367	7.83	127days
46.0 h (= 2 d)	866	64.1	7.1	6.278	7.82	135 days
95.3 h (= 4 d)	829	99.2	8.0	6.344	7.68	211 days
170.3 h (= 7 d)	782	144	9.1	6.430	7.72	

At pH 8.4 the trend was the same as in pH 7.8: as the CHPTAC concentration decreased, concentration of both EPTAC and DIOL increased. EPTAC concentration was at the beginning of the test 2.8 mg/l and after 15 days 535 mg/l. Increase of DIOL concentration was much smaller: from 7.9 mg/l to 37.3 mg/l. The test continued for 15 days, but due to decrease of pH only results till day 7 are comparable with each other due to stable pH (8.4 ± 0.1). EPTAC half-lives ranged from 91 days to 109 days at pH 8.4 (average 98.5). Hydrolysis was faster in pH 8.4 that in pH 7.8

Total mass (molar) balance throughout the CHPTAC conversion studies has been sufficiently under control. The maximum deviations at pH 7.0 and pH 7.8 replicates and pH 8.4 are 0.166, 0.287, 0.152 and 0.238 mmol consequently.

To conclude: the conversion of EPTAC in the latter studies (Tables 3.8, 3.9, 3.10 and 3.11) seems to be considerably slower than in the former study (10.5 days in pH 7)(Table 3.7). This could be partly explained by higher testing temperature in the former study, from where the results have been calculated. As the latter studies (EPTAC hydrolysis and CHPTAC conversion) are conducted in environmentally relevant conditions, results from these studies seem to be more reliable. In addition, the hydrolysis half-lives for EPTAC calculated from these studies are close to each other i.e. 177 days and 138 days at pH 7.8. Furthermore these hydrolysis half-lives are clearly longer compared to CHPTAC conversion rate (21 days at pH 7.8) whereas in the first EPTAC hydrolysis test half-life is shorter compared to CHPTAC. Longer EPTAC hydrolysis half-lives compared to CHPTAC can be observed from two other tests, namely adsorption test to sludge and the chronic Daphnia test. In the sludge test abiotic removal of EPTAC was slower (4-6 % in 3 days in abiotic and sterile controls) compared to

CHPTAC (22-27 % in 3 days) (see 3.1.3.2.1). In the 21 day Daphnia test with EPTAC no significant removal of EPTAC was observed after 2 days, but in the similar test with CHPTAC approximately 30 % of the total sum was converted to EPTAC after 2 days. Therefore results from the latter EPTAC hydrolysis study (Table 3.8) will be used in the assessment.

Based on the European GEMS database 50-percentile value for the pH of the European surface water is about 7.8. Therefore the half-live of 177 days at pH 7.8 will be used further in the regional and continental risk assessment.

The hydrolysis rate of EPTAC in aquatic environment is not fast enough that it would have any direct influence on local aquatic concentrations. However, the hydrolysis rate may have a crucial influence on local risk in the case that the regional PEC (added to local concentration) turns the local PEC/PNEC ratios above 1. In the case of current assessment of EPTAC, it seems that local aquatic risks are not triggered by regional PECs (when added to the local PEC). Therefore, we can conclude, that the actual outcome of this assessment is not very dependent on the actual hydrolysis rate used.

Biotic

A decrease of DOC by 61 % was found after 28 days in the inherent test following OECD test guideline 302B (Zahn-Wellens/EMPA test) (CEFIC, 1998c) (Table 3.12). After 42 days 94 % of the EPTAC was degraded. The inoculum used in the test was non adapted activated sludge from the sewage treatment plant and the concentration of the test substance was 685 mg/l. Both the concentration of the substance 685 mg/l (250 mg DOC/l) and the concentration of the inoculum (1000 mg/l dry matter) were in the range of the test guideline. The pH in the test was checked at each sampling day and adjusted to pH 7-8 and the temperature was in the required range (19 – 23 ˚C). The criteria to be classified as "inherently biodegradable" was not fulfilled in this test (70 % in 28 days).

In 2005 an STP simulation test (Porous pot test) was conducted for EPTAC according to OECD 303A guideline (Table 3.12). Test period was 135 days, where DOC elimination of the organic medium reached a degradation rate > 80 % after 9 days and test item application started on day 40. Once the DOC results indicated removal of EPTAC, the specific analysis of EPTAC, CHPTAC and DIOL were carried out via LC-MS/MS i.e. on day 40. Influent and effluent concentrations and adsorption on the activated sludge were determined for selected samples. Influent concentration of EPTAC was 60.7 mg/l, which is in the range of measured influent concentrations at starch cationisation sites. The primary degradation of EPTAC was in the range of 0-30 %. No clear degradation tendency was observed and no plateau was reached. Mean primary degradation was calculated from 14 (out of total 24) measurements which were done on days 100 – 113, corresponding to days 61 – 74 of test item application. The mean primary degradation of EPTAC was 15 ± 9.7 %. As the sludge retention time was 6 hours, an average half-life of 20 hours can be calculated. This can be translated to a rate constant of 0.0347 h-1. With this rate constant a degradation of 19.2 % at STP can be calculated with EUSES (Simple Treat).

Indication of rather slow degradation can also be seen from four BOD_5-values reported. Three of the BOD_5 –values were zero and one was 0.03 g/g with very high dilution (Bridié et al., 1979); (Shell Oil Company, 1982); (Degussa, 1986b); (Degussa, 1991a) (Table 3.12). However documentation was in sufficient for detailed assessment of the tests.

Table 3.12 Summary table of biodegradation test results for the aquatic environment

No.	Type of test	Detection	Degradation	Period	Conc.	conc. of inoculum	Reference
1	Inherent: Zahn Wellens OECD 302B	DOC	61 % after 28 d 94 % after 43 d	28 d	685 mg/l (250 mg/l DOC)	1000 mg/l	(CEFIC, 1998c)
2	STP simulation OECD 303A	DOC EPTAC CHPTAC DIOL	15 ± 9.7 % in 6 hours (primary degradation)	135 d	60.7 mg/l	2.5 g/l	(CEFIC, 2006)
3	BOD_5	BOD/COD	0 %	5	no details available	no details available	(Bridié et al., 1979)
4	BOD_5	BOD/COD	0 %	5	no details available	no details available	(Shell Oil Company, 1982)

Furthermore nine starch cationisation sites have provided measured EPTAC influent and effluent concentrations (see 3.1.4.1.2, Table 3.15). For six of the sites EPTAC concentration in untreated waste water at WWTP is higher than measured concentration in the effluent i.e. removal of 52, 82, 90, 95, 96 and 98 % of EPTAC can be seen. This decrease could be partly due to biodegradation, but also due to hydrolysis and dilution, and therefore it has not been possible to estimate the general biodegradation rate based on this data. The starch cationisation process is a batch process and based on info from industry the number of days in operation has ranged from 10 to 360, with majority between 300 to 350 days. Therefore the exposure of EPTAC to microbes at WWTP may not be constant at all cationisation sites, and thus microbes may not be adapted to degrade EPTAC at all sites.

As a conclusion results from the simulation test will be used in further calculations for estimation of degradation at STP. Based on the information available regarding degradation in the environment EPTAC can be regarded as inherently biodegradable but not fulfilling the criteria set in the TGD. As a consequence the EPTAC half-lives will in STP be 20 hours, in surface water 150 days and in sediment 300 d.

Biodegradability of the hydrolysis product of EPTAC

Biodegradability of the hydrolysis product of EPTAC, 2,3-dihydroxypropyltrimethyl-ammonium chloride (CAS 34004-36-9), has been studied in a ready test (Degussa, 1988c

). In a Modified OECD screening test (301E) GLP study, two test substance concentrations 10 and 20 mg /l (5 and 9 mg DOC respectively) were tested in non adapted domestic sewage STP sludge inoculum (3 mg/l) for 28 days. Results: complete biodegradation was reached in one week at 20 mg/l initial concentration (no variability between replicates) and 67-100 % degradation was reached in one week at 10 mg/l initial concentration (slight variability between replicates). Inoculum activity was sufficient, test substance was stable under sterile control and it was not toxic for the inoculum. According to this study dihydroxypropyl-trimethylammonium chloride may be regarded as readily biodegradable (fulfilling the "10 day window" criteria).

3.1.3.1.3 Degradation in soil

No degradation studies have been carried out for EPTAC in soil. Hence, rate constant will be estimated from the aquatic degradation test results. As the substance is regarded as inherently biodegradable but not fulfilling the criteria, a degradation half-life of 300 day in soil will be assumed.

3.1.3.2 Distribution

The theoretical distribution of EPTAC between four environmental compartments at equilibrium has been calculated using the fugacity model EQC v.1.1 (Mackay level I). The results clearly indicate that EPTAC will partition to water almost totally (100 %) and distribution to other compartments is negligible (soil 3.53 x 10^{-5} %, sediment 7.83 x 10^{-7} % and air 3.59 x 10^{-6} %). Similar results can been seen from Level III fugacity model EPIWIN v3.20, where 99.8 % of the substance remain in water, when the release is to water compartment.

3.1.3.2.1 Adsorption

Octanol-water partition was measured with Shake Flask Method (OECD 107) at pH 9 (CEFIC, 1998a). As the EPTAC could not be detected in the 1-octanol phase, the detection limit of 50 mg/l was used to calculate a result: Pow < 0.05 or log Pow < -1.3. The result from test with pH 7 could not be used, because EPTAC hydrolysed too fast at neutral conditions. Also under pH 9 the concentration of EPTAC decreased during the test.

It can be assumed that some degree of adsorption to sludge, sediment or soil may occur due to cationic group and positive charge of the EPTAC. However, in a new adsorption test on activated sludge only a slight adsorption could be observed. In a 72 h test with ISO 18749 test guideline the removal of EPTAC from water was 7 %, but also at the abiotic control (without the sludge) and sterile control (with sterile sludge) the removals were similar, 4 % and 6 % respectively (CEFIC 2003a). Therefore the removal was mostly due to abiotic degradation, but partly also due to adsorption and/or biodegradation. Concentration of EPTAC in the sludge was not measured at the end of test. Based on a small concentration difference, 2.6 mg/l, between the test vessel and abiotic control vessel, Kd on sludge has been calculated as follows: after 72 hours from the start 2.6 mg/g of the substance was in sludge and 101.5 mg/l was in water. Kp_{sludge} = conc. in sludge/conc. in water= 2600 mg kg^{-1}/101.5 mg l^{-1} = 25.6 l/kg. As the organic carbon content of the sludge was not measured during the test, calculation of distribution coefficient to organic carbon (Koc) is not possible. However, if we assume the proportion of the OC in sludge to be 50 % , this would result a Koc of 51.2. Adsorption of EPTAC to soil or sediment may differ from adsorption to sludge due to higher content of clay/minerals in soil and sediment.

A distribution coefficient can also be estimated from a STP degradation simulation test (conducted according to OECD 303A) (CEFIC, 2006). Test period was 135 days in the degradation test, but the sludge and water sampling was carried out only in 6 days (on days 57, 61, 64, 111, 112 and 113 from the start of the test). Concentrations of EPTAC in activated sludge ranged between 0.326 mg/g – 3.2 mg/g (average 1.3 mg/g) and in the aqueous phase between 38.5 mg/l – 55.6 mg/l (average 48.25 mg/l). Adsorption to sludge can be calculated as follows: Kp_{sludge} = conc. in sludge/conc. in water = 1300 mg kg^{-1} / 48.25 mg l^{-1} = 26.9 l/kg. Although the organic carbon content of the sludge was not measured during the test, it has

been assumed that the proportion of the organic carbon in sludge is 50 %. This will result a Koc of 53.8 which is very close to the Koc received from the previous adsorption study.

In addition, at one starch cationisation plant concentration of EPTAC and CHPTAC has been measured from the sludge. The EPTAC concentrations ranged from < 1 mg/kg to 6 mg/kg (90^{th} percentile 5.4 mg/kg) in the sludge. The EPTAC waste water concentrations (90^{th} percentile) were at the same time 84.6 mg/l (influent) and 4 mg/l (effluent). These sludge concentrations are 1000 times lower compared to concentrations in degradation simulation and adsorption studies above.

Adsorption of a similar kind of quaternary ammonium compound to soil and sediment

In adsorption studies with chloroethyltrimethylammonium–cation ($C_5H_{13}Cl\ N^+$, chlormequat-chloride, CCC) with four soils the degree of adsorption ranged from 6.9 % to 44.9 % depending on the soil type (Hansen, 1993). The predominant adsorption mechanism seemed to be ion exchange and the adsorption was mainly controlled by cation exchange capacity (CEC) of the test soils. Test contained 50 g soil and 250 ml solution. CEC values varied between 3.5-12.4 mmol/100g soil and other soil parameters were pH 6.0-7.7, OC 0.47 – 2.55 % sand 66-90 %. In another study with three different soils adsorptions were higher, from 54.2 % to 70.1 %, but also the pH was very low in the soil with 70 % adsorption (Hansen, 1993). Test contained 2 g soil and 10 ml solution. Kp to soil has been reported only on one soil out of the seven soil types tested. In this soil (Pfungstadt) adsorption was 44.9 % and the Kp_{soil} was 2.4 (Koc 203). Properties of the Pfungstadt soil were pH 7.7, sand 66 %, OC 1.2 % and CEC 12.4 mmol/100 g soil. Both tests were carried out according to OECD test guidelines. Based on these two studies adsorption seems not to be highly related to the content of organic carbon in soil.

In a water/sediment biodegradation test with two natural sediments an average 40 % adsorption of C^{14} labeled chloroethyltrimethyl-ammonium-cation was observed after 7 days (Hansen, 1993). The test system contained 100 ml ditch water and 1 g dry sediment and nominal test concentrations were 0.3 and 1 mg/l. Tested materials were ditch water and sediments from Netherlands: from Delft area and Kromme Rijn. For Delft sediment sand-silt-clay-OM content (%) was 41-30-7.8-12.5 and for Kromme Rijn 85-7.5-28-1.6. After 7 days, 43 % (Delft) and 39.5 % (Kromme Ruijn) of the chloroethyltrimethylammonium-cation was adsorbed to the sediment. As the content of organic matter in the two sediments differed from each other considerably, 12.5 vs. 1.6, it can be concluded that the adsorption was not highly related to content of organic matter in sediment.

From this study, a partition coefficient between solids and water in sediment for chloroethyl-trimethylammonium-cation can be calculated. If it is assumed an average adsorption percentage of ca. 40%, then 0.04 mg/g of the substance would be in the sediment and 0.06 mg/100 ml in the water (corresponding to 40 mg/kg in sediment and 0.6 mg/l in water). Calculated solids-water partition coefficient in sediment, on a L/kg basis, is $Kp_{sediment}$ = conc. in sediment/conc. in water= 40 mg kg^{-1}/0.6 mg l^{-1} = 66.7 L/kg .

Conclusion on adsorption

Since measured values for adsorption of EPTAC to soil, sediment or suspended matter are not available, the calculated value for the chlormequat-chloride could serve as a realistic surrogate

value for EPTAC (with known limitations). Like the chlormequat-chloride also positively charged quaternary nitrogen group in EPTAC is adsorbed by ion exchange mechanism to anionic groups of sediment mineral particles and to organic matter. Therefore this surrogate value, sediment-water partition coefficient (Kp_{sed}) 67 l/kg, could describe better the adsorption of EPTAC to sediments than Kp derived from log P_{ow}. Adsorption to suspended matter is usually assumed to be two times higher than adsorption to sediment due to two times higher organic carbon content of solids. As the adsorption of EPTAC is not assumed to correlate highly on the organic carbon content, the same Kp value (67 l/kg) could be used for suspended matter. Taken the same arguments presented above on sediment it could be possible to use a Kp_{soil} from chlormequat-chloride (2.4) to describe adsorption of EPTAC to soil. However, as there is information on EPTAC adsorption to STP sludge, an Koc value has been derived for EPTAC from this study. This Koc (53.8 l/kg) can be used to estimate Kp values for EPTAC in soil, suspended matter and sediment. Partitioning coefficients (Kp) based on the measured log Pow (< -1.3) and estimated from measured Koc have been presented in Table 3.13. Partition coefficients estimated from the measured Koc for soil, suspended matter and sediment will be used in further calculations.

Table 3.13 Partition coefficients for EPTAC.

	Calculated (from log Pow)	Calculated (from measured Koc)	Definition
Koc	0.112 l/kg	53.8 l/kg	Partition coefficient organic carbon-water
Kp_{soil}	2.23 x 10^{-3} l/kg	1.08 l/kg	Partition coefficient solid-water in soil
Kp_{susp}	0.0112 l/kg	5.38 l/kg	Partition coefficient solid–water in suspended matter
Kp_{sed}	5.58 x 10^{-3} l/kg	2.69 l/kg	Partition coefficient solid-water in sediment

The dimensionless form of Kp to be used in further calculation can be derived by using fractions of water and solid and their densities as presented in the TGD.

Table 3.14 Partition coefficients for EPTAC (dimensionless).

	Calculated (from log Pow)	Calculated (from measured Koc)	
$K_{soil-water}$	0.203 m^3/m^3	1.81 m^3/m^3	Partition coefficient soil-water
$K_{susp-water}$	0.903 m^3/m^3	2.25 m^3/m^3	Partition coefficient suspended matter-water
$K_{sed-water}$	0.803 m^3/m^3	2.15 m^3/m^3	Partition coefficient sediment-water

Even if bound to sediment, EPTAC (and the epoxide group in it) is believed to be still subject to hydrolysis to "DIOL". Since clay minerals can often act as catalytical surfaces to chemical reactions, faster hydrolysis of EPTAC may take place in sediment conditions compared to non adsorbed dissolved molecules. However, no actual study results for enhanced hydrolysis rates are available.

3.1.3.2.2 Volatilisation

A Henry's law constant of $1.78 \cdot 10^{-7}$ Pa m^3/mol can be calculated using a vapour pressure of < 0.001 Pa (at 22 °C - 80 °C) and a water solubility of 852 000 mg/l (at 20 °C and at pH >11). This indicates that EPTAC does not volatise from water to air.

3.1.3.2.3 Distribution in wastewater treatment plants

Based on the test data available 19.2 % of the EPTAC will be degraded at STP when estimated with EUSES. Adsorption of EPTAC to sludge is low at the wastewater treatment plant: according to EUSES only 0.6 % of the substance will adsorb to sludge. As the EPTAC does not volatilize, the rest i.e. 80.2 % of the substance is assumed to be directed to receiving water.

3.1.3.3 Accumulation and metabolism

No experimental test result on bioaccumulation of EPTAC is available. Bioconcentration factors (BCF) for fish and earthworm can in principle be estimated according to TGD from certain relationship using known Kow. However, the equation in the TGD is relevant only for substances with a log Kow 1 – 6 (for EPTAC log Kow < -1.3). In addition for certain types of chemicals e.g. those which ionise in water, log Kow values may not be suitable for calculation of a BCF value. Therefore precaution should be taken to interpret the results from the calculations.

BCFs calculated according to EUSES are: BCF_{Fish} =1.41 l/kg and BCF_{Worm} = 3.34 kg/kg. Based on calculated BCFs no significant bioaccumulation is expected.

3.1.4 Aquatic compartment (incl. sediment)

3.1.4.1 Calculation of predicted environmental concentrations (PEC_{local})

3.1.4.1.1 Calculation of PEC_{local} for production

Based on site-specific information from producer A2 no waste water will be distributed to the waste water treatment plant. For producer A3 waste waters from the cleaning of the reactor will be collected to storage vessels, where residual EPTAC will be converted to DIOL. After that waste water is discharged to WWTP. Due to conversion EPTAC releases are expected to be negligible. Producer A1 has ceased the production of EPTAC in 1998.

3.1.4.1.2 Calculation of PEC_{local} for industrial/professional use

The local concentration of EPTAC in surface water will be calculated as follows (if no monitoring data is available):

$Clocal_{water} = (Clocal_{inf} \times Fstp_{water}) / (1 + Kp_{susp} \times SUSP_{water} \times 10^{-6}) \times DILUTION$

where $Clocal_{inf}$ = concentration in untreated wastewater (mg/l)
$Fstp_{water}$ = fraction of emission directed to water from WWTP (0.802 i.e. 80.2%)
Kp_{susp} = solids-water partitioning coefficient of suspended matter (5.38 l/kg)
$SUSP_{water}$ = concentration of suspended matter in river (15 mg/l)
DILUTION = dilution factor (default 10)
$Clocal_{water}$ = concentration of the substance in the STP effluent (mg/l)

In these calculations 19.2 % biodegradation and 0.6 % adsorption will be taken into account at WWTP. It is assumed that 80.2 % of the EPTAC will be distributed from WWTP to water. Adsorption to the suspended matter in the environment has so minor effect on the local water concentration that there is no need correct the dilution factor with the adsorption in further local calculations. Therefore the default dilution factor to receiving water is 10 if no site-specific data is available.

Cationisation of starches (industrial use scenario1)

In Table 3.15 site-specific monitoring data on EPTAC has been used to calculate EPTAC concentration in the surface water. PEC_{local} has been calculated from the measured WWTP effluent concentration ($Clocal_{effluent}$), but for several sites this is the detection limit or close to it. Due to rather high detection limit (0.7- 10 mg/l) the local PECs will be high compared to PNEC (16 µg/l i.e. 0.016 mg/l).

From monitoring data in Table 3.15 it can be seen that the removal of EPTAC will take place in WWTP at most of the starch cationisation plants. For 6 sites removal ranges between 52-98 % as for three sites (B4, B5 and B17) it is impossible to conclude on degradation rate because most of the influent and the effluent concentrations were below the detection limit. Removals are theoretical and have been calculated from the measured concentrations in the effluent and from the calculated (theoretical) concentrations in untreated waste water. Calculated concentrations in the untreated waste water have not been presented in the Table.

Table 3.15 Concentration of EPTAC in water from starch cationisation with EPTAC or CHPTAC – based on effluent monitoring data (bold= measured). If municipal WWTP available, the removal of 19.2 % taken into account

Site	Concentration in water from the starch cationisation plant, partial stream (mg/l)	Concentration in WWTP effluent $Clocal_{effluent}$ (mg/l)	Removal (%)	WTTP effluent flow (m^3/d)	Release to municipal WTTP (or to receiving water) (kg/d)	Concentration at municipal WWTP effluent $Clocal_{effluent}$ (mg/l)	Dilution	Clocal (µg/l)	PEC_{local} (µg/l)
B3	**20** (highest concentr.)	< **3** (detection limit)	82	2400	< 7.2	< 0.275	206.7	< 1.33	< 3.12
B4	<**10** (detection limit)	<**10** (detection limit)	0	800	(8.0)	(<10)	596	<16.80	< 18.6
B5	**8.2** (min.), **9.0** (avg.), **10.0** (max) (90^{th} percentile)	**0.97** (min), **4.6** (avg.), **9.1** (max) (90^{th} percentile)	0	2760	12.70 (avg)	0.0283 (avg)	3.22	8.78 (avg.)	10.6 (avg)
B14	**84.6** (90^{th} percentile)	**4** (90^{th} percentile)	52	6900	(27.6)	(4)	1000	4	5.79
B16	**107.70** (highest concentration)	< **2.4** (detection limit)	98	300	< 0.720	< 0.089	16	< 5.55	< 7.35
B17	**8.0** (90^{th} percentile)	< **0.7** (detection limit)	0	8570	< 1.54	< **0.06**	7.17	< 8.37	< 10.16
B18	**24.8** (highest concentration)	< **2.44** (avg.)	90	160	< 0.39	0.0313	1000	0.0313	< 1.82
B21	**180** (90^{th} percentile)	< **0.7** (90^{th} percent.)	95	3192	< 2.23	< 0.066	5.8	<11.44	< 13.24
B25	**272**(90^{th} percentile)	< **0.7** (90^{th} percentile)	96	7500	(5.25)	(<0.7)	11	< 63.6	< 65.4
Total					65.63				

In the absence of site-specific monitoring data PECs in Table 3.16 have been calculated by using a release factor of 1.32 %, which is from a another starch cationisation plant. In addition biodegradation of 19.2 % and adsorption of 0.6 % have been taken into account. However, these sites have provided other site-specific information i.e. volume of effluent flow and dilution to receiving water, which have been used in calculations.

Table 3.16 Concentration of EPTAC in water from starch cationisation with EPTAC or CHPTAC – based on calculated release factor of 1.32 % (biodegradation of 19.2 % and adsorption of 0.6 % to sludge at the WWTP is assumed)

Site	Release to industrial WWTP (kg/d)	Concentration in untreated waste water $Clocal_{infl uent}$ (mg/l)	Concentration in WWTP effluent $Clocal_{effluent}$ (mg/l)	WTTP effluent flow (m^3/d)	Release to municipal WTTP (or to receiving water) (kg/d)	Dilution	PEC_{local} (µg/l)
	EPTAC users						
B9	21.9	6.26	5.02	3500	(17.57)	23.22	218
B19[1)]	-	-	-	-	-	-	-
	CHPTAC users						
B10	14.3	4.09	3.28	3500	(11.47)	23.22	143
B23	74.16	10.91	8.75	6800	(59.48)	2.04	4291
B26[2)]	-	-	-	-	-	-	-
Total					88.52		

[1)] This site has been closed at the end of 2002

[2)] This site has been closed in 2004

In addition there are four sites which are producing cationic starch with dry process (i.e. B11, B13, B22 and B28) and 3 sites with wet process but no releases to water (B6, B15 and B12) (see Table 3.4). For these sites PEClocal = 0 mg/l to aquatic environment.

Use of starch with residual EPTAC and CHPTAC in paper making (industrial use scenario 2)

<u>High grade board for books (case 1)</u>
Releases due to residual levels of EPTAC in the cationised starch used in the production of board have been estimated to be 1.161 kg/day from the wet-end use (section 3.1.2.3.2). If the average production of waste water is 15 m^3/ton, which means 42 855 m^3/day, then the concentration in the WWTP would be 0.027 mg/l. When we take further biodegradation (19.2 %), adsorption (0.6 %) and dilution to the receiving water into account (by using a default factor of 10), this will result a local concentration of 2.2 µg/l in the surface water. When the $PEC_{regional}$ of 1.79 µg/l is added, the PEC_{local} will be 3.99 µg/l.

For comparison, if we have a smaller mill which produces 620 000 ton of board per year (i.e.1938 ton/d x 320 d), we get slightly lower releases per day i.e. 0.985 kg/day (i.e.1938

ton/d x 0.508 g/ton) to waste water. However, this existing mill has much lower waste water volume i.e. 16 000 m^3/day (about 8 m^3/ton) and therefore the concentration in the waste water will be more than two times higher, 0.062 mg/l, than in the previous bigger mill. Further biodegradation (19.2 %), adsorption (0.6 %) and dilution (by a factor of 10) would result a local concentration of 4.9 µg/l in the surface water. When the $PEC_{regional}$ of 1.79 µg/l is added, the PEC_{local} will be 6.69 µg/l. This case has been presented in EUSES run.

Printing and writing paper (case 2)

EPTAC releases to water from production of printing and writing paper have been estimated to be 0.881 kg/d . If the average production of waste water is 15 m^3/ton, which means 42 855 m^3/day, then the concentration in the WWTP would be 0.021 mg/l. When we take further biodegradation (19.2 %), adsorption (0.6 %) and dilution to the receiving water into account (by using a default factor of 10), this will result a local concentration of 1.7 µg/l in the surface water. When the $PEC_{regional}$ of 1.79 µg/l is added, the PEC_{local} will be 3.49 µg/l.

For comparison, if we have a smaller mill which produces 620 000 ton of paper per year (i.e.1938 ton/d x 320 d), we get lower releases per day i.e. 0.797 kg/day (i.e.1938 ton/d x 0.411 g/ton) to waste water. However, this existing mill has much lower waste water volume i.e. 16 000 m^3/day (about 8 m^3/ton) and therefore the concentration in the WWTP will be more than two times higher, i.e. 0.050 mg/l, than in the previous bigger mill. Further biodegradation (19.2 %), adsorption (0.6 %) and dilution (by a factor of 10) would result a local concentration of 4.0 µg/l in the surface water. When the $PEC_{regional}$ of 1.79 µg/l is added, the PEC_{local} will be 5.79 µg/l. This case has been presented in EUSES run.

Food grade board (case 3)

As the dosage used for this purpose is lower than in cases 1 and 2, no local estimation has been carried out.

Residual EPTAC and CHPTAC in paper recycling (industrial use scenario 3)

Releases due to residual levels of EPTAC in recovered printing and writing paper material used in recycling plant (incl. deinking process) have been estimated to be 0.05 kg/day. Adsorption of EPTAC to sludge is low, only 0.6 % is calculated (EUSES) to adsorb to sludge. Taking adsorption and further biodegradation (19.2%) into account 80.2 % of EPTAC i.e. 0.0401 kg/d is emitted to water. If the average production of waste water is 2880 m^3/d, the EPTAC concentration in water is then 0.014 mg/l. Further dilution by a factor of 10 to the receiving water will result the concentration of 1.4 µg/l in the surface water. When $PEC_{regional}$ of 1.79 µg/l is added, the PEC_{local} will be 3.19 µg/l.

Use of starch with residual EPTAC in formulation of AKDs (industrial use scenario 4)

At the AKD formulation plant the release of cationic starch could be 15 t/y, when using an TGD emission factor of 2 % to waste water. As the EPTAC residue in cationic starches is 15.3 mg/kg (90^{th} percentile) this will result an EPTAC release of 0.229 kg/y. If we further divide this with number of operation days (300 days assumed) we get 765 mg/d.

Biodegradation of 19.2 % and adsorption of 0.6 % at the municipal WWTP (2000 m^3/d, TGD default) has been assumed.. This results a concentration of 0.31 µg/l at the WWTP. Taking also further dilution to receiving water into account (10, TGD default), the concentration of

EPTAC in the receiving water will be 0.03 µg/l. When PECregional of 1.79 µg/l is added the local PEC will be 1.82 µg/l.

Other uses of EPTAC and CHPTAC (industrial use scenario 5)

Industry has provided monitoring data on two small sites, which use EPTAC for quaternisation of substances other than starch. Based on site-specific data concentrations in marine water are low (Table 3.17). In both sites estimation is based on measured influent concentration at industrial site, dilution factor of 100 has been used as the releases are to estuary and the background concentration in sea water (0.166 µg/l) has been used to derive PEClocal.

Majority of the volume in this scenario is used by one site (CHPTAC user), which has provided site-specific information on releases. According to monitoring data from waste water at the industrial site a local PEC for surface water from this site will be 7.45 µg/l (Table 3.17)

Table 3.17 Monitored concentrations of EPTAC in water from other uses

Site	**Concentration in untreated waste water Clocal$_{linfluent}$ (mg/l)**	**Concentration in WWTP effluent Clocal$_{effluent}$ (mg/l)**	**WTTP effluent flow (m^3/d)**	Release to municipal WWTP (to receiving water) (kg/d)	Concentration at municipal WWTP effluent Clocal$_{effluent}$ (mg/l)	**Dilution**	**Clocal (µg/l)**	**PEC$_{local}$ (µg/l)**
B1	2.7×10^{-4}	2.2×10^{-4}	2960	(6.51×10^{-4})	(2.2×10^{-4})	100	2.2×10^{-3}	0.168 (marine)
B2	**1.1**	**1.1**	0.8	8.8×10^{-4}	1.36×10^{-5}	100	1.36×10^{-4}	0.166 (marine)
B29	15	< 10 (detection limit)	150	< 1.5	< 0.0301	5.32	< 5.65	< 7.45

Sediment

PEC_{local} for sediment can be derived from the corresponding water body concentration by assuming a thermodynamical partition equilibrium:

$$PEClocal_{sediment} = (K_{susp\text{-}water} / RHO_{susp}) \cdot PEClocal_{water} \cdot 1000,$$

where $PEClocal_{water}$ = concentration in surface water during emission episode (mg/l)
$K_{susp\text{-}water}$ = suspended matter- water partition coefficient (2.25 m^3/m^3)
RHO_{susp} = bulk density of suspended matter (1150 kg/m^3)

PEC's for different scenarios have been presented in Table 3.18.

Table 3.18 PECs in the sediment

Life cycle step	**PEC in sediment (**mg/kg wwt)
Industrial use 1 (starch cationisation)	
B3	< 6.1E-03
B4	< 0.0363
B5	0.0207
B9	0.426
B10	0.279
B14	0.0113
B16	< 0.014
B17	< 0.0198
B18	< 3.56E-03
B21	< 0.0258
B23	8.37
B25	< 0.128
Industrial use 2 (case 1, board production)	7.83E-03 (0.0131) *
Industrial use 2 (case 2, paper production)	6.85E-03 (0.0113) *
Industrial use 3 (paper recycling)	6.22E-03
Industrial use 4 (AKD formulation)	3.56E-03
Industrial use 5 (other uses)	
B1	3.29E-04 (marine)
B2	3.25E-04 (marine)
B29	< 0.0145

* value in brackets is from a smaller paper/board mill

3.1.5 Terrestrial compartment

3.1.5.1 Calculation of PEC_{local}

The EUSES 2.0.3 model takes into account both the application of STP sludge on agricultural soil and the deposition from air for the calculation of EPTAC concentrations in the terrestrial compartment. Table 3.19 gives the terrestrial PECs at a local scale (i.e. the concentration measured 30 days after sludge application).

Table 3.19 Local PECs in agricultural soil.

Life cycle step	**PEC_{local} terrestrial (**mg/kg wwt)

Life cycle step	PEC_{local} terrestrial (mg/kg wwt)
Industrial use 1 (starch cationisation)	
B3	< 0.0102
B4	< 1.89E-05
B5	1.06E-03
B9	1.12E-05
B10	8.99E-06
B14	2.38E-05
B16	< 3.31E-03
B17	< 2.23E-03
B18	< 1.17E-03
B21	< 2.46E-03
B23	2.85E-05
B25	< 4.09E-05
Industrial use 2 (case 1, board production)	1.83E-03
Industrial use 2 (case 2, paper production)	1.48E-03
Industrial use 3 (paper recycling)	5.2E-04
Industrial use 4(AKD formulation)	1.62E-05
Industrial use 5 (other uses)	
B1	1.2E-05
B2	5.37E-06
B29	< 1.13E-03

3.1.6 Atmosphere

3.1.6.1 Calculation of PEC_{local}

Annual average EPTAC concentrations in air (100 m from point source) estimated according to EUSES 2.0.3 are presented in Table 3.20. According to TGD there are no releases to air from board and paper production or paper recycling, so no local assessment has been carried out for these scenarios. For AKD formulation there are small releases to air, but as the volume of EPTAC as a residue in the starch in the AKD formulation is so low, emissions to air will be negligible and no local air estimation has been carried out for this scenario.

Table 3.20 Local PECs in air.

Life cycle step	Annual average concentration in air (mg/m^3)
Industrial use scenario 1 (starch cationisation)	2.48×10^{-6} - 5.7×10^{-5}
Industrial use scenario 2 (board and paper production)	-
Industrial use scenario 3 (paper recycling)	-

Life cycle step	Annual average concentration in air (mg/m^3)
Industrial use scenario 4 (AKD formulation)	Negligible
Industrial use scenario 5 (other uses – B29)	6.99×10^{-6}

According to site-specific information there are six sites using EPTAC to produce cationized starch (Industrial use 1), where emissions to air have been estimated. Concentrations in the exhaust stream in the stack at two sites have been 8.4×10^{-5} and 2×10^{-4} mg/m^3. CHPTAC concentrations from the CHPTAC plants have been at the same range. Volumes of exhaust streams have ranged from 24 000 to 4 135 400 m^3/d. (QUAS, 2000b). Measured concentrations are higher than estimated according to EUSES, because the monitoring concentration is from the stack, but the EUSES calculates the concentration 100 meters from the site.

3.1.7 Secondary poisoning

For the secondary poisoning indications for bioaccumulation potential should be considered. EPTAC is highly water soluble, rather small size organic cation with low log Kow (< -1.3). Low log Kow indicates that the substance might not bioaccumulate. Therefore no assessment of secondary poisoning is necessary.

3.1.8 Calculation of $PEC_{regional}$

Table 3.21 shows the calculated PECs for air, water, soil and sediment at the regional scale.

Table 3.21 Regional PECs in air, water and soil

Compartment	PEC regional
Surface water (total)	1.79 [µg/l]
Surface water (dissolved)	1.79 [µg/l]
Sea water (total)	0.166 [µg/l]
Air (total)	9.46×10^{-14} [mg/m^{-3}]
Agricultural soil (total)	3.31×10^{-5} [mg/kg wwt]
Pore water of agricultural soils	3.1×10^{-5} [mg/l]
Natural soil (total)	4.84×10^{-6} [mg/kg wwt]
Industrial soil (total)	1.28×10^{-3} [mg/kg wwt]
Sediment (total)	3.38×10^{-3} [mg/kg wwt]
Sea water sediment (total)	3.1×10^{-4} [mg/kg wwt]

3.2 EFFECTS ASSESSMENT: HAZARD IDENTIFICATION AND DOSE (CONCENTRATION) - RESPONSE (EFFECT ASSESSMENT)

3.2.1 Aquatic compartment (incl. sediment)

3.2.1.1 Toxicity test results

There are two short term toxicity studies on fish and Daphnia and one study on algae available on EPTAC. Nominal concentrations were used in all studies. However, in a recent algae study analytical verification of the test substance, without the algae, was carried out after 0 and 72 hours. Concentrations deviated only slightly (less than 20 %) from each other. In addition toxicity of EPTAC to micro-organism has been tested in one study and there is also one chronic Daphnia reproduction study available. In the chronic study concentrations of EPTAC were measured. Studies that are considered valid are cited in the following tables.

Some of the studies were performed with aqueous solution of EPTAC (72-92 %) and also results in the study reports were expressed as diluted EPTAC. Therefore results from the test reports have been corrected as 100 % EPTAC.

3.2.1.1.1 Fish

EPTAC short-term toxicity studies for fish are summarised in Table 3.22. Acute LC_{50}-values for fish is 1992 mg/l. In the second test no toxic effects could be seen in fish with the highest concentration tested (900 mg/l).

Table 3.22 Short-term toxicity data for fish.

Type of test	Species	Endpoint LC_{50}, (NOEC) mg/l nominal	Exposure period	Method	Test substance	Reference
Semistatic	Brachydanio rerio	1992 (725)	96 h	OECD 203	72.5 % EPTAC, 3.0 % CHPTAC, 2.9 % 1,3-bis (trimethylammonium) propanol-2-chloride	(Degussa, 1987a)
Static	Salmo gairdneri	(ca. 900)	96 h	no info	92 % EPTAC, 5 % CHPTAC, 2.5 % DIOL	(Shell Oil Company, 1979)

3.2.1.1.2 Aquatic invertebrates

EPTAC short-term toxicity studies for aquatic invertebrates are summarised in Table 3.23. Acute EC_{50}-values for invertebrates range from 16.4-46 mg/l. Aquatic invertebrates seem to be more sensitive species to the toxic effects of EPTAC than fish.

Table 3.23 Short-term toxicity data for aquatic invertebrates.

Type of test	Species	Endpoint EC_{50}, (NOEC) mg/l nominal	Exposure period	Method	Test substance	Reference
Static	Daphnia magna	16.4 (6.3)	48 h	EPA OTS 797.1300	EPTAC	(DOW Chemical Company, 1996)
Static	Daphnia magna	46	24 h	No info	92 % EPTAC, 5 % CHPTAC, 2.5 % DIOL	(Shell Oil Company, 1979)

Results from the chronic (21 day) Daphnia reproduction test are presented in Table 3.24. The test was semi-static and test solutions were renewed 3 times per week. The concentrations of EPTAC were determined at all test concentrations (0.05, 0.16. 0.49, 1.45 and 4.35 mg/l) and in controls. Samples were taken and analysed on days 0, 7, 14, 19 (fresh media, 0 h) and on days 2, 9, 16, 21 (old media, 48 h). The mean recovery rates were > 80 %. All effect values are given based on the nominal concentrations of the active ingredient i.e. EPTAC. The NOEC for Daphnia reproduction rate is 0.16 mg/l, the LOEC 0.49 mg/l and the EC50 is 0.55 mg/l.

Table 3.24. Chronic toxicity data for aquatic invertebrates

Type of test	Species	Endpoint NOEC reproduction mg/l nominal	Exposure period	Method	Test substance	Reference
Semi-static	Daphnia magna	0.16 LOEC: 0.49 EC50: 0.55	21 days	OECD 211	72.5 % EPTAC	(QUAS, 2004b)

3.2.1.1.3 Algae

Two short term algae studies with nominal concentrations are available. EbC_{50}-value of 23.8 mg/l and ErC_{50}-value of 37.8 mg/l for *Chlorella vulgaris* have been reported (Degussa, 1991b). However, the validity criteria of the study were not fulfilled, because the cell concentration in the control cultures was not increased by a factor of at least 16 within three days. The cell concentration in the controls within three days was 66-88 % of the required concentration. Therefore the results from the study will not be used in the risk assessment.

A new study on green algae *Desmodesmus subspicatus* (renamed, former name *Scenedesmus subspicatus)* was performed in 2003. The stability of the test substance was checked before the main test by measuring the concentrations of the substance, without the algae, after 0 and 72 hours. Concentrations deviated only slightly (less than 20 %) from each other. Therefore, the main test was performed with nominal concentrations. No EC_{50}-value could be detected with the highest concentration tested i.e. E_rC_{50} was higher than 1000 mg/l (Table 3.25). Graphically evaluated EC_{10} was 814 mg/l based on growth rate and the NOEC was 580 mg/l.

Table 3.25. Toxicity data for algae.

Type of test	Species	Endpoint EbC_{50} (ErC_{50}) mg/l nominal	Exposure period h	Method	Test substance	Reference
Growth inhibition test	Desmodesmus subspicatus	> 1000	72	OECD 201	71 % EPTAC, 2.4 % CHPTAC	(CEFIC, 2003)

3.2.1.1.4 Micro-organisms

EPTAC is only slightly toxic to micro-organisms. In a activated sludge respiration inhibition test (OECD 209) performed in 2002 no EC_{50}-value could be found with the highest test concentration of 2000 mg/l (Table 3.26). EC_{10}-value of 443 mg/l estimated with regression analysis according to Cavalli-Sforza (1972) has been presented in the test report and this will be used for the PNEC derivation.

Table 3.26 Toxicity data for micro-organisms.

Species	Endpoint ErC_{50} (mg/l)	Exposure period	Method	Test substance	Reference
Activated sludge from sewage treatment plant	> 2000	3 h	OECD 209	71.1 % EPTAC (+2.4 % CHPTAC)	(CEFIC, 2002)

In addition to the respiration inhibition test the effect of EPTAC on the dehydrogenase activity of active sludge has been tested (Degussa, 1988). However, this test does not fulfil the requirements for the micro-organisms toxicity test, since it only measures the inhibition of dehydrogenase activity of the sludge. Many micro-organisms can suffer or even be dead although the enzyme activity can be detected. Therefore this study can not be used in derivation of PNEC micro-organisms.

3.2.1.1.5 Toxicity of the degradation product of EPTAC

Toxicity of DIOL (2,3-Dihydroxypropyltrimethylammonium chloride, CAS 34004-36-9) has been studied in one fish test, two Daphnia tests and one bacteria test. Test with algae is not available. All tests were carried out at nominal concentrations, but it is unlikely that the substance would evaporate or eliminate substantially (or no more than CHPTAC or EPTAC) during tests.

The fish study (*Brachydanio rerio*) was carried out according to OECD Guideline 203. Nominal test concentrations ranged from 320 mg/l to 3200 mg/l. Test and control solutions were renewed daily. Purity of the substance was 96.6 %, pH varied between 7.8 and 8.3, oxygen concentration was higher than 7.1 mg/l and the temperature was 24 ± 1˚C. After 96 h exposure at the highest test concentration, the number of fish and their condition, visually assessed, were the same as those of the control fish. Therefore the LC50 was higher than 3200 mg/l (Degussa, 1987a).

In a study with Daphnia carried out according to OECD Guideline 202 the 48 hour EC_{50} value was 707 mg/l (DOW Chemical Company, 1996). Nominal test concentrations were 125 – 2000 mg/l. Purity of the substance was 99.6 %, pH varied between 7.5 and 7.8, oxygen concentration was higher than 8.1 mg/l and the temperature was 19.8-20.9 ˚C.

In another study with Daphnia 24 h EC50 was found to be > 1000 mg/l, but < 3200 mg/l (Degussa, 1987b). At 1000 mg/l all animals were mobile after 24 h, but at 3200 mg/l all animals were immobile after 24 h. At 1800 mg/l 11 animals of 20 were immobile and the rest 9 were somewhat slower and swam somewhat closer to the bottom of the test vessels, so the EC50 was somewhere around 1800 mg/l. The actual concentrations of the test substance in the test solutions were not determined by chemical analysis. Purity of the substance was 96.6 %, pH varied between 7.7 and 8.1, oxygen concentration was higher than 5.9 mg/l and the temperature was 19 ± 1˚C.

Toxicity of DIOL to the bacterium *Pseudomonas putida* was determined in a growth inhibition test according to the Umweltbundesamt Guideline "Bewertung wassergefährdender Stoffe" (Degussa, 1988d). The test measures optical density of cultures with different concentrations of DIOL after 18.5 hours of incubation. Five test concentrations ranging from 1.0 to 32 g/l were used. At the highest concentration tested (32 g/l) a growth inhibition of 10 % was observed. The toxicity threshold is therefore 32 g/l. Purity of the substance was 96.6 %.

Although information on toxicity to algae is not available, it may be assumed from the low toxicity of CHPTAC and EPTAC to algae that the toxicity of DIOL to algae is also low. As a result it can be concluded that the toxicity of DIOL to aquatic organisms in general seems to be low.

3.2.1.2 Calculation of Predicted No Effect Concentration (PNEC)

There is a full base set available on short term toxicity with EPTAC. Daphnids seem to be clearly more sensitive to EPTAC than other organisms. There is additionally a NOEC from an algae test and a NOEC from a chronic Daphnia reproduction test.

According to the TGD an assessment factor of 10 will normally only be applied when long-term toxicity NOECs are available for at least three species across three trophic levels. It may sometimes be possible to determine with high probability that the most sensitive species has been examined, i.e. that a further long-term NOEC from a different taxonomic group would not be lower than the data already available.

The acute toxicity test results of EPTAC show clearly that Daphnia is the most sensitive species of the species tested. There are long term NOECs for algae and Daphnia and it is very unlikely that a chronic fish test would give a lower NOEC than the Daphnia test. Accordingly the PNEC will be derived from the 21 day Daphnia reproduction rate NOEC of 0.16 mg/l with an assessment factor of 10.

$AF_{aquatic} = 10$

This results a **$PNEC_{aquatic}$ of 16 µg/l.**

PNEC for micro-organisms can be estimated from the recent activated sludge respiration inhibition test. An EC_{10}-value of 443 could be derived from the test, and according to TGD an assessment factor of 10 should be used for a EC_{10}- or NOEC –value from this kind of test.

This results a PNEC of 44.3 mg/l for micro-organisms.

3.2.1.3 Toxicity test results for sediment organisms

No toxicity studies have been carried out for sediment organisms with EPTAC.

3.2.1.4 Calculation of Predicted No Effect Concentration (PNEC) for sediment organisms

As there is no tests with sediment organisms, $PNEC_{sediment}$ has to be estimated by using $PNEC_{aquatic}$ with the following equation:

$$\mathbf{PNEC_{sediment}} = \frac{K_{susp\text{-}water} \times PNEC_{aquatic} \times 1000}{RHO_{susp}}$$

where $K_{susp\text{-}water}$ = suspended matter- water partition coefficient (2.25 m^3/m^3),
RHO_{susp} = bulk density of suspended matter **(**1150 kg/m^3) and
$PNEC_{aquatic}$ = 0.016 mg/l

$PNEC_{sediment}$ will be **0.0313 mg/kg ,** when using fresh water toxicity data for EPTAC and a suspended matter-water partition coefficient.

3.2.2 Terrestrial compartment

3.2.2.1 Toxicity test results

No toxicity studies have been carried out for terrestrial organisms.

3.2.2.2 Calculation of Predicted No Effect Concentration (PNEC)

As there is no tests with soil organisms, $PNEC_{soil}$ has to be estimated by using $PNEC_{aquatic}$ with the following equation:

$$\mathbf{PNEC_{soil}} = \frac{K_{soil\text{-}water} \times PNEC_{aquatic} \times 1000}{RHO_{soil}}$$

where $K_{soil\text{-}water}$ = soil-water partition coefficient (1.81 m^3/m^3),
RHO_{soil} = bulk density of wet soil (1700 kg/m^3) and
$PNEC_{aquatic}$ = 0.016 mg/l

$PNEC_{soil}$ will be **0.0170 mg/kg,** when using fresh water toxicity data for EPTAC and a soil-water partition coefficient.

3.2.3 Atmosphere

There is no toxicity data available on EPTAC via atmospheric exposure. Concerning abiotic effects EPTAC is not expected to have effects on stratospheric ozone depletion, tropospheric ozone formation or acidification since it evaporates from the water very slowly (Henry's law constant $1.78 \cdot 10^{-7}$ Pa m^3/mol).

Possible impact of a substance on global warming could be estimated from its IR adsorption characteristis and its atmospheric lifetime. Such information is not available on EPTAC. However, as EPTAC has low vapour pressure and small Henry's law constant, it is not expected that EPTAC could have effect on global warming.

3.2.4 Secondary poisoning

It seems likely, that EPTAC would not bioconcentrate in high degree (see section 3.1.7). Therefore no assessment of secondary poisoning is necessary.

3.3 MARINE RISK ASSESSMENT

EPTAC may be released to the marine environment mainly through direct or indirect (via rivers) aquatic emissions from prosessing plants. In the year 2004 none of the EPTAC (or CHPTAC) production plants or starch cationizing sites (processing EPTAC) were situated in the vicinity of or by the sea. There are two known sites (B1 and B2), which use EPTAC for processing purposes (other than starch cationisation) and which are discharging to an estuary. In addition several paper manufacturing sites are known to be situated by the sea. Emission estimations in this marine assessment are mainly based on default values, and utilizes the overall emission data available in this risk assessment of EPTAC & CHPTAC.

The main goals in the marine risk assessment according to the TGD are to identify if a hazardous substance may accumulate in parts of the marine environment and that the effects of such accumulation are unpredictable in the long-term. Even if EPTAC is persistent, it has low potential to cause secondary poisoning. The bioaccumulation potential of EPTAC is low. This conclusion is mainly based on physicochemical and structural properties of the substance assessed earlier in this risk assessment. Therefore EPTAC can not be regarded as a PBT substance (see chapters on PBT assessment). However, EPTAC needs further consideration regarding marine environment according to the TGD.

3.3.1.1 Partitioning and Fate in Sea Environment

Environmental partitioning of EPTAC may be somewhat different in marine water compared to fresh water. EPTAC is a dissociating, cationic substance and there may be changes of the chemical structure in salty marine -water at rather high pH (ca. 8) compared to fresh water environment.

The hydrolysis rate of EPTAC to DIOL is pH dependent. The base (OH-) mediated process generally dominates in sea water. The estimated hydrolysis half-life in pH 7.0 is ca. 70 days, pH 7.8 177 days and pH 8.4 ca. 100 days at 12 °C(chapter 3.1.3.1.2).

In general, the salinity (ionic strength) of water may have influence on hydrolysis rates of ionic compounds. However, the hydrolysis test results may be regarded well representing "salty" water, since the test conditions under which the hydrolysis tests were carried out represents rather high ionic strength because of high concentrations of buffers used.

The water solubility of EPTAC is very high. From this point of view the substance may be present almost entirely in the water phase. Cationic binding and adsorption to clay minerals and sedimentation may still be a more remarkable process, than could be expected from the high water solubility figures.

3.3.1.2 Degradation

Abiotic degradation

Hydrolysis of EPTAC to DIOL at pH conditions relevant for the marine environment (ca. pH 7.8) takes approximately t½= 177 days at 12 ˚C.

Biodegradation

Existing fresh water biodegradation studies show that EPTAC is not readily biodegradable. Furthermore in STP simulation test only 15 ± 9.7 % primary degradation was observed in 6 hours. In adapted systems (industrial STP) fairly high biodegradation percentages may however be reached. There is no data available on standard or non-standard degradation test of EPTAC in marine water or marine sediment.

The number of potentially competent degraders and the adaptation pressure in marine water is typically low. Biodegradation figures of EPTAC in fresh water most obviously holds true in marine water as well and degradation rate is obviously still lower compared to fresh water.

Conclusion on degradation

It can be concluded that EPTAC is slowly degraded in the marine environment. Abiotic hydrolysis to less toxic and more easily biodegradable substance (ch. 3.1.3.1.2) is believed to be the main removal process of the substance. A half–life of 177 days for degradation is used in further marine assessment. It is also expected that hydrolysis to DIOL may take place for adsorbed and sedimented EPTAC at the same rate even if the actual hydrolysis rates may be faster due to catalytic action of clay minerals to the epoxide group. In addition, EPTAC is regarded as inherently biodegradable, but not fulfilling the criteria set in TGD.

3.3.1.3 Exposure assessment for the local marine environment

The two known EPTAC production sites do not distribute waste waters to the sea. Therefore it is not regarded necessary to carry out any generic local PEC calculations for the production. However, if known, release to the sea has been taken into account in local PEC calculations under chapters dealing with general local exposure assessment (EPTAC & CHPTAC RAR). A generic local PEC calculations for use scenarios are carried out here.

Generic local concentration in sea water is determined using the equation no: 83 (TGD 2003):

Clocal seawater = Clocal eff /(1 + Kp susp [SUSP water • 10^{-6}*]) • DILUTION*

for EPTAC it is => *Clocal eff /(1 + 5.38 l/kg* 15* • 10^{-6} *kg/l) • 100*

Generic local concentration in freshly deposited bulk sea sediment is determined using the equation no: 87 in TGD 2003. For EPTAC *Kp susp - water* = 5.38 l/kg is used (see chapters on environmental fate/adsorption):

*PEClocal sed = (Kp susp - water / RHO susp) * PEClocalwater *1000*
*= 5.38 l/kg/1.150 * PEClocalwater *1000*

Secondary poisoning evaluation has not been carried out because of low bio concentration potential of EPTAC.

Based on EUSES (version 2.0.3) calculation, the regional marine PEC (dissolved) is 1.66 x 10^{-4} mg/l. The EUSES input emission data, the EPTAC+CHPTAC regional + continental total emissions to surface water, is estimated to be 522.4 kg/d (Table 3.6).

PEC's for different use scenarios have been calculated using same local release volumes as with fresh water sites because lack of site-specific data on sites by the sea (Table 3.27). It is known only for two sites (B1 and B2), that they are situated by the sea. According to information provided by CEFIC QUAS, none of the existing cationisation plants under this risk evaluation is located by the sea and therefore this scenario (Industrial use 1) has not been included in the local marine assessment.

Table 3.27 Local Exposure to the Marine Environment

Life cycle step	Daily emission (kg)	Release days/y	PEC local_sea, (mg/l)	PEC local, seawater, annual (mg/l)	PEClocal, sediment (mg/kgwwt)
Industrial use 2 (board manuf.)	0.985	350	7.82E-04	7.56E-04	1.53E-03
Industrial use 2 (paper manuf.)	0.797	350	6.64E-04	6.44E-04	1.3E-03
Industrial use 3 (paper recycling)	0.05	350	3.05E-04	3.0E-04	5.96E-04
Industrial use 4 (AKD formulation .)	7.65E-04	300	1.7E-04	1.69E-04	3.32E-04
Industrial use 5 (other uses)					
B1	6.51E-04	12	1.68E-04	1.66E-04	3.29E-04
B2	8.8E-04	6	1.66E-04	1.66E-04	3.25E-04

There are not known other relevant emission sources to marine environment, other than industrial uses already described (current scenarios). Diffuse sources from end products (paper) exist but regarded very small.

Since adsorption of EPTAC to suspended material is poor, no additional adsorption correction for EPTAC is regarded necessary.

3.3.1.4 Effects assessment for the marine environment

Short term aquatic toxicity study results are available on EPTAC for three trophic levels. There are no entirely marine species tested for EPTAC. The base-set for EPTAC for the derivation of aquatic PNEC is available. Invertebrates (Daphnia) are the most sensitive group of species to the toxic effects of EPTAC. There are long term NOECs for algae and Daphnia. The $PNEC_{\mathbf{marinewater}}$ will be derived from the 21 day Daphnia reproduction rate NOEC of 0.16 mg/l.

According to TGD an assessment factor of 500 should be applied in the marine assessment to the lowest of two NOECs covering two tropic levels. However, lowering of assessment factor can be considered in cases when it is possible to determine with a high probability that the most sensitive species covering fish, crustacean and algae has been examined, and that a further long-term NOEC from a third taxonomic group would not be lower than the data already available. In the risk assessment of EPTAC acute test results showed Daphnids to be clearly the most sensitive species and therefore lowering of assessment factor is justified. Therefore an assessment factor of 100 is chosen for the marine environment.

This results a **$PNEC_{\mathbf{marinewater}}$ of 1.6 µg/l**

In the absence of any ecotoxicological data for sediment-dwelling organisms, the $PNEC_{sediment}$ 0.00313 mg/kgwwt is provisionally calculated using the equilibrium partitioning method from the $PNEC_{marine}$

$PNEC_{\mathbf{marinesediment}}$ will be **3.13 µg/kg**

3.3.2 PBT- assessment

3.3.2.1 Conclusions for the PBT- assessment

According to existing data and assessment of inherent PBT –properties, it can be concluded that EPTAC can not be regarded as a PBT-substance or a vPvB –substance, as it does not meet the B criterion. The screening level P-criterion is fulfilled. T-criterion is fulfilled based on human toxicity endpoints, but not for ecotoxicological endpoints. Conclusion for the PBT-assessment has been drawn from the following facts.

3.3.2.2 Persistence-criterion

According to existing biodegradation study results EPTAC is not readily biodegradable. There are two tests available: one regarding inherent biodegradability and the other on STP degradation simulation of EPTAC. In Zahn-Wellens test, 61% of the substance was mineralized after 28 days and 94% after 42 days, showing moderate degradation in this inherent study. In a 135 day STP simulation test 15 ± 9.7 % primary degradation was

observed in 6 hours (sludge retention time 6 hours). These results indicate that competent degraders of EPTAC exist and they are not very rare. Anyway, available data shows that degradation rate of EPTAC in the environment is slow and the screening P criterion is fulfilled regarding biodegradation.

Hydrolysis of EPTAC to readily biodegradable product DIOL (Dihydroxy-2,3-propyltrimethylammonium chloride) at neutral conditions (pH 7.0) takes approximately t½= 60-80 days at 12 ˚C. At pH 7.8 and pH 8.4 hydrolysis was somewhat slower (177 days and 98.5 days, respectively).

Conclusion: Under normal environmental conditions biodegradation of EPTAC is so slow that it can be initially classified as a potentially persistent substance meeting the screening P criterion. Under pH neutral environmental conditions EPTAC hydrolyses into readily biodegradable product DIOL. However, the hydrolysis rate is so slow that it does not change the conclusion of P assessment for EPTAC.

3.3.2.3 Bioaccumulation-criterion

There are no bioaccumulation study results available for EPTAC. The substance is highly water soluble and rather small size organic cation. Measured octanol/water partition coefficient value is << 1 (log Kow). It is very unlikely that a substance having these properties would bioconcentrate in high degree. Therefore it is concluded here that EPTAC does not meet the screening B-criterion (BCF > 2000 criterion) for bioaccumulation.

3.3.2.4 Toxicity-criterion

The lowest aquatic acute LC50 is 16.4 mg/l and therefore acute T-criterion of 0.1mg/l is not met. The lowest chronic NOEC is 0.16 mg/l and this is also above chronic T-criterion 0.01 mg/l). Hence EPTAC does not meet the T criteria for ecotoxicological endpoints.

Based on the human health toxicity classification, EPTAC fulfills the T-criterion because of possible potential to cause cancer and reprotox effects (Xn, Xi, Carc. Cat 2, Muta. Cat 3, Repro. Cat 3).

3.4 RISK CHARACTERISATION

During main use of EPTAC and CHPTAC i.e. cationisation of starch the process conditions are very alkaline (pH > 10) and therefore most of the chemical, EPTAC or CHPTAC, is in form of EPTAC which is the reactive form. This leads to releases of EPTAC despite which of the chemical is used. Thus EPTAC releases from use of EPTAC and CHPTAC will be considered at the local scale in the risk assessment of EPTAC.

In addition, the conversion of CHPTAC to EPTAC in waste water treatment plant and in the environment is likely as the conversion half-life is 21 days at pH 7.8 (at 12˚C) in pure water. These converted EPTAC releases will be considered at the regional scale in the EPTAC risk assessment report.

3.4.1 Aquatic compartment (incl. sediment)

3.4.1.1 Fresh water and sediment

PNEC for fresh water organisms is 16 µg/l. $PNEC_{sediment}$ has been calculated from $PNEC_{aquatic}$ and is 0.0313 mg/kg. There are PECs based on monitoring available from production, cationisation of starch and other use of EPTAC and CHPTAC.

According to producer A2 there are no releases to water from the plant and for producer A3 releases of EPTAC due to cleaning are assumed to be negligible. Production has stopped at site A1.

Site-specific PECs and PEC/PNEC ratios for surface water and sediment from starch cationisation are presented in Table 3.28. PECs for sediment have been derived from PECs for water by using equilibrium partitioning method, as no monitoring has been conducted from sediment. PEC/PNEC ratios for surface water and sediment are higher than one for two sites (out of 9), where EPTAC has been measured from the waste water. For sites, where no monitoring data is available (3 sites), releases are estimated with an emission factor of 1.32 % from another cationisation site (Table 3.29). At these sites all PEC/PNEC ratios are higher than one.

Sites presented in Tables 3.28 and 3.29 are all using wet process for production of cationised starch. In addition there are also 4 sites which produce cationised starch with dry process and three sites with wet process but without releases to water (Table 3.30). As there are no releases of EPTAC to water from these sites, the risk ratios from these sites to aquatic environment are zero.

Table 3.28: Site-specific PECs in surface water and sediment and corresponding PEC/PNEC ratios from starch cationisation. At these sites EPTAC has been measured from the waste water effluent.

Site	$PEC_{aquatic}$ (µg/l)	$PEC_{sediment}$ (mg/kg)	PEC/PNEC $_{aquatic\ (\&\ sediment)}$
CHPTAC users			
B3	< 3.12	< 6.1E-03	< 0.195
B4	< 18.6	< 0.0363	< 1.16

Site	$PEC_{aquatic}$ (µg/l)	$PEC_{sediment}$ (mg/kg)	PEC/PNEC aquatic (& sediment)
B5	10.6(average)	0.0207	0.661
B14	5.79	0.0113	0.36
B16	< 7.35	< 0.014	< 0.46
B17	< 10.16	< 0.0198	< 0.635
B18	< 1.82	< 3.56E-03	< 0.114
B21	< 13.24	< 0.0258	< 0.826
B25	< 65.4	< 0.128	< 4.09

Table 3.29: Site-specific PECs in surface water and sediment and corresponding PEC/PNECratios from starch cationisation. At these sites EPTAC has not been measured from the waste water, but there are other site-specific information available.

Site	$PEC_{aquatic}$ (µg/l)	$PEC_{sediment}$ (mg/kg)	PEC/PNEC aquatic (& sediment)
EPTAC users			
B9	218	0.426	13.6
B19[1)]	-	-	-
CHPTAC users			
B10	143	0.279	8.93
B23	4291	8.37	268
B26[2)]	-	-	-

[1)] *This site has been closed at the end of 2002

[2)] This site has been closed in 2004

Table 3.30 Risk ratios from starch cationisation sites with dry process or with wet process, but no releases to water.

Site	$PEC/PNEC_{aquatic}$ (& sediment)	Justification
EPTAC users		
B6	0	No waste water from normal process. Cleaning waters are diluted and sprayed on green fields.
B11	0	Dry process, no emissions to water.
B13	0	Dry process, no emissions to water.
B15	0	No waste waters generated. Cleaning waters are re-used in the process.
B22	0	Dry process, no emissions to water. Industrial and municipal WWTP available.
CHPTAC users		
B12	0	Waste water is evaporated and concentrated solution is incinerated, partly dry process
B28	0	Dry process, no emissions to water.

PEC/PNEC ratios for surface water and sediment from industrial uses 2, 3, 4 and 5 are presented in Table 3.31. PECs for sediment have been derived from PECs for water by using equilibrium partitioning method. PEC/PNEC ratios are lower than 1 for all use scenarios.

Table 3.31 PECs in surface water and in sediment and corresponding PEC/PNEC ratios

Life cycle step	PEC in surface water (µg/l)	$PEC_{sediment}$ (mg/kg)	PEC/PNEC aquatic (& sediment)
Use of starch with residual EPTAC and CHPTAC (Industrial use 2) * high grade board(case 1) *printing and writing paper(case 2)	4.0 (6.7) * 3.5 (5.79) *	7.83E-03 (0.0131) * 6.85E-03 (0.0113) *	0.25 (0.421)* 0.219 (0.362)*
Paper recycling (Industrial use 3)	3.19	6.22E-03	0.199
AKD formulation (Industrial use 4)	1.82	3.56E-03	0.114
Other uses of CHPTAC and EPTAC (Industrial use 5) * site B1 * site B2 * site B29	1.68 (marine) 1.66 (marine) < 7.45	3.29E-04 (marine) 3.25E-04 (marine) < 0.0145	0.105 0.104 < 0.465

* value in brackets is from a smaller paper/board mill

Regional risk characterisation

The regional fresh water concentration is 1.79 µg/l and as the PNEC is 16 µg/l, a PEC/PNEC ratio is 0.11. This indicates that there is no risk at regional level in surface water.

The regional sediment concentration is 0.0034 mg/kg and as the PNEC is 0.0313 mg/kg, a PEC/PNEC ratio is 0.11. This indicates that there is no risk at regional level in sediment.

3.4.1.2 Wastewater treatment plant

PNEC for micro-organisms is 44.3 mg/l for EPTAC. PEC/PNEC ratios for starch cationisation (industrial use 1) are presented in Table 3.32 and for industrial uses 2, 3, 4 and 5 in Table 3.33. PEC/PNEC ratios are lower than 1 for all use scenarios.

As there are no releases from EPTAC production sites to waste water treatment plants, risk ratios are zero for production.

Table 3.32: Site-specific PECs and corresponding PEC/PNEC ratios at WWTP from cationisation of starch.

Site	$PEC_{micro\text{-}organisms}$ (mg/l)	$PEC/PNEC_{micro\text{-}organisms}$
EPTAC users		
B9	5.02	0.11
B16	< 0.089	< 2.01E-03
B18	< 0.031	< 7.06E-04
B19 [1)]	-	-

Site	$PEC_{micro\text{-}organisms}$ (mg/l)	$PEC/PNEC_{micro\text{-}organisms}$
CHPTAC users		
B3	< 0.275	< 0.006
B4	< 10	< 0.23
B5	0.0283	6.39E-04
B10	3.28	0.074
B14	4.0	0.09
B17	< 0.06	< 1.35E-03
B21	< 0.0662	< 1.5E-03
B23	8.75	0.20
B25	< 0.7	< 0.016
B26 [2)]	-	-

[1)]This site has been closed at the end of 2002

[2)] This site has been closed in 2004

Table 3.33 PEC/PNEC ratios at WWTP for industrial use scenarios 2,3, 4 and 5.

Life cycle step	PEC in WTTP (mg/l)	PEC/PNEC
Use of starch with residual EPTAC and CHPTAC (Industrial use 2) * high grade board (case 1) *printing and writing paper (case 2)	 0.022 (0.0494) * 0.017 (0.04) *	 4.89E-04 (1.11E-03) * 3.80E-04 (9.02E-04) *
Paper recycling (Industrial use 3)	0.0139	3.14E-04
AKD formulation (Industrial use 4)	3.07E-04	6.93E-06
Other uses of EPTAC and CHPTAC (Industrial use 5) * site B1 * site B2 * site B29	 2.2E-04 1.36E-05 0.0301	 4.9E-06 3.06E-07 < 6.79E-04

* value in brackets is from a smaller paper/board mill

Conclusions to the risk assessment for the aquatic compartment:

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to surface water and sediment from cationisation of starch with wet process (Industrial use scenario 1) at the local scale for five sites (i.e. sites B4, B9, B10, B23 and B25).

From these five starch cationisation sites, which have risk ratio higher than one, two sites (B4, B25) have monitoring data on EPTAC releases to waste water. The detection limit of EPTAC from waste water effluent (0.7 - 10 mg/l) is rather high compared to PNEC (0.016 mg/l l). Use of lower detection limit might decrease risks from these two sites. For those three sites where no monitoring data is available (B9, B10, B23), releases have been calculated with an actual emission factor from a starch cationisation site with highest release factor (1.32 %). Biodegradation at the WWTP has been assumed to take place at these sites.

The PNEC for water and sediment has been calculated from the chronic NOEC for Daphnia using an assessment factor of 10. Refinement of PNEC is therefore not possible with the dataset currently available.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to fresh water and sediment from production of EPTAC and cationisation of starch with dry process for seven sites (B6, B11, B12, B13, B15, B22 and B28) and with wet process for seven sites (B3, B5, B14, B16, B17, B18 and B21) (Industrial use 1). Conclusion (ii) also applies to paper and board scenario (Industrial use 2), paper recycling (Industrial use 3), AKD formulation (Industrial use 4) and other uses of CHPTAC and EPTAC (Industrial use 5). Conclusion applies also to waste water treatment plants from all scenarios.

3.4.2 Terrestrial compartment

For the estimation of $PNEC_{soil}$ a partition coefficient and $PNEC_{aquatic}$ is used. $PNEC_{soil}$ will be 0.0170 mg/kg. Local EPTAC concentrations and PEC/PNEC ratios for soil are presented in Table 3.34. Risk ratio is below 1 for all use scenarios.

Table 3.34 PEC/PNEC ratios for soil

Life cycle step	PEC_{local} terrestrial (mg/kg wwt)	PEC/PNEC
Industrial use 1 (starch cationisation)		
B3	< 0.0102	< 0.596
B4	< 1.89E-05	< 1.11E-03
B5	1.06E-03	0.0619
B9	1.12E-05	6.55E-04
B10	8.99E-06	5.26E-04
B14	2.38E-05	1.4E-03
B16	< 3.31E-03	< 0.194
B17	2.23E-03	< 0.131
B18	< 1.17E-03	< 0.069
B21	< 2.46E-03	< 0.144
B23	2.85E-05	1.67E-03
B25	< 4.09E-05	< 2.4E-03

Life cycle step	**PEC_{local} terrestrial (**mg/kg wwt)	**PEC/PNEC**
Industrial use 2 (case 1, board production)	1.83E-03	0.107
Industrial use 2 (case 2, paper production)	1.48E-03	0.0868
Industrial use 3 (paper recycling)	5.2E-04	0.0304
Industrial use 4 (AKD formulation)	1.62E-05	9.48E-04
Industrial use 5 (other uses)		
B1	1.2E-05	7.05E-04
B2	5.37E-06	3.15E-04
B29	< 1.13E-03	< 0.0661

Regional risk characterisation

The regional EPTAC concentration in agricultural soil is 3.11E-05 mg/kg and as the PNEC is 17.0E-03 mg/kg, a PEC/PNEC ratio is 1.83 E-03. This indicates that there is no risk at regional level in soil.

Conclusions to the risk assessment for the terrestrial compartment:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those, which are being applied already.

Conclusion applies to production and all use scenarios.

3.4.3 Atmosphere

No quantitative risk assessment has been carried out for the atmospheric compartment due to lack of effect data via air.

Due to low volatility of EPTAC no significant exposure to the atmosphere is expected. EPTAC releases to air are likely during cationisation of starch as a residue in the starch dust. However, based on a few measurements releases are fairly low.

Conclusions to the risk assessment for the atmosphere:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion applies to production and all use scenarios.

3.4.4 Secondary poisoning

It seems likely, that EPTAC would not bioconcentrate in high degree (see section 3.1.7). Therefore no assessment of secondary poisoning has been carried out.

3.4.5 Marine environment

There are no releases from the two EPTAC production sites to marine environment. For industrial uses (scenarios 2-5) local risk characterisation ratios to sea water and sediment have been presented in Table 3.35. For use scenario 1 (starch cationisation) no local estimation has been carried out as no sites were located by the sea (in year 2004) according to EPTAC and CHPTAC producers. The $PNEC_{marine}$ is 1.6 µg/l and $PNEC_{marinesediment}$ is 3.13 µg/kg.

Table 3.35 Marine Risk Characterisation for Industrial use scenarios

Emission scenario	PEC_{local} marine water (µg/l)	PEC_{local} marine sediment (µg/kg)	$PEC/PNEC_{marine}$ water (& sediment)
Industrial use 2 (board manufacturing) Industrial use 2 (paper manufacturing)	0.782 0.664	1.53 1.3	0.489 0.415
Industrial use 3 (paper recycling)	0.305	0.596	0.191
Industrial use 4(AKD-wax production)	0.17	0.332	0.106
Industrial use 5(other uses of EPTAC and CHPTAC) B1 B2	0.168 0.166	0.33 0.325	0.105 0.104
Regional marine water	0.166		0.104
Regional marine sediment		0.31	0.0992

All risk characterisation ratios are below 1 for the marine environment.

Conclusions to the risk assessment for the marine environment:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion applies to production and all use scenarios.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY)

4.1.1 Exposure assessment

4.1.1.1 General discussion

2,3-Epoxypropyltrimethylammonium chloride (EPTAC) is a non-volatile organic salt, which is handled as a water solution in concentrations of 70-75%. The vapour pressure for this chemical is below 0.001 Pa at temperatures 20-80°C with decomposition beginning at 120°C. No aerosol forming processes are used and thus the substance is unlikely to be found in the air. The main route of potential exposure to this chemical is by dermal contact. Exposure to EPTAC may arise from working processes and indirectly via food and the environment. Consumer exposure may take place through the residual amounts of EPTAC in the final products, paper and board, manufactured from cationised starches.

During use of the chemical, the exposure assessment of 2,3-epoxypropyltrimethylammonium chloride (EPTAC) is very much related to exposure assessment of (3-chloro-2-hydroxypropyl) trimethylammonium chloride (CHPTAC) and vice versa. These two chemicals are both used for cationising of starch. The actual reactive form is the epoxide form into which CHPTAC is also converted with the addition of alkaline. Therefore, after the cationising agent has been added into the process, the exposure assessments are the same. Then there is no matter which one of the chemicals has been used, because the reactions and exposure situations are the same. The main concern is the concentration of EPTAC, because of its health effects. Consequently the exposure assessment document of EPTAC is also relevant for CHPTAC for the use scenarios concerned.

4.1.1.2 Occupational exposure

The present data concerning occupational exposure to EPTAC was found to be limited. Exposure information has been gathered through questionnaires by the CEFIC Quas Sector group from producers and all customers of the sector group members. EPTAC is manufactured and handled only in aqueous solution and is pumped and handled automatically avoiding as much as possible human exposure. As the substance has a very low vapour pressure and is not used as an aerosol, inhalation exposure is unlikely. Workplace analysis in some production and use sites has revealed that inhalation exposure is minimal and not considered relevant. This was confirmed by a few exemplary measurements of airborne concentrations which were provided by the industry.

Dermal and in some case inhalation exposure was evaluated with the EASE (Estimation and Assessment of Substance Exposure) model (EASE for Windows Version 2.0, August 1997). EASE is an electronic, knowledge based, expert system which is used when measured exposure data are limited or not available. Domestic factories manufacturing and using this chemical were visited, and production managers and workers interviewed about the processes, use of the chemical and the working habits.

The occupational exposure to EPTAC is discussed further in sections like manufacture of this chemical, loading and unloading operations, use in cationisation of starch by different methods and use of products with residual amounts of the chemical.

The exposure is assessed without taking account of the possible influence of personal protective equipment (PPE). However, the information on the use of PPE gathered by the industry is mentioned in the text when available. Knowledge of the suitability of PPE in practical situations is very limited. Furthermore, the suitability is dependent on site-specific aspects of management, procedures and training of workers. According to the information received from the industry, many companies have detailed guidelines for handling these chemicals. In these cases the exposure may be significantly lower than estimated here as a reasonable worst case (RWC).

Usually the upper limit of the EASE range is selected as RWC. For typical exposure the middle of the EASE range or even the lower limit is used depending on the exposure time. In the calculations of exposure to residual levels of the substance in cationised products, the 90th percentile is used as RWC and 50th percentile for typical exposure. The typical exposure values are presented only in the summary table.

All the measured or modelled exposure concentrations are calculated to pure EPTAC (or CHPTAC).

Occupational exposure limits for EPTAC have not been established.

4.1.1.2.1 Occupational exposure from production

EPTAC is synthesised from epichlorohydrin, trimethylamine and water. Hydrochloric acid and sodium hydroxide are needed as catalysts. The product is a water solution containing EPTAC 70-75%. According to the producers, this chemical in dry form is not manufactured any more. Also other ways to synthesise EPTAC have been described in the literature.

Manufacturing process is a closed system, which is operated from a remote control room.

According to the producers, people work intermittently at the production plant. There are two production plants for EPTAC in the EU area.

Possible exposure to EPTAC for the worker has been identified in sampling, laboratory work, maintenance and clean-up. Dermal exposure is the main route causing concern, since no aerosol forming processes take place.

Personal protective equipment (PPE) has to be used according to the standard operating procedures. During sampling and analysing in the laboratory, disposable gloves (e.g. nitrile) and safety goggles are used. According to the safety instructions, if exposure is anticipated also rubber boots, protective suit and respirator are used. Several glove materials have been tested for permeability and breakthrough times according to BS EN 374-3 and the suitable materials, natural rubber or polychloroprene with natural latex liner, are recommended in the manufacturers safety data sheets.

Dermal exposure

Modelled data

Sampling

Samples are taken at the end of the process and from the storage tanks. The concentration of the chemical in the samples is 70-75%. Several samples are taken per shift. The process worker takes the samples. Taking a sample is considered to last a few minutes. Exposure to EPTAC may take place due to spilling while taking a sample and due to contact to contaminated surfaces.

For sampling, the input parameters in EASE are closed system, breached, direct handling and intermittent contact (2 to 10 per shift).

The predicted dermal exposure to liquid containing EPTAC is 0.1-1 mg/cm2/day. Because the concentration of this chemical in the sample is about 75 %, the predicted dermal exposure is 0.075-0.75 mg/cm2/day. Considering an exposed area of 210 cm2 (fingers, palm side) the exposure level amounts to 15-150 mg/person/day. Because the exposure time in sampling is only about 30 minutes per shift and low quantities are handled, typical exposure level is likely to be in the lower end of the range. PPE, properly selected and worn will significantly reduce exposure. It is estimated that a reasonable worst case, RWC (deposition to the skin) would be 150 mg/person/day.

Laboratory work

Samples are analysed in the laboratory. In the production plant, the laboratory technician spends about half of her working day handling samples containing EPTAC about 70-75%. Exposure may happen due to splashing e.g. in opening the sample bottle and due to contact to contaminated surfaces. If high standard working procedures (for carcinogenic substances) are followed contacts would rather be accidental. However the procedures are site-specific and therefore the worst case is estimated here.

For laboratory work, the input parameters in EASE are non-dispersive use, direct handling and intermittent contact.

The predicted dermal exposure to liquid containing EPTAC is 0.1-1 mg/cm2/day. Because the concentration of this chemical in the sample is about 75 %, the predicted dermal exposure is 0.075-0.75 mg/cm2/day. Considering an exposed area of 420 cm2 (palms of hands) the exposure level amounts to 30-300 mg/person/day. Because rather small quantities are handled, typical exposure level is likely to be in the lower end of the range. PPE, properly selected and worn will significantly reduce exposure. It is estimated that a reasonable worst case, RWC (deposition to the skin) would be 300 mg/person/day.

Maintenance and clean-up

Maintenance of pumps, etc. is cared for by the maintenance worker of the factory. Also external maintenance services can be used. Repairing pipe blockages and maintenance of pumps may cause exposure due to residuals of the chemical.

For maintenance work, the input parameters are non-dispersive use, direct handling, incidental contact (one per shift).

The predicted dermal exposure to liquid containing EPTAC is 0-0.1 mg/cm2/day. Because the concentration of this chemical in the sample is about 75 %, the predicted dermal exposure is 0-0.075 mg/cm2/day. Considering an exposed area of 840 cm2 (hands) the exposure level amounts to 0-63 mg/person/day.

Typical situation is that the equipment is either rinsed free of the substance prior to the work and/or full protective equipment is used. PPE, properly selected and worn will significantly reduce exposure. Because also external services are used there is no full certainty how the PPE instructions are followed and how good PPE actually is. It is estimated that a reasonable worst case, RWC (deposition to the skin) would be 63 mg/person/day.

Summary/statement of the exposure level

The highest exposure level by dermal route was found in the laboratory work. The reasonable worst case was 300 mg/person/day.

4.1.1.2.2 Occupational exposure from loading operations

Occupational exposure during loading and unloading operations

EPTAC is transported to the users by road tankers.

The production worker does the loading with the driver assisting. Before loading, the cleanness of the tank is checked by the worker. Loading can be done by pumping via the top or the bottom valves of the tank. After loading the worker takes a sample into a plastic bottle. This sampling scenario is no longer a common practice. The worker wears disposable gloves, chemical resistant overalls, safety goggles and rubber boots.

Driver does the unloading with the factory worker assisting using gloves for personal protection. The standard procedure is pumping the liquid directly from the tank car into the storage tank. In unloading, the tank car and the transfer pump are on a concrete pad that can be washed with water in case of a spill. The unloading takes about one hour to complete. Frequency of deliveries varies from several per week to twice a month.

Membrane pumps are used to suck the tubes so empty that any drips may be avoided. External surfaces of the tubes may however be contaminated with the chemical and handling them spreads the chemical further. The maintenance of gloves to keep them clean is therefore of importance for driver's safety.

After the transportation, the tank is washed with water by the transportation firm. Water used in the clean up is taken up and put for further treatment.

Inhalation exposure

<u>Measured data</u>

According to one producer, EPTAC was not shown during filling of tank trucks and Intermediate Bulk Containers, IBC's (worst case strategy). Five measurements were conducted over 10 to 68 min with the detection limit of 0.08 mg/m3. Half of the detection limit can be used as RWC.

Modelled data

For loading, the input parameters in EASE are exposure-type is gas/vapour/liquid aerosol, aerosol-formed no, non-dispersive use, pattern-of-control is segregation, the volatility of the substance is very low.

The predicted inhalation exposure in loading is 0-0.06 mg/m3 (0-0.1 ppm). With the chemical concentration of 75%, the estimated exposure is 0-0.05 mg/m3 (0-0.08 ppm).

Summary/statement of the exposure level
The inhalation exposure during loading was low. Half of the detection limit (0.04 mg/m3) can be used as RWC.

Dermal exposure

Modelled data

For loading and sampling after loading, the input parameters in EASE are closed system, breached, direct handling, incidental contact (1 per shift).

The predicted dermal exposure to liquid containing EPTAC is 0-0.1 mg/cm2/day. Because the concentration of this chemical in the sample is about 75 %, the predicted dermal exposure is 0-0.075 mg/cm2/day. Considering an exposed area of 420 cm2 (palms of hands) the exposure level amounts to 0-30 mg/person/day. PPE, properly selected and worn will significantly reduce exposure. It is estimated that a reasonable worst case, RWC (deposition to the skin) would be 30 mg/person/day.

In unloading, the standard operating procedure is pumping the liquid directly from the tank car into the storage tank. Exposure can potentially occur only for a short time during connection of the pipes. Additionally gloves are used and detailed instructions how to properly avoid dermal exposure are given and management systems applied.

However, there is some uncertainty how gloves are really worn and handled. There might be situations where hand is first contaminated or gloves contaminated inside are used. In these situations, EASE can not be used. Quantitatively exposure could be at least in the same magnitude as above was modelled.

Summary/statement of the exposure level

The reasonable worst case was 30 mg/person/day during loading and sampling after loading.

4.1.1.2.3 Occupational exposure from end uses

According to the information from industry, 98.5 % of the volume of EPTAC was used for cationisation of starch and the rest 1.5 % for quaternisation of cellulose, proteins, guar, carnitine and other derivatives.

Cationic starch products are used in paper making to improve paper strength and printing quality, to improve retention, and to reduce effluent load. These paper chemicals are called cationic surface sizing starches and wet-end starches. Cationic starches are also used as additives in some paper chemicals, e.g. as stabilisers in emulsions. Starches used to increase the internal strength of paper are added in the beginning (wet end) of the paper/cardboard

machine, whereas starch used to increase surface strength are added after the wire at the size press as dry end chemicals.

Minor uses of EPTAC are for quartenisation of cellulose, proteins and other derivatives. These cationic compounds may be used in personal care products (information from Colipa, 2003).

According to the industry, 81 workers (4 females) were reported to be continuously working, and 63 workers (12 females) were intermittently working in the use processes. The number of sites using EPTAC was 11 (QUAS, 2000a).

The processes were described as batch, closed, semiautomated processes in four cases; batch, closed, automated processes in five cases; and continuous, closed, automated processes in two cases.

Residual levels of EPTAC and CHPTAC in end-products

A survey of residual levels of EPTAC and CHPTAC in commercial cationic starches has been carried out by the industry in spring 2003 (QUAS, 2003). Samples were provided by cationised starch producers (AAC) from different batches of the grades marketed in the largest volumes, representing about 75 to 80% of the cationic starches market share in the EU. All samples were analysed with the same analytical method by the same external laboratory. The residues were measured in 58 samples. The residual values depend on the type of the product and process parameters. For the worst case calculations in exposure assessment, the values of 90th percentile have been selected. The values are 15 mg/kg for EPTAC and 450 mg/kg for CHPTAC. The 50th percentile values of 3 for EPTAC and 12 mg/kg for CHPTAC are used in the calculations for typical exposure presented in the summary table.

Wet cationisation

In the wet or slurry cationisation process, aqueous starch slurry (about 40 % w/w) is pumped to a closed reactor or tank system. To this slurry the necessary quantity of EPTAC is added through closed pipes and dosing systems from the storage facilities. With diluted sodium hydroxide solution the pH is increased to 11. The reaction mixture is stirred for 6-24 hours at about 40°C until the reaction is complete. The slurry is neutralised by addition of hydrochloric acid, cooled and the slurry is filtrated. The starch may be washed with water before or after the filtration. This process is a closed system operated from the remote control room.

The high-cationic starch solutions are produced by reaction in at least two successive steps, in the first of which a temperature of about 5-40ºC is maintained, and in the second step a temperature of about 70-180ºC.

During cationisation the exposure concerns qualitatively EPTAC. When the reaction is completed, starch is neutralised and then the final product contains also CHPTAC.

As the processes are usually closed, exposure situations may occur in sampling and maintenance.

Dermal exposure

Modelled data in wet cationisation

Sampling

During reaction of starch and cationising agent, control samples for checking the pH of the mixture are taken from the reactor several times per shift. Sampling during reaction may not be a common practice anymore. Instead only the end-products are sampled and analysed in the laboratory. In the reactions at high temperatures samples are not taken. Overflow or splashing may occur during sampling due to the hydrostatic pressure in the reactor. In the best case the process worker taking the sample wears gloves (e.g. vinyl) and safety goggles.

For sampling, the input parameters in EASE are closed system, breached, direct handling and intermittent contact.

The predicted dermal exposure to liquid containing EPTAC is 0.1-1 mg/cm2/day. Based on the concentration in the sample (about 3 %, maximum amount based on the information by industry), the predicted dermal exposure is 0.003-0.03 mg/cm2/day. Considering an exposed area of 210 cm2 (fingers, palm side) the exposure level amounts to 0.5-5 mg/person/day. Because the exposure time in sampling is rather short and low quantities are handled, typical exposure level is likely to be in the lower end of the range. PPE, properly selected and worn will significantly reduce exposure. It is estimated that a reasonable worst case, RWC (deposition to the skin) would be 5 mg/person/day for EPTAC.

Laboratory work

Samples are analysed by the process worker and the laboratory technician. Exposure may happen due to splashing in mixing and measuring operations and due to contact to contaminated surfaces. If high standard working procedures (for carcinogenic substances) are followed contacts would rather be accidental. However the procedures are site-specific and therefore the worst case is estimated here.

For laboratory work, the input parameters in EASE are non-dispersive use, direct handling and intermittent contact.

The predicted dermal exposure to liquid containing EPTAC is 0.1-1 mg/cm2/day. Because the concentration of this chemical in the sample is only about 3 %, the predicted dermal exposure is 0.003-0.03 mg/cm2/day. Considering an exposed area of 420 cm2 (palms of hands) the exposure level amounts to 1-10 mg/person/day. Because rather small quantities are handled, typical exposure level is likely to be in the lower end of the range. PPE, properly selected and worn will significantly reduce exposure. It is estimated that a reasonable worst case, RWC (deposition to the skin) would be 10 mg/person/day for EPTAC.

Maintenance and clean-up

In the case of equipment failure or leak, cleaning and maintenance work causes an exposure risk. Pump leaks may incidentally occur causing the spread of the reaction product on the factory floor. The maintenance is usually taken care by special firms but the workers in the factory do the cleaning. Gloves, goggles and protective suit are usually worn as PPE.

For maintenance work, the input parameters in EASE are non-dispersive use, direct handling and incidental contact.

The predicted dermal exposure to liquid containing EPTAC is 0-0.1 mg/cm2/day. Because the concentration of this chemical in the sample is about 3 %, the predicted dermal exposure is 0-0.003 mg/cm2/day. Considering an exposed area of 840 cm2 (hands) the exposure level amounts to 0-3 mg/person/day. PPE, properly selected and worn will significantly reduce exposure. It is estimated that a reasonable worst case, RWC (deposition to the skin) would be 3 mg/person/day for EPTAC.

Filling

In wet cationisation the end product is transferred into storage silos or large containers. Workers in this area may be exposed dermally to the cationised starch sludge with residual amounts of EPTAC and CHPTAC. Gloves, goggles and usually also protective suit are reported as PPE.

For filling, the input parameters in EASE are non-dispersive use, direct handling and incidental contact.

Dermal exposure to cationised starch during filling is 0-0.1 mg/cm2/day with incidental contact. With the residual concentration 15 mg/kg of EPTAC the value is 0-0.0000015 mg/cm2/day. Considering an exposed area of 420 cm2 (palms of hands) the exposure level amounts to 0-0.0006 mg/person/day. PPE, properly selected and worn will significantly reduce exposure.

It is estimated that a reasonable worst case, RWC (deposition to the skin) would be 0.0006 mg/person/day for EPTAC.

For CHPTAC the estimate would be 0.02 mg/person/day (residual concentration 450 mg/kg).

Summary/statement of the exposure level

The highest exposure level by dermal route was found in the laboratory work. The reasonable worst case was 10 mg/person/day.

Wet cationisation with drying

Dry modified starch can be produced by dry cationisation process or drying the end product of wet cationisation process. According to the industry, the drying process takes place in a closed flash dryer. The slurry product is dried into a dry content of 80%. The dry product is packed into big bags or transferred to storage silos.

Exposure scenarios as sampling and laboratory work are the same already described in wet cationisation in addition to that drying section. Bagging and loading scenarios are described in dry cationisation section. The residual concentrations of EPTAC and CHPTAC in this kind of dry cationic starch dust are expected to be in the same range as in dry cationised starch.

Drying

In drying section some exposure to cationised starch may occur during sampling or maintenance work. There was not enough information for EASE estimations. The scenarios assessed in dry cationisation can be applied.

Dry cationisation

In the dry cationisation process starch remains all the time in powdered form. In the process granular, air dry starch and alkali (e.g. sodium hydroxide solution, calcium hydroxide) are intensively mixed in a high shear force mixer and subsequently EPTAC is sprayed onto the mixture. The process takes place in a closed reactor. The mixture is then either discharged into silos or to heat jacketed mixing systems. Solid organic acids (e.g. adipic acid) are added to the starch mixture after the reaction is complete to decrease the pH to 5-7 and the cationic starch product is filled into the appropriate transport containers without further treatment.

Engineering controls are used in dry cationisation processes including separate ventilation systems with filters and under-pressure systems.

The particle size of dry cationised starch is not known. Native potato starch has the particle size between 10 to 100 μm and waxy maize 4 to 30 μm.

Inhalation exposure to cationised starch

Measured data

A few workplace measurements were reported by the industry (QUAS, 2000a). In filling operations, area measurements were performed by measuring exposure to cationic starch dust with the results of 0.53 to 20.38 mg/m3 (method Standard NF X 43-261, worst case strategy). The maximum residual content of CHPTAC in this cationic starch was 0.55 mg/g. Calculated content of CHPTAC in cationic starch dust was 0.0026 mg/m3 (median). The 13 measurements were performed in 1994 to 1997 as 8 h TWA.

The second report of workplace measurement was monitoring of EPTAC (in 1997, method dust sampling NEN-EN 68 g, MDHb 14, detection limit 25 μg). Area measurements were conducted with random strategy, personal measurements following worst case strategy. Area concentrations were 0.002-0.004 mg/m3 (TWA, n=5). Personal concentrations were reported as 0.02-0.04 mg/m3 (TWA, n=5). Residual contents of EPTAC were reported as 20-100 mg/kg in cold soluble starches and below 20 mg/kg in cationic starches. Levels of CHPTAC were below detection limits.

In the Exposure Measurement Database of Finnish Institute of Occupational Health (FIOH 1994), a few dust exposure measurements were found carried out in the bag filling area of dried cationised starch. Two of the measurements were personal samples and two area samples in bag filling as gravimetric analysis of total dust. These measurements were done during process leaks and before modification of the engineering control at the site. Personal samples during bagging gave results of 34 and 75 mg/m3. These results were not considered reliable, because of the possibility of extra contamination of the filter. General air samples were 21 and 38 mg/m3.

Recently new data on exposure to cationised starch has been provided by the industry. Dust measurements were conducted by personal monitoring in the bagging area. The average value for inhalable dust was 0.75 mg/m^3 (range 0.50-0.90 mg/m^3). Other measurements were carried out during bulk loading and bagging. The range for total dust values was 0.22-5.08 mg/m^3 (9 values). For alveolar dust, the range was 0.07-1.01 mg/m^3 with the average value of about 0.36 mg/m^3. The maximum value of total dust 5.08 mg/m^3 is taken for the RWC and the average value 2.1 mg/m^3 for typical case. The EPTAC concentrations would be 0.00008 and 0.000006 mg/m^3 in reasonable worst case and typical case respectively. For CHPTAC the concentrations are 0.002 and 0.00003 mg/m^3, respectively.

Modelled data in dry cationisation

Sampling and laboratory work are not considered here as potential exposure scenarios by inhalation as such a small quantities of cationised starch are handled.

Maintenance and clean-up

Sometimes maintenance and clean-up work will be needed in the area where the worker may come in contact with the chemical or unreacted product. These maintenance activities include also changing of filters. In the best case the maintenance personnel are reported to wear disposable overalls, gloves, eye protection and respiratory protective equipment. The frequency of maintenance and clean-up is around once a week according to data by industry.

For maintenance work, the input parameters in EASE are dust-inhalation, mobile-solid, no solid-vp, dust particle size inhalable, dry manipulation, non-fibrous, no aggregation, without LEV.

The predicted dust exposure range is 5-50 mg/m3 of cationised starch. The concentration of EPTAC in powder form can vary a lot, depending on the state of the reaction. Engineering control and PPE, properly selected and worn, will significantly reduce exposure.

It is estimated that a reasonable worst case, RWC, would be 0.0008 mg/m3 calculated with the residual concentration 15 mg/kg of EPTAC and the highest estimate.

For CHPTAC the estimated air concentration would be 0.02 mg/m3 (with 450 mg/kg residual concentration).

Bagging

Dry cationised starch is packed into big bags or transferred to storage silos. Workers in this area may be exposed by inhalation to the dust of the cationised starch with residual amounts of EPTAC and CHPTAC, especially during bagging.

For bagging, the input parameters in EASE are dust-inhalation, mobile-solid, no solid-vp, dust particle size inhalable, low dust techniques, non-fibrous, no aggregation, with LEV.

The predicted dust exposure range is 0-1 mg/m3. According to the industry, filling operations were in most cases reported to be either fully contained or segregated. General ventilation was additionally reported on some sites and use of gloves, goggles and protective suit. PPE, properly selected and worn will significantly reduce exposure.

It is estimated that a reasonable worst case, RWC, would be 0.00002 mg/m3 calculated with the residual concentration 15 mg/kg of EPTAC. For CHPTAC the estimated air concentration would be 0.0005 mg/m3 (with 450 mg/kg residual concentration).

Summary/statement of the exposure level

The inhalation exposure was found highest in maintenance and clean-up operations.

Dermal exposure

Modelled data in dry cationisation

Sampling

In dry cationisation, approximately 4 to 12 samples are taken per shift from the area where the reaction has already happened. Only special evaluations need sampling from the unreacted area. Production worker spends about 20 to 60 minutes per shift in sampling. Protection used in sampling includes gloves and eye protection.

For sampling, the input parameters in EASE are closed system, breached, direct handling, intermittent contact.

The predicted dermal exposure to sample containing residual EPTAC is 0.1-1 mg/cm2/day. With the residual concentration 15 mg/kg of EPTAC the values are 0.0000015-0.000015 mg/cm2/day. Considering an exposed area of 210 cm2 (fingers, palm side) the exposure level amounts to 0.0003-0.003 mg/person/day. PPE, properly selected and worn will significantly reduce exposure.

It is estimated that a reasonable worst case, RWC (deposition to the skin) would be 0.003 mg/person/day for EPTAC.

For CHPTAC the estimate would be 0.1 mg/person/day (with the residual concentration of 450 mg/kg)

Laboratory work

A laboratory technician works about 6 hours per day analysing samples with residual concentration of EPTAC.

For laboratory work, the input parameters in EASE are non-dispersive use, direct handling and intermittent contact.

The predicted dermal exposure to the sample containing EPTAC is 0.1-1 mg/cm2/day. With the residual concentration 15 mg/kg of EPTAC the values are 0.0000015-0.000015 mg/cm2/day. Considering an exposed area of 420 cm2 (palms of hands) the exposure level amounts to 0.0006-0.006 mg/person/day. Because rather small quantities are handled, typical exposure level is likely to be in the lower end of the range. PPE, properly selected and worn will significantly reduce exposure.

It is estimated that a reasonable worst case, RWC (deposition to the skin) would be 0.006 mg/person/day for EPTAC.

For CHPTAC the estimate would be 0.2 mg/person/day (with the residual concentration of 450 mg/kg).

Maintenance and clean-up work

Sometimes maintenance and clean-up work will be needed in the area where the worker may come in contact with the chemical or unreacted product. These maintenance activities include also changing of filters. The maintenance personnel are reported to wear disposable overalls, gloves, eye protection and respiratory protective equipment.

For maintenance work, the input parameters in EASE are non-dispersive use, direct handling, incidental contact.

The predicted dermal exposure to the substance containing residual EPTAC is 0-0.1 mg/cm2/day in maintenance work. For clean-up, intermittent contact is more probable giving exposure range of 0.1-1 mg/cm2/day. With the residual concentration 15 mg/kg of EPTAC the values are 0-0.0000015 in maintenance work and 0.0000015-0.000015 mg/cm2/day in clean-up. An exposed area of 840 cm2 (two hands) is chosen for this kind of work where exposure to solid dusty material is possible. In addition, the dust may be deposited on the face and neck, but the quantity is difficult to determine. With these parameters the exposure levels are 0-0.001 in maintenance and 0.001-0.01 mg/person/day in clean-up work. PPE, properly selected and worn will significantly reduce exposure.

It is estimated that a reasonable worst case, RWC (deposition to the skin) would be 0.001 mg/person/day in maintenance work and 0.01 mg/person/day in clean-up work for EPTAC.

For CHPTAC the estimate would be 0.04 mg/person/day in maintenance work and 0.4 mg/person/day in clean-up work (with the residual concentration of 450 mg/kg).

Bagging

Dry cationised starch is packed into big bags or transferred to storage silos. Workers in this area may be exposed also dermally to dust of the cationised starch with residual amounts of EPTAC and CHPTAC, especially during bagging.

For bagging, the input parameters in EASE are non-dispersive use, direct handling, intermittent contact.

Dermal exposure to cationised starch during bagging is 0.1-1 mg/cm2/day. With the residual concentration 15 mg/kg of EPTAC the value is 0.0000015-0.000015 mg/cm2/day. Considering an exposed area of 840 cm2 (two hands) the exposure level amounts to 0.001-0.01 mg/person/day. In addition, the dust may be deposited on the face and neck, but the quantity is difficult to determine. PPE, properly selected and worn will significantly reduce exposure. Typical exposure will be low on sites where effective engineering controls like full containment or segregation are in use.

It is estimated that a reasonable worst case, RWC (deposition to the skin) would be 0.01 mg/person/day for EPTAC.

For CHPTAC the estimate would be 0.4 mg/person/day (with the residual concentration of 450 mg/kg).

Summary/statement of the exposure level

The highest exposure level by dermal route was found in clean-up work and bagging. The reasonable worst case was 0.01 mg/person/day for EPTAC.

Occupational exposure during other possible uses

According to the patent literature many kinds of other possible uses for EPTAC have been invented. The actual utilisation of these inventions in the industry is not known.

EPTAC can be used to manufacture cationic polymers for cosmetic industry. For example, hydroxyethylcellulose can be modified to a compound with an INCI name polyquaternium-10 which is used as a conditioner, emollient and viscosity-controlling agent in cosmetics. This

and other cationic compounds are used primarily in hair care products, skin cleansers and skin moisturisers in concentrations of ≤0.1%-2% (information from Colipa, 2003). The information on possible EPTAC and CHPTAC residues in these cationic compounds is limited, but usually the residual concentrations are <200 mg/kg.

EPTAC modified products can be used as dry strength additives for paper, retention aids, flocculants, electroconductive resins, antistatic agents, dye assists, asphalt emulsifiers and emollients.

There is no data available to make a proper assessment but there could be some exposure in this scenario.

4.1.1.2.4 Occupational exposure during use of products with residual EPTAC and CHPTAC

Cationised starch in paper manufacturing

As cationised starch products may contain residual EPTAC and CHPTAC, handling these in the paper factory may expose workers to low amounts of this chemical depending on the procedures.

The usage of cationised starch varies from hundreds to thousands of tons per year depending on the paper-grade manufactured in the factory. Cationised starch is always used as a solution in paper factory. When it comes as a dry form in road container it is transferred into the storage silo by a fully closed pneumatic conveyor. Big bag is put on the funnel and all of its content flows into the daily hopper. Smaller bags are opened and poured manually into the hopper. Possible exposure times in bags operation are estimated to be a few minutes. Dry starch is slurried to water. Both slurry and dry form starch are cooked in the temperature of 120-135°C before putting into the process as a dilute solution (e.g. 3 to 8 %).

Worker might be exposed to dust or splashes of cationised starch during unloading the starch (systems without the filter), in sampling from suspender and cooker, and in maintenance work of dust filters, suspenders and storage silos. PPE is usually worn in these situations.

It is estimated by the industry that 45% of the residual EPTAC is degraded during cooking. However, in the process residual CHPTAC converts to EPTAC, so for the calculations in the exposure assessment the value 15 mg/kg as a residual EPTAC is still used. The industry estimates that 37% of CHPTAC is degraded during cooking, so for the calculations in the exposure assessment the value of 300 mg/kg as a residual concentration is used.

A few measurements of starch dust in the production of coated, laminated or impregnated papers or paperboards in the Exposure Measurement Database of FIOH were found. The results were 2 to 8.8 mg/m3 in glue kitchen. Supposing cationised starch was used an estimated exposure to EPTAC would be 0.00003 to 0.0001 mg/m3. For CHPTAC the exposure would be 0.001 to 0.003 mg/m3.

There was not enough information for EASE estimations.

As a conclusion some exposure to residual levels of this chemical may occur in the paper factory e.g. in glue kitchen or as an aerosol beside the paper machine. However reliable measurements could not be found. The probable exposure is considered to be lower than in cationisation.

Copy paper and newspaper

This scenario is described in the consumer exposure part. The possible exposure was found negligible.

4.1.1.2.5 Summary of occupational exposure

According to the information received recently from the industry, many companies have detailed guidelines for handling and management of these two cationising chemicals. In these cases if instructions are strictly followed, the exposure may be significantly lower than estimated here as a reasonable worst case.

Inhalation exposure

The inhalation exposure data used in this risk assessment is summarised in table 4.1 A.

As EPTAC is a non-volatile organic salt handled in water solutions, inhalation exposure to this chemical does not occur. In loading operations where 75% water solution of this chemical is handled, EASE estimation for exposure is 0-0.05 mg/m3 (0-0.08 ppm). Measurements have confirmed that the concentration was below the detection limit of the method of 0.08 mg/m^3.

During the use in dry cationisation workers may be exposed to the dust containing residual amounts of cationising chemicals. In maintenance and clean-up work EASE calculations gave results of 0.0008 mg/m3 for EPTAC and 0.02 mg/m3 for CHPTAC with the estimated residual amounts of 15 mg/kg and 450 mg/kg, respectively. In bagging the estimated exposure concentrations were 0.00002 mg/m3 and 0.0005 mg/m3, respectively. Based on the total dust measurements in bagging, the reasonable worst case exposure concentrations would be 0.00008 mg/m^3 for EPTAC and 0.002 mg/m^3 for CHPTAC.

The particle size of dry cationised starch is not known. Native potato starch has the particle size between 10 to 100 μm.

Dermal exposure

The dermal exposure data used in this risk assessment is summarised in table 4.1 B.

The EPTAC manufacturing process is an enclosed system with breaches for product sampling, tanker or silo filling and some maintenance activities.

Using the EASE model, dermal exposure during sampling was estimated to be in the range of 15 to 150 mg/person/day. Typical exposure level is likely to be in the lower end of the range as the activity takes about five minutes to complete making the exposure time to about 30 minutes per shift.

Analysing samples may expose workers in the laboratory to this chemical in the range of 30 to 300 mg/person/day according to the EASE modelling. This activity lasts about four hours daily.

In maintenance and cleanup work EASE estimation for dermal exposure is 0 to 63 mg/person/day. In loading and sampling after loading the range was 0 to 30 mg/person/day.

In wet cationisation process workers may expose to liquids containing EPTAC about 3%. EASE estimation gave the range of 0.5 to 5 mg/person/day in sampling 1-10 mg/person/day in laboratory work.

In dry cationisation exposure may happen to solid or dust of cationised starch containing residual amounts of cationising chemicals. EASE gave highest estimations in bagging operations where the range was 0.001 to 0.01 mg/person/day for EPTAC and 0.04 to 0.4 mg/person/day for CHPTAC.

If personal protection is properly worn exposure to EPTAC can be assumed low. Main risks of exposure are in sampling of process materials, analysing and performing maintenance tasks. Contamination of work sites and careless use and handling of gloves may expose worker to this chemical. Bagging operations of dry cationised starch expose workers to dust containing residual amounts of this chemical.

Since EPTAC is a genotoxic carcinogen, more analytical data is not considered essential at this stage, but the estimated occupational exposure are sufficient for the purpose of the risk assessment

Table 4.1A: Summary of inhalation exposure data of 2,3-epoxypropyltrimethylammonium chloride (EPTAC) and (3-chloro-2-hydroxypropyl) trimethylammonium chloride (CHPTAC).

Scenario	Frequency Days/year	Duration Hours/day	EPTAC				CHPTAC			
			Reasonable worst case		Typical concentration		Reasonable worst case		Typical concentration	
			Unit mg/m³	Method[2]	Unit mg/m³	Method [2]	Unit mg/m³	Method [2]	Unit mg/m³	Method [2]
Production (EPTAC conc. 75%)										
Loading/Unloading	Daily	2	0.04[3]	Measured	-	-	-	-	-	-
			0.05	EASE	-	-	-	-	-	-
Use in dry cationisation or wet cationisation with drying (EPTAC conc. 15 mg/kg, CHPTAC conc. 450 mg/kg for RWC; EPTAC 3 mg/kg, CHPTAC 12 mg/kg for typical)										
Bagging	Daily	Shift length	0.00008	Measured	0.00006	Measured-	0.002	Measured	0.00003	Measured
			0.00002	EASE	0.000002[4]	EASE	0.0005	EASE	0.000006[4]	EASE
Maintenance and clean-up work	Weekly		0.0008	EASE	0.00002[4]	EASE	0.02	EASE	0.00006[4]	EASE

1: Full shift, short term, etc.
2: Measured, EASE, Expert judgment, Calculated, etc.

3: half of the detection limit

4: using the 50th percentile of the residual level in starch and the middle of the EASE estimate in bagging and the lower estimate of EASE in maintenance and clean-up

Note: The exposure scenario "Use of products with residual EPTAC" was left out from the table as it is considered negligible.

Table 4.1 B: Summary of dermal exposure data of 2,3-epoxypropyltrimethylammonium chloride (EPTAC) and (3-chloro-2-hydroxypropyl)trimethylammonium chloride (CHPTAC).

Scenario	Frequency Days/year	Duration Hours/ day	Contact level (EASE)	Level of exposure (mg/cm²/day)	Exposed area (cm²)	EPTAC		CHPTAC		Method [2]
						RWC mg/p/day	Typical conc. mg/p/day	RWC mg/p/day	Typical conc. mg/p/day	
Production (EPTAC conc. 75%)										
Sampling	Daily	0.5	Intermittent	0.075-0.75	210	150	15[b]	-	-	EASE
Laboratory work	Daily	4	Intermittent	0.075-0.75	420	300	30[b]	-	-	EASE
Maintenance and clean-up	Weekly	4	Incidental	0-0.075	840	63	6[b]	-	-	EASE
Loading/Unloading	Daily	2	Incidental	0-0.075	420	30	3[b]	-	-	EASE
Use in wet cationisation (EPTAC conc. 3% in starch slurry)										
Sampling	Daily	0.5	Intermittent	0.003-0.03	210	5	0.6[b]	-	-	EASE
Laboratory work	Daily	4	Intermittent	0.003-0.03	420	10	1.3[b]	-	-	EASE
Maintenance work	Weekly	4	Incidental	0-0.003	840	3	0.3[b]	-	-	EASE
Filling (end-product EPTAC 15 mg/kg, CHPTAC 450 mg/kg, RWC, EPTAC 3 mg/kg, CHPTAC 12 mg/kg, typ	Daily	8	Incidental	0-0.1 cat. starch	420	0.0006	0.00006[a]	0.02	0.00025[a]	EASE
Use in dry cationisation or wet cationisation with drying (EPTAC conc. 15 mg/kg, CHPTAC 450 mg/kg for RWC; EPTAC 3 mg/kg, CHPTAC 12 mg/kg for typical) There was not enough information for EASE estimations for wet cationising with drying. The scenarios were assessed by applying the dry cationisation scenario.										
Sampling	Daily	0.5	Intermittent	0.1-1 cat.starch	210	0.003	0.00006[b]	0.1	0.00025[b]	EASE
Laboratory work	Daily	6	Intermittent	0.1-1 cat. starch	420	0.006	0.0001[b]	0.2	0.0005[b]	EASE
Maintenance work	Weekly	4	Incidental	0-0.1 cat. starch	840	0.001	0.000025[b]	0.04	0.0001[b]	EASE
Clean-up work	Daily	2	Intermittent	0.1-1 cat. starch	840	0.01	0.00025[b]	0.4	0.001[b]	EASE
Bagging	Daily	8	Intermittent	0.1-1 cat.starch	840	0.01	0.00025[b]	0.4	0.005	EASE

1: Full shift, short term, etc., 2: Measured, EASE, Expert judgment, Calculated, etc; a: middle of the EASE estimate used; b: lower estimate or one tenth of the upper estimate of EASE used. Note: The exposure scenario ”Use of products with residual EPTAC” was left out from the table as it is considered negligible.

4.1.1.3 Consumer exposure

4.1.1.3.1 Products and scenarios

2,3-epoxypropyltrimethylammonium chloride (EPTAC) is not intentionally used for products, which are directly marketed as consumer products. Possible exposure to the substance may occur due to the residues of the substance in products prepared with cationic starches. Cationic starches are mainly used in paper and board industry (around 98 %). In paper industry, cationic starches are used to produce e.g. copy paper, newsprint and food packaging materials.

Also applications of cationised compounds in cosmetic and textile industry have been reported. It seems that there are patented applications in the textile industry, which have not reached the production scale. Some ingredients of cosmetic products (e.g. guar gum and starch) may contain EPTAC as a residue. In Finland, uses in cosmetic or textile industry were not identified. There is information on other minor uses or sources of residues (e.g. isotonic drinks).

For the risk assessment, one of the relevant exposure scenarios concerns the books of small children as they could be exposed to the substance via the skin and when mouthing the books. Another scenario taken into account is a food grade board (triple layer board), which is used in the packaging of dry food like corn flakes, pasta etc. If the paper or board becomes in direct contact with aqueous and fatty foods the surface is coated with barrier materials (e.g. polyethylene). Therefore the relevant scenario concerns dry foods. Third, because the substance is reported to be a skin sensitiser, the scenario where skin contact is possible while reading the newspapers, has been assessed. Fourth, exposure caused by cosmetic products has been assessed.

Residues

In a recent compilation of studies sponsored by industry (Quaternisation of Starch Producers Association 10 June 2003), 58 analyses of EPTAC in cationised starch were reported. The 95 percentile was 24 mg/kg. This percentile could be used for estimation of reasonable worst case exposures according to the draft TGD (21.2.2002). Samples were provided by cationised starch producers (AAC, 2003) from different batches of the grades marketed in the largest volumes, representing about 75 to 80% of the cationic starches market share in the EU. All samples were analysed with the same analytical mehtod by the same external laboratory. These analyses replaced the data provided earlier by the industry. Process optimisation and improved analytical methods have reduced the concentrations measured (Oral communication from the representatives of the industry, 29 August 2003).

In the end-products, i.e. papers and boards concentration of EPTAC is obviously lower than in the cationised starch. Some estimates are presented below. The concentrations of the substances decrease during the storage of the starch and the product. The following parameters were used for calculation of residue level in the end-products:

- Residual levels of 2,3-epoxypropyltrimethylammonium chloride in cationised starches, average (7 mg/kg) and reasonable worst case (24 mg/kg) concentrations, or

- Dosage of the cationised starch into furnish,

- Adsorption of the substance to paper fibres (and board?), and

- Degradation of the substance in the cooking and in the drying section of the paper and board machines

Differences in manufacturing conditions like dosages, consistencies, pH, machine types, machine speeds affect the amount of residues in paper. These factors are recognised but can not be taken into consideration due to complexity of data. Analytical data on residue levels in the end-products are not available, so far, due to analytical difficulties, i.e. lack of repeatability of the extraction results.

In the exposure scenarios presented below, a reasonable worst case has been assessed, and therefore 95 percentile of the measured levels, i.e. 24 ppm of EPTAC in the cationised starch, has been used in calculations.

Migration

Migration may take place when skin, saliva of children or food items are in contact with paper or board. In migration studies, the conditions and duration of the contact should be simulated. Migration modelling for plastic items has been developed but it is not directly applicable for the paper and board materials. So far, no specific data on migration rate are available. Performing such a study is challenging, partly due to difficulties with the extraction process and the very low levels of residual reagents expected in extracts. A sufficiently sensitive method does not exist at the moment.

Dose

Transfer rate and duration of the skin contact and on the other hand, ingested amount will be used to calculate the dose. Since the endpoints of relevance (carcinogenicity and sensitivity) may be regarded as non-threshold effects, the calculation of safe levels will be complicated.

4.1.1.3.2 Exposure from uses

Food packaging material

There are several national approval procedures concerning cationic starch to be used in food contact paper and board (BfR 2001, FDA 21 CFR 2003, Code of Federal Regulations, 21, revised as of April 1, 2003, KTMp 143/ 1993). These approvals do not give any limitations to the residual amounts of EPTAC or CHPTAC in food packaging materials, but there are general limitations, which are relevant. Anyway the approval procedure covers the safety evaluation of the end product (cationic starch) including its impurities when used in food contact application.

Table 4. 2. Food contact approvals of cationic starches in some countries.

Country and agency	Limitation	Reference
Germany, BgfR	Maximum nitrogen content in starch ethers: 4 %, epichlorohydrin max. 1 mg/kg	BgfR, December 2001, 51. Lfg , Recommendation XXXVI
USA, FDA	Maximum EPTAC usage 5 % Food Contact Notification by Lyckeby stärkelse: EPTAC max. 21 %	Code of Federal Regulations, 21, , revised as of April 1, 2001, § 178.3520 http://www.cfsan.fda.gov/~dms/opa-fcn.html
Netherlands	Maximum EPTAC dosage 7 %	Verpakkingen- en Gebruiksartikelenbeslut, Warenwet 2001

Also cationising of grain flower with EPTAC is approved by the German BgVV (epichlorohydrin max. 1 mg/kg) and cationising of guar gum with EPTAC max. 25 % is approved the U.S. FDA under § 176.170 limiting the finished product to have maximum chlorine content of 4,5 %, the maximum nitrogen content of 3,0 % and the viscosity of the aqueous solution of the finished product.

Barrier materials are used (e.g. polyethylene) in food packages when the package material is in contact with fatty or aqueous food, and therefore, migration of EPTAC from the paper/board is unlikely. Migration, however, could take place in case food packages without barrier materials (used for dry foods) are moistened.

Reasonable worst case

The food grade paper board, in this exposure scenario, is a triple layer board, which is used in the packaging of dry food like corn flakes, pasta etc. The weight of the package is 5-20 g, the respective weight of starch is 0.05-0.2 g (assuming that the weight of the starch is 1 % of the paper board), and the (worst case i.e. 95 percentile) concentration of EPTAC in starch is 24 mg/kg. In this scenario it is assumed that 10 % of the food and the package is non-intentionally moistened during the storage, handling or preparation of food. Thus, the amount of EPTAC, which could migrate, is 0.12-0.48 µg. Since EPTAC is highly water soluble it is assessed that all that amount will migrate to the moistened food in the package.

It is unlikely that all the moistened and therefore spoiled food would be ingested; in the worst case, a small amount of the spoiled food (10 %) is consumed (e.g. by children). Therefore it is estimated that 0.012-0.048 µg of EPTAC could actually be ingested. This exposure obviously doesn't take place daily but occasionally. Average long-term exposure is therefore 2 or 3 orders of magnitude lower that that presented above, and even lower as calculated per kilogram of body weight, i.e., about 0.0000012 µg/kg bw.

Skin absorption rate of EPTAC has not been studied. However, the skin absorption of CHPTAC has been studied recently in mouse and human skin *in vitro*. The results of this study are used as the worst case estimate for EPTAC as well. (See chapter 4.1.2.1). In most cases, hands are washed after the moist food package has been handled, which minimises the skin absorption

Normal scenario

Since it is assessed that in the normal scenario, food in the spoiled package is not consumed, exposure via the intestinal and dermal routes would not occur.

Books of small children

This scenario concerns the small children, who have the mouthing habit. According to EPA

Child-Specific Exposure Factors Handbook (2000) the daily mouthing time is highest (44 min) among the children, who are 6-12 month old. It is estimated that in the worst case, during one day, about 5-10% of the EPTAC residues in the surface of the book could either be ingested by the child or becomes into contact with the skin. This would represent the worst case scenario. It is unlikely that a child could destroy (by chewing and biting) the booklet completely and be exposed to all of the substance it contains. On the other hand, since some of the children of this age have got teeth, they could in the worst case moisten and ingest some of the book.

The association of the major European cationic starch producers (Association des Amidonneries de Céréales de l'Union Européenne) informed the rapporteur that to the best of its members' knowledge, cationic starch is not used in board. Its main application is paper, to improve its printing quality. Cationic starch may be used in thin laminated paper outer layer of children cover book (60-100g/m2, typically 80 g/m2) to enhance their printing properties (retention of fibre and mineral charges). Quantity is typically 0.3 g cationic starch/m2 laminated paper (ranging from 0.1 g/m2 to 0.5 g/m2). In the downstream process, the surface is treated with other starches.

Assuming that cationic starch can be found only in the book cover i.e. two pages, 22*15 cm i.e. 0.033 m^2, total 0.066 m^2 each, the amount of cationic starch in such a book is 0.02 g (0.3 g/m^2 * 0.066 m^2). Using the 95 percentile of the measured residues levels in the starch (i.e. 24 ppm), is calculated that a booklet may contain up to 0.5 µg of EPTAC. If 5-10 % of this amount would be ingested or would expose the skin, the maximum daily exposure via these routes is 0.025-0.05 ug. The weight of a child at the age of 6-12 months is 7.5-9.9 kg and thus the daily dose 0.0025-0.006 µg/kg of b.w.

Measurement of how EPTAC migrates from a booklet, when exposed to child's saliva and mouthing activity, have not been made and therefore, this estimate is based on worst case assumptions.

Copy paper and newspapers

One of the QUAS members has estimated that the concentration of EPTAC in the copy paper is 1200 µg/kg (Raisio Chemicals, 2001). It is assumed that an office worker deals daily with 100 pages, which have a total weight of 0.5 kg; thus containing 600 µg of EPTAC. Assuming that 1 % of the surface of copy papers is touched and that 10% of the EPTAC on that surface will migrate due to small amount of acidic sweat on the fingertips, the daily exposure on the skin is 0.6 µg. This calculation is theoretical and cannot be substantiated, since no migration studies on this scenario are available. Because the absorption rate of EPTAC for the human skin is low (~6 %), the exposure in this scenario appears negligible.

In a newsprint, the residue of EPTAC was estimated to be much lower (i.e. 14 µg/kg), than in copy paper (Raisio 2001b). Also the daily dermal exposure to EPTAC in this scenario is considerably lower than that given above for copy paper.

Cosmetic products

Colipa has collected data on the use of relevant raw materials, i.e. cationised proteins, which contain EPTAC (Quaternisation of Starch Producers Association 10 June 2003). A great variety of cationised casein, collagen and wheat proteins as well as cationised guar, ginseng and dextran are ingredients of cosmetic products, such as shampoos, body wash, shower gel, hair care and skin care products. In all the raw materials, the reported concentrations of EPTAC are below 200 ppm. The average concentration of these raw materials in 24 cosmetic products listed by the Colipa is 0.37%. Thus, the concentration of EPTAC is below 0.74 ppm.

According the revised TGD (2003), the typical amount of these (hair care/conditioner, skin care/body lotion, shampoo, shower gel) cosmetic products used per application is 5-14 grams. These cosmetics are used 1-2/week or 1-2/day, i.e. 0.7-28 gram per day. Using the maximum concentration given above (0.74 ppm) the daily dose of EPTAC on the skin is 0.5-20.7 µg, i.e., 0.007-0.29 µg/kg of b.w. This applies to stay on products e.g. skin care/body lotion. However, for rinse off products such as shampoos and shower gels, it can be roughly estimated that the dose is 100 times less, 0.07-2.9 ng/kg of b.w.

4.1.1.3.3 Summary of consumer exposure

Consumer exposure to EPTAC is negligible. Residues in cosmetics, such as shampoos and shower gels, which expose skin or scalp cause the greatest consumer exposure. Lesser sources of exposure are skin exposure from paper, books or oral exposure from food packaging residues. The following table summarises the exposure ranges from different sources.

Table 4.3. Consumer exposure to EPTAC

Product	Scenario	Total exposure
Food packaging	Transfer to product from wet packaging	0.0000012 µg/kg bw
Children's books	Small children chewing a book, which can lead to ingestion or skin exposure.	0.006 µg/kg bw
Copy paper and news papers	Skin exposure from paper surface.	0.009 µg/ kg bw
Cosmetics	EPTAC residues in cosmetic products expose skin and scalp. Rinse-off products	0.007-0.29 µg/kg bw 0.07-2.9 ng/kg bw.

The reasonable worst case exposure to be taken to the risk characterisation is a daily dermal dose of 0.29 µg/kg of b.w.

4.1.1.4 Humans exposed via the environment

Concentrations of EPTAC in the surface water (PEClocal) near to starch cationisation plants are given in table 3.15. These concentrations were calculated from the measured WWTP concentrations which were available for nine sites. EPTAC concentrations in the environment ranged between 1.82-65.4 µg/l (15.12 µg/l avg.) but based on the rather high detection limits at WWTP measurement the actual concentrations in the environment might be lower. The dilution factors applied in the calculations varied between 3.22 and 1000.

On the other hand, when the monitoring data was not available the concentration of EPTAC was estimated using EUSES based on the release factor 1.32 % and assumed biodegradation and adsorption figures. The range of calculated PEClocal was 143 - 4291 µg/l (table 3.16).

Since the actual biodegradation in all wastewater treatment plants is not known and the EUSES estimates are based on assumptions, the average of the calculated concentrations (nine sites) in the surface water is considered more realistic and therefore 15.12 µg/l is used as a reasonable worst case concentration in the drinking water. This average value comes from the first paragraph of this chapter. This figure would only apply to a small population which would live near one of the nine starch cationisation plants and actually use the surface water (1000 m downstream from the release) as a source of drinking water. Starch cationisation plants are located in industrial regions and it is unlikely that drinking water abstraction would take place so close to such a site. However, that scenario cannot be excluded and it is taken here as a reasonable worst case assumption. Moreover, the detection limits reported in the monitoring data were high and in many cases the actual concentration could not be determined. In these cases the detection limit was used. Some degradation of EPTAC may take place in the drinking water processing, but no data is available on the possible removal efficiency of EPTAC during drinking water process. It is probable that there would be some removal by filtration and purification processes. Using a high figure of 2 l/day as a maximum

consumption of drinking water and 60 kg as the weight of an adult person, an estimate of 0.0005 mg/kg of b.w. is derived (table 4.1).

Using EUSES, the average (local) concentration of EPTAC in fish is estimated to be 0.0206 mg/kg in wet weight. The average (RWC) human daily intake via fish is 0.000034 mg/kg of b.w. These averages have been calculated using EUSES estimates from nine monitored sites (table 4.1).

Regional and average local daily doses, expressed as mg/kg of b.w, due to drinking water, air and certain food items are presented in table 4.1. Estimates are added up, although, for total exposure it is unlikely that all food that a particular consumer group is exposed to, is grown in a region where sewage sludge is spread from a plant where EPTAC is used. In addition, estimate of intake from leaf crops might represent quite unlikely exposure.

The estimated concentration of EPTAC in drinking water is relatively high. The respective daily dose is higher than from consumer product.

Table 4.1 Indirect human exposure to EPTAC, averages based on the EUSES estimations (local scenario) for nine monitored sites.

Source of exposure and concentration	**Local daily dose (mg/kg of b.w)**	**Regional daily dose (mg/kg of b.w)**
Drinking water, 15.12 µg/l (average of nine sites)	0.0005 (nine sites)	5.12E-05
Fish, 0.0206 mg/kg in wet weight	0.000034	4.16E-06
Leaf crops	0.0013	1.74E-07
Root crops	1.11E-05	1.58E-07
Meat	2.04E-08	3.39E-10
Milk	3.81E-07	6.32E-09
Air	2.48E-06	2.7E-14
Total	**0.0019**	**5.57E-05**

4.1.1.5 Combined exposure

No assessment of combined exposure will be conducted due to negligible impact on total exposure situation.

4.1.2 Effects assessment: Hazard identification and dose (concentration)-response (effect) assessment

4.1.2.1 Toxicokinetics, metabolism and distribution

4.1.2.1.1 Studies in animals

In vitro studies

Percutaneous absorption

CHPTAC's percutaneous absorption was examined in a study, which used a 2-14C-radiolabelled CHPTAC and viable human and mouse skin membranes (TNO, 2003). The results of this study can serve as a worst case estimate for EPTAC as well. Because EPTAC is slightly more polar and is likely to bind to a higher extend to the stratum corneum due to its reactive epoxide function than CHPTAC, it is therefore likely that in human skin a lower amount is dermally absorbed to lower layers of the skin and systemically available. For mouse skin the results are likely to be comparable as the stratum corneum is thin and a very low amount of the substance is retained in the skin. The tests were conducted using four concentrations: 0.1, 1, 20 and 65% CHPTAC in water. 14C-testosterone was used as the reference compound. The amount of radioactivity in the receptor fluid and the residual radioactivity remaining in the skin and the stratum corneum 48-h post exposure were determined. Samples were prepared so that the labelled and non-labelled test substances were mixed to give a concentration of 2.46 MBq of the radiolabel and the above mentioned CHPTAC percentages. The human skin sample was obtained from a 51-year female after abdominal surgery. The sample was taken to the laboratory within one hour of dissection and directly after that the skin placed in culture. Mouse skin was taken from a 10-week-old male NMRI mouse. Subcutaneous fat was removed and part of the human skin was removed until the thickness was about 0.5 mm. The measured thicknesses were: mouse skin 0.437±0.08 mm, human skin 0.531±0.043 mm. A two-compartment model was used so that the basal membrane was in contact with the receptor fluid and the stratum corneum was exposed to the air. A glass ring was glued to the skin membranes, which left an internal area of 0.64 cm2 for the test substance, which was applied 10 ul/cm2. The absorption was measured for 48 hours, during which the viability was monitored by the presence of lactate in the receptor fluid. Receptor fluid samples (500 ul of total 1200 ul) were collected at 1, 2, 4, 6, 8, 20, 24, 28, 44 and 48 hours, except for the 20 % dose. The controls were sampled for lactate at 4, 8, 20, 28 and 48 hours. After the sampling of receptor fluid, fresh fluid was added to restore the original volume. The cumulative absorption was determined by calculating the sum of sampled radioactivity. Flux constant is defined as DCTx-Ty/(x-y), where the numerator is the increase in penetrant concentration during the linear portion of the curve and where x refers to the beginning and y to the end of linear portion of the curve. The permeability coefficient (Kp = flux constant [ug x cm-2x h-1]/applied concentration [ug/cm-3]) was determined using tritiated water. To determine mass balance, the remaining test substance was removed with cotton swabs and the stratum corneum was isolated by tape stripping at the end of the study. The remaining skin membrane was digested with KOH and the receptor fluid was collected. Using scintillation counting the total radioactivity was measured in each compartment separately.

Results

The results are summarised in table 4.1.2.1.1 for mouse skin and in table 4.1.2.1.2 for human skin.

Table 4.4 Results of the skin permeation study in mouse skin

Concentration of CHPTAC	65%	20%	1%	0.1 %
Kp-values [cm h^{-1}]	0.026	0.107	0.065	0.151
Flux constants µg cm^{-2} h^{-1}	18.5	21	0.61	0.15
Relative absorption (% in receptor fluid)	13.9	40.9	22.6	43.6
Mean total abosrption (% of the radioactivity present in the receptor fluid, the receptor compartment wash and the skin (excluding tape strips)	13.0	44.9	29.2	45.0
Mean total abosrption (% of the radioactivity present in the receptor fluid, the receptor compartment wash and the skin (including tape strips)	13.1	45.2	30.8	50.3

Table 4.5 Results of the skin permeation study in human skin

Concentration of CHPTAC	65%	20%	1%	0.1 %
Kp-values [cm h^{-1}]	0.0005 x 10-3	0.0009 x 10-3	0.0015 x 10-3	0.0022 x 10-3
Flux constants µg cm^{-2} h^{-1}	0.36	0.18	0.014	0.002
Relative absorption (% in receptor fluid)	0.053	0.148	0.534	0.685
Mean total abosrption (% of the radioactivity present in the receptor fluid, the receptor compartment wash and the skin (excluding tape strips)	0.46	0.46	3.74	5.79
Mean total abosrption (% of the radioactivity present in the receptor fluid, the receptor compartment wash and the skin (including tape strips)	0.8	1.8	15,2	14.2

In the viable human skin membranes, the amount of radioactivity in the skin after tape stripping was between 0.5 and 6.8 fold higher than the amount in the receptor fluid. In mouse skin, the amount of radioactivity was 5.3 to 17.6 times lower than the amount of radioactivity in the receptor fluid. The mean recovery of radioactivity was between 91.2 and 102.2 % in mouse and human skin membranes.

4.1.2.1.2 Other information

Basic physico-chemical characteristics are available, which can be used to estimate toxicokinetic behaviour. The molecular size of EPTAC is relatively small (MW 151.5 g/mol), which can be a facilitating factor in absorption through membranes. Dermal absorption through passive diffusion could be expected to be low because the molecule is charged. Data from toxicological tests show that at least some absorption occurs via the gastro-intestinal (G-I) tract and skin. Being a small molecule, it is possible that EPTAC pass through G-I tract membranes by passive penetration through aqueous pores at the tight junction. Findings from acute dermal toxicity data indicate that absorption occurs via the dermal route. More importantly, an *in vitro* skin penetration study is available for CHPTAC, a substance which has a closely related molecular structure. This allows also the assessment of the skin penetration properties of EPTAC. EPTAC can enter lungs as a residue in cationised starch dust. Theoretically, EPTAC could enter lungs also in water solution as aerosol particles. Depending on the particle size various parts of the respiratory system could be affected. The majority of big (> 10 µm) dust particles would probably stay in the nasopharyngeal mucous membranes. There, the residual EPTAC could dissolve in the mucus and be directly absorbed to blood circulation or it could be carried to the pharynx where it might enter the gastro-intestinal tract. Smaller (<1 µm) particles could enter the tracheobronchial or alveolar space of the lungs where the substance could be released and enter the blood or be removed by the lymph circulation.

Distribution of EPTAC from vascular space to extracellular or intracellular compartment is probably slow due to the poor membrane passing quality. It may be possible for EPTAC to pass from the vascular space to the extracellular or intracellular compartment via aqueous pores. Entrance into fat is expected to be slow because of the low lipid/water partition coefficient [log P_{ow} = -1.23].

Because EPTAC has a highly electrophilic epoxy group the metabolism is likely to occur mainly in the liver either via hydrolysis by an epoxide hydrolase or phase 2 enzymes, viz. different conjugation reactions such as glutathione S-transferases. These hydrophilic products are normally excreted effectively into urine.

4.1.2.1.3 Summary of toxicokinetics, metabolism and distribution

In the absence of data for inhalation, 75% absorption is assumed. For oral route, an assumption of 50 % is used. Based on the findings in the *in vitro* skin penetration assay, a maximum penetration rate of 0.685 % was reached in the human skin. Since it is recommended by the TGD that the dose retained is the skin should also be taken in consideration 5 % would then be more appropriate (0.685+ (0.685 x 6.8)). However, this factor does not take into account the amount retained in the stratum corneum. Accounting for the amount retained in the stratum corneum the average absorbed ranged between 0.1-15 %. Taking the highest percentage retained in the stratum corneum would probably be too conservative, due to factors like exfoliation, washing and other processes in which the substance is lost to outside. Moreover, the epidermal uptake is likely to occur slowly because of high water solubility (>800 g/l) and a log P of less than zero. Therefore, an absorption percentage of 6 % will be taken for the risk characterisation.

4.1.2.2 Acute toxicity

4.1.2.2.1 Studies in animals

In vivo studies

Inhalation

According to test performed by (Dow, 1984) a 7-hour inhalation exposure at a nominal concentration of 8.17 mg/l EPTAC caused no lethality or systemic effects in 4 female rats. The only observed effect was irritation to the eyes. No properly conducted test to obtain a 4-hr LC50 value is available.

Dermal

Only limited information is available on dermal toxicity. There is no information about methodology. Two groups of three rabbits each were administered dermally either 1500 or 3000 mg/kg EPTAC in an aqueous solution (Shellengberger, 1962). In the lower dose group one rabbit died after 7 days of administration. In the higher dose group, two rabbits died in 5 h - 2 days. LD50 was estimated to be between 1500 – 3000 mg/kg. The validity of this study is limited. The reporting is scarce.

Oral

Five male and five female young adult, SPF-albino rats per dose and per sex were administered a single oral dose of EPTAC at volumes ranging from 4.0, 4.8, 5.8, 6.9 and 8.5 ml/kg in aqueous solution (Degussa, 1981a). The 71.9% test substance in aqueous solution was diluted with water to 20% EPTAC (v/v). The original solution had about 10% impurities, apparently resulting from the synthesis. The rats were observed for signs of toxicity for 14 days after which an autopsy was conducted on the survived animals. LD50-value was calculated. Although the test did not follow a known guideline, it was considered to be valid for risk assessment purposes.
Within few hours of dosing, the rats showed sedation, dark-coloured eyes, tremors and convulsions. No details were given about the doses at which the non-lethal effects occurred. Later, diarrhoea and loss of consciousness was observed. The animals died between 1 and 48 hours.

Table 4.6 Animal mortality vs. actual dose of EPTAC

Dose (ml 20% EPTAC/kg)	Males	Females
4.0	0/5	1/5
4.8	1/5	1/5
5.8	1/5	2/5
6.9	0/5	4/5
8.5	4/5	4/5

The surviving animals appeared to have recovered at the end of the observation period. When observed macroscopically, animals had no treatment-related alterations. An LD_{50} value of 1.34 ml/kg (CI_{95} 1.18 and 1.52) for the 71.9% test substance was calculated according to the method of Weil. This can be converted to approximate milligrams using the density value of 1129 mg/cm^3 available for 70% EPTAC. The resulting LD_{50} is 1513 mg/kg of the 71.9% test substance or 1088 mg/kg pure EPTAC.

Another acute toxicity test reports an LD50 value of 1720 mg/kg obtained from an experiment where ten rats per dose group were administered orally 1250, 1575, 1988, 2500 mg/kg (Shellengberger, 1962). In the highest dose, group all animals died within 15 hours, in the 1988 dose group, 7/10 animals died, all within 1 day, at 1575 mg/kg dose 3/10 rats died within 2 days and in the lowest dose group 2/10 died within 3 days. Transient depression at lower doses, dyspnea, salivation sanguineous ocular discharge and clonic convulsions at higher doses were recorded as clinical signs. The reporting of study details was limited.

4.1.2.2.2 Summary of acute toxicity

The LD50 value for acute oral toxicity is 1080 mg/kg when expressed as pure substance. Dermal toxicity test is available only in rabbit. The study results indicated that dermal acute toxicity LD50-value is probably 1500-3000 mg/kg. Based on a study in which rats were exposed to an EPTAC concentration of 8.17 mg/l for 7-hour the 4-hr-LC50 value is above 5 mg/l, which is the limit for classification. However, due to the study quality no definite conclusion can be drawn on the acute for the acute toxicity via inhalation route.The classification and labelling working group has agreed to classify EPTAC Xn;R22/21.

4.1.2.3 Irritation

4.1.2.3.1 Skin

Studies in animals

Three albino rabbits were exposed to 0.5 ml of the commercial preparation of EPTAC (QUAB 151) for 4h under occlusive patch (Degussa, 1985). The concentration was not given but according to IUCLID it varies between 70-75%. The sample was instilled on four separate shaved locations. One side of the back the skin was abraded while the other remained intact. For the calculation of irritation index, the scores from the intact areas were included only. The scoring was done after 1, 24, 48 and 72 hours. The study was in conformity with the OECD 404 and EU-guideline 84/449/EEC B.4.

All the individual scores were zero at all time points.

In a non-guideline patch test, the irritating properties were investigated on 12 albino rabbits (Degussa, 1981c). On six rabbits, 0.5 ml of the test substance was instilled on an intact clipped area which was covered with a 1 sq. inch patch. Another group of six rabbits received the 0.5 ml of the substance on a skin area with slight abrasions to the stratum cornea, again covered with a patch wrapped with adhesive tape. The 2,3-epoxypropyltrimethyl ammonium chloride content of the test substance was 72%. Exposure time was 24 hours. Draize-scoring was used to calculate the irritation index at 24 and 72 hours after application on intact and abraded skin.

The skin irritation effects were described as severe. They included well-defined erythema, slight ischemia, haemorrhages and slight to distinct incrustation and slight to moderate oedema. The average 24-h score on intact skin was 4.3 and 3.8 after 72 h and for abraded skin 6.3 both at 48 and at 72 hours. However, current guideline recommends only a 4 h exposure period.

Other information

In the sensitisation test described below (Degussa, 1981d) guinea pigs were first induced intradermally with 5 % solution of EPTAC in water. A week after the intradermal induction, a second induction followed where 5 % EPTAC was applied topically in vaseline to the same dorsal area. Slight erythema was seen in 7/20 animals.

4.1.2.3.2 Eye

Studies in animals

In a study conducted following the n OECD guideline 405 protocol, three albino rabbits were instilled 0.1 ml of the test substance (QUAB 151, commercial grade, purity assumed 70-75%) into the conjunctival sac of the right eye without rinsing the (Degussa, 1986a). Cornea, iris and conjunctiva was examined and scored qualitatively and quantitatively after 1, 24, 48 and 72 hours. The rabbits were observed for 21 days. In one animal, congestion of the iris persisted after the 21 day observation period.

Table 4.5: The mean 24, 48, 72 h -scores for 70% EPTAC

Observed effect \ Duration from application	Conjunctiva						Damage to Iris			Cornea Clouding		
	Redness			Chemosis								
Animal number	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
24 h	3	3	3	2	1	3	2	2	2	2	1	1
48 h	3	3	3	3	2	3	2	1	2	1	1	1
72 h	3	3	3	3	2	3	2	1	2	2	1	1
Mean	**3.0**	**3.0**	**3.0**	**2.7**	**1.7**	**3.0**	**2.0**	**1.3**	**2.0**	**1.7**	**1.0**	**1.0**

4.1.2.3.3 Summary of irritation

EPTAC is a severe eye irritant when 70 % solution is applied. Classification and labelling working group has agreed to classify EPTAC Xi;R41.

Although severe signs of skin irritation are seen in the Degussa-study (1981), the results of this assay are not considered relevant when drawing a conclusion on skin irritation of EPTAC. The method of the study is non-guideline and the exposure time is six times of the normally used. Based on a study conducted according to OECD guideline, EPTAC is not a skin irritant.

4.1.2.4 Corrosivity

Based on the findings in the skin irritation study EPTAC is not corrosive.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

Skin

In vivo studies

Twenty guinea pigs/group were used each to test the skin sensitising properties in a maximisation test of EPTAC (Degussa, 1981d). The original substance was 72 % EPTAC in water solution. A group of same size was used for control. The dorsal area of the skin was shaved to which a two-stage induction was performed. In the first stage three different preparations were injected intradermally in to three different sites on left and right side of the dorsal area. The three solutions were 5% test substance in water, Freund's Complete Adjuvant (FCA) and test substance diluted with FCA. Control animals were given only FCA, water or FCA and water 1:1. One week after the intradermal induction, test substance was applied topically putting a filter paper with 5% test substance in Vaseline onto the dorsal area which was left under an occlusive dressing for 48 hours. Controls were treated with Vaseline only. The animals were challenged two weeks after the topical induction in using a similar procedure as in the topical induction but only 24 h exposure and 2.5% test substance. The results were read immediately, 24 h and 48 h after challenge.

In the topical induction phase, there was slight erythema noted after 24 hours. The challenge results showed erythema in 11 animals, right after the challenge and in 14 animals after 24 hours. At 48 h, still three animals showed a skin reaction. The control animals had no signs of erythema.

Another test for delayed contact hypersensitivity used a similar approach as previously but now only 0.5% solution was used in the intradermal application on a shaved dorsal area of ten guinea-pigs (Elliott et al., 1979). There were no details about the content of the test substance, other than the trade name OGT AC-85. One week after the first induction a filter paper with 0.4 ml of 90% OGT AC-85 in water was placed under a occlusive dressing which was left in place for 48 h. Evaluations were made after 24, 48 and 72 hours.

All the scores were zero at all time points. However, this study is not considered reliable due to lack of information of the test substance.

4.1.2.5.2 Studies in humans

Skin

In vivo studies

As a part of a doctoral dissertation (Jolanki, 1991), 3713 patients were examined for occupational skin disorders at the Finnish Institute for Occupational Health. Of the examined patients, 130 were diagnosed 1974-1990 as having an occupational skin disease caused by exposure to epoxy compounds. This survey, (Estlander et al., 1986), reports four cases allergic responses in workers at a starch modification plant. The process was automated and

closed but process workers and a laboratory technician took daily samples from the process liquid to control the pH. The purity of the EPTAC used in cationising was 50%. Two of the process workers had used protective rubber gloves almost regularly, one never wore gloves and the laboratory technician used them occasionally. Patch tests were conducted to diagnose type IV allergy. Solid material such as gloves and cationic starch were also tested. In the patch test, the substances were applied on patients' backs and the application time was 24 h, except for the glove material, which was left in place for 48 h. The results were read 24, 48 and 72 h after the removal. Prick tests were made with 24 standard allergens. The patch test results were reported for EPTAC concentrations ranging from 0.05 to 1%. Dermatologists assessed and scored the reactions after at least three readings. Score scale was - = negative, +=erythema, ++=erythema and oedema, +++=erythema and oedema and vesicles, ++++= bullous or ulcerative reaction. The scores ++ to ++++ were considered allergic reactions. The control antigens included those recommended by ICDRG.

Table 4.6 Patch test results of 4 patients allergic to EPTAC

Case	1	2	3	4
EPTAC 1%	++	+++	+++	No tested
EPTAC 0.5%	No tested	No tested	No tested	++
EPTAC 0.2%	++	+++	+++	++
EPTAC 0.1%	No tested	No tested	No tested	++
EPTAC 0.05%	No tested	+	No tested	No tested

Four of eight workers working in manufacture of cationising starch had developed contact dermatitis within three months of the beginning of their work. All cases were diagnosed in years 1982-1983.
The authors also report three other cases from another starch cationising plant. The patients worked in the production phase where the cationised starch (CS) is dried. The work was to follow the automated drying process and take samples. Two patients (1 and 2) had worn gloves daily while one patient (3) only wore them occasionally. All worked with CS in three shifts. The application time in the patch tests was two days. The reading times were as described above. A modified epoxy and gloves and plastics series were used as standards. EPTAC (65-75%) was tested in dilution series, the glove materials were tested in a chamber with a small amount of water/acetone, and the CS was tested as such. Latex materials and common environmental allergens were used in the Prick test. Patient number 3 reacted "++" to 0.2% ECT and + to 0.1%. The other two had weaker "?+" and "+" reactions. Prick tests were negative, except in one case of pollen.
In a report from another plant where three workers where examined for EPTAC contact allergy because of recurring contact dermatitis (Estlander et al., 1997). There were 18 workers working in production and they had access to all sites at the plant. The three process men, whose work involved drying of cationic starch and occasional direct contact with EPTAC. The workers' main task was to follow the automatic drying process, to take samples of the cationic starch and take the samples to the laboratory and also take care of maintenance in other parts of the factory when necessary. Two of the patients (1 and 2) were confirmed allergic to EPTAC and had had variable dermatitis for 8-12 years. Both men had worked for 3 years before dermatitis. One patient (3) had had dermatitis for 1 year after having worked for 7 years before dermatitis. The sites of dermatitis occurrence were in hands, arms, legs, feet and face. The use of PVC or nitrile rubber gloves varied from occasional (patient 3) to 1.5-2 h a day (patients 1 and 2). Patch tests were done on the patients backs with EPTAC dilution series of 0.05 0.1, 0.2, 0.5 and 1.0 %, 4-5 samples of cationic starch, glove material and various chemicals included in a standard European standard patch test diagnostic series. The following table summarises the results seen in the patch tests.

Table 4.7. Patch test results of three process workers in a cationising plant

Test substance	Patient 1	Patient 2	Patient 3
1 % EPTAC in petrolatum	+++	++	++
0.5 % EPTAC in petrolatum	+++	++	++
0.1 % EPTAC in petrolatum	+	?+	
0.05 % EPTAC in petrolatum	-	-	-
11 own materials	-	b	

b = PVC glove in a drop of water or acetone tested ++, second test negative.

The authors concluded that the skin symptoms in the patients developed slowly, after some years rather than months, suggesting that contamination of work sites and gloves was the the main reason of sensitisation and recurrence of symptoms. Contamination was considered probable because all 18 workers had access to all place in the factory and drying site could be accessed only by crossing though the cationisation section. Although protective gloves were used, they were not in personal use but everyone used everyone's gloves, which might have further promoted sensitisation. The results are in line with the previous study (Estlander et al., 1986) and confirm that EPTAC is a strong human sensitiser by skin contact.
All three patients continued working in the plant but they adopted a more careful hand-care system, use of *personal* protective gloves and avoided contact with all process chemicals. The patients were also informed of the sensitisation risks of the process chemicals and their careful handling. When retested 2 months later, patient no: 2 had only mild dermatitis and patients 1 and 3 were symptomless after 6 months.
A female chemists working in a pharmaceutical company was reported to have papular itching dermatitis of the forearms after handling the powder (commercial names: G-MAC or EPTAC) once a week for few months. The patient had worn protective clothing and followed the strictest safety precautions, such as working under evacuation hood, but still had developed dermatitis. Contamination from the glove was suspected because of the sticky and hygroscopic nature of the substance. Another female in the same factory had developed papular itching dermatitis of the dorsum of the right hand. She had handled EPTACin the powder form and a substance named OG-TAC 85 (concentrated aqueous solution of EPTAC) about every other day for two months. Both patients tested positive in the patch test with 1% dilution of the commercial product (G-MAC). One of the patients had a positive, although slight, response already at 0.1% of the test substance (Berqvist-Karlsson, 1995).
In an investigation performed by industry, companies using EPTAC in starch or other cationising use were asked details about their EPTAC use and possible allergy cases. Eleven cases of allergies were reported. Contact occurred during process sampling or laboratory work. According to reports, personal protection measures were improved and most persons are still working in the same workplace without complications. No new cases were observed in the companies concerned as protective measures to avoid skin contact have been efficiently improved in the last 5 years. However, not all companies answered the questionnaire or the answer given was incomplete.

4.1.2.5.3 Summary of sensitisation

Based on the positive test results in guinea-pig maximisation tests and the patch tests in humans it can be concluded that EPTAC is sensitiser by skin contact. Classification and labelling working group has agreed to classify EPTAC Xi; R43.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

In vivo studies

Oral

Wistar rats were administered by oral gavage 0, 3.16, 10.0, 31.6 or 100 mg/kg EPTAC (72.6 %) for 28 days (Degussa, 1990). The control and high dose group had 10 males and 10 female whereas the low- and mid-dose groups had five rats of each sex. Five high and five control group animals also had a 4-week post-exposure observation period. The purity of the administered substance was 72.6 %. The study was conducted under GLP regulations and OECD guideline 407 was followed as the study protocol. Urinalysis was performed in weeks 4 and 8 (recovery groups). Samples for histopathological evaluation were prepared of adrenal glands, bone marrow from sternum, bone marrow smear, brain, various sections of the intestine, heart, kidneys, liver, lungs, ovaries, spleen, stomach, ovaries, testes and thymus. Haematology and clinical chemistry measurements were those recommended in the guideline and they were determined at 4 and 8 weeks.

Most high dose animals exhibited in their clinical picture piloerection and sunken sides. Two females and one male showed disturbed general condition before death or decreased muscle tone. In the high dose group, four females and one male died during the last week of administration. One female was sacrificed moribund at day 16 of treatment. The food consumption decreased in the mid- and high-dose groups. The food consumption dropped to less than 50 % of the controls within two weeks in high dose females and within four weeks in high dose males. Unlike the female rats, who had an almost complete recovery in their food consumption one week after the end of administration, the male recovery returned to normal after seven weeks. In the 31.6 and 100 mg/kg groups, the bodyweight development slowed in parallel with the changes in food consumption. The body weight gain in the 31.6 and 100 mg/kg dose groups was significantly reduced during weeks 2-4 of the treatment period. The body weight in the 100 mg/kg group males at day 28 was about 45% lower than the control group and in the 31.6 mg/kg group at that time the mean weight was about 18% lower and in the 10 mg/kg group a 12 % reduction was noted. The 100 mg/kg dose females had about 38 % lower mean body weight than the control. No significant difference was noted in other groups or in the recovery group. After the recovery period, the male 100 mg/kg recovery group had still about 29% lower mean body weight, when compared to control.

In **haematology**, both sexes of the 100 mg/kg group had statistically significantly increased red blood cell count (RBCM100: 8%; RBCF100: 11%), haemoglobin content (HbM100: 8%; HbF100: 11%) and relative and absolute monocyte count (MonMctrl: 3, MonM%100: 5; MonFctrl: 2, MonF100: 6). In the males of the 100 mg/kg group, white blood cell count (-32%) and relative (%LymRELCtrlM: 90, %LymREL100M: 80) and absolute (LymABSCtrlM: 11.16, LymREL100M: 6.84) lymphocyte numbers decreased. Males of the 100 mg/kg group had statistically significantly increased number of segmented neutrophils (%NeuSEGCtrlM: 6, %NeuSEG100M: 15). Females additionally exhibited statistically significantly increased haematocrit (15%) and relative lymphocyte counts (%LymRELCtrlF: 92, %LymREL100F: 80) and a decreased platelet count (-14%). The changes in the neutrophil values persisted in males until the end of the recovery period. After the recovery period males exhibited slightly reduced values for erythrocytes, haematocrit, haemoglobin, leucocytes and

lymphocytes. In the females of the recovery group, only RBC and Hb figures were significantly reduced.

In **clinical chemistry**, the males and females of the high dose group had an increase (M: 28%, F: 63%)) in the activity of aspartate aminotransferase (ASAT) and gamma-glutamyltransferase. The males and females of the high dose group also had statistically significantly increased (M: 117 %, F: 667 %) gamma-glutamyltransferase (GGT), and, only in the 10 (31%) and 31.6 (41%) mg/kg group males, an increased alanine aminotransferase (ALT). Male rats of the high dose group had higher chlorine level (99 vs. 96 mmol/l). Alkaline phosphatase (M:-42 %, F:51 %), total protein (M:-9 %, F: 13) were reduced in both sexes of the high dose group. Glucose (-14 %) and cholesterol (-35 %) values were reduced additionally in high dose males. Blood urea was decreased in the high dose males (-28 %) and dose-dependently in all but the lowest dose females (-22 %, -30 % and -42 %). Only females had a reduction in cholinesterase, which was significant in all but the 10 mg/kg dose group. Triglycerides in males of 31.6 mg/kg dose group (-46 %) and in males and females at 100 mg/kg (M:-38 %, F: -34 %) were decreased. Additionally, K+ and Ca2+ -levels of the high dose males (Ca2+ and K+: -7 %) and females (Ca2+: 15 %, K+: 8 %) were statistically significantly reduced. In males, the deviations in clinical chemistry the decrease in blood urea and triglycerides did not return to normal after 8 weeks. In the female recovery group, total protein, blood urea, cholinesterase and albumin levels were significantly reduced at week 8. The authors considered the changes in clinical chemistry parameters as adaptive to exposure and decreased food intake.

In **organ weight** measurements, male testis (-35-40%) and brain weight (-10 %) were reduced in the high dose group and remained so in the recovery group at week 9. Also the brain to body weight ratio and brain to testis weight ratio were bigger in that group. As stated above, the body weight in the high dose group was about 50% less than that of the control animals. The male absolute liver weight was slightly reduced in the 10 (19 %) mg/kg and 100 mg/kg (50 %) group with no change in the ratio to body weight. The only significant organ weight change that correlated with the administrated dose was found in the heart (Males from low to high dose: -21 %, -26 %, 43 %). In females, the absolute weighs of liver (41 %) and heart (-38 %) were decreased in the high dose group without a change in the ratio to body. Ovary weights were reduced in the 31.6 (~40 %) and 100 mg/kg (max 60 %) groups.

Gross **macroscopical** examination revealed small spleen and thymus in both sexes of the high dose group than in other groups, which in microscopy was seen as a reduction of lymphatic tissue. The effect on thymus could not be adequately assessed in the intermediate dose groups, as this organ was not taken at necropsy. The uterus of the two highest doses was reduced in size. However, the spleen, thymus or uterus weights were not reported.

In the **microscopic observations,** the proximal convoluted tubule (PCT) of the kidneys had dose related necrosis and vacuolisation (lipid or fat deposits). In the 3.16 mg/kg dose group 3/5 males had minimal and 2/5 slight vacuolisation. All female rats of the 3.16 mg/kg group had minimal vacuolisation. In the 10 mg/kg dose group, slight vacuolisation was present also in females (3/5). There was one case of minimal necrosis and hyperplasia, both in male rats of the 3.16 mg/kg group. One control male also showed tubular hyperplasia. In the 10 mg/kg group, proximal tubular vacuolisation was minimal in 5/10 and slight in 5/10 animals, minimal necrosis and hyperplasia were present in 7/10 animals. Nuclear polyploidy was present in 7/10 rats and 6/10 of those also had hyperplasia.

The 31.6 mg/kg 7/10 animals of both sexes showed slight to 3/10 moderate vacuolisation of the kidney proximal tubular cells, proximal tubular hyperplasia (minimal in 8/10, slight in

2/10), and polyploid nuclei in the proximal tubules and one case of an abnormal mitotic figure and reduced cellularity of the bone marrow. Minimal PCT-necrosis was present 9/10 animals of this group. Minimal testicular atrophy was observed in 1/5 males and follicular atrophy of the ovaries was observed in 5/5 females (1/5 slight, 2/5 moderate, 4/5 marked). Persistent corpora lutea were reported in 4/5 females (2/5 moderate, 2/5 marked)

In the high dose group, vacuolisation was seen the proximal tubular cells of the kidney of in all animals and graded slight (1/10), moderate (5/10), marked (3/10) or massive (1/10). In the recovery group, the changes were slight in 5/10, moderate in 5/10 animals. Minimal PCT hyperplasia was present in 6/10 animals of the dose group, two of the remaining animals had moderate to marked hyperplasia of the collective tubules and transepithelial cells. In the recovery group PCT hyperplasia (minimal to moderate) was observed in 8/10 animals. Also minimal to moderate nuclear polyploidy was seen in 9/10 dose group and 9/10 recovery group animals. Minimal to moderate necrosis was present in the PCT epithelium of all animals which was noted in the papilla of one male rat as marked.

Testicular atrophy was minimal in 1/5 males, moderate in 1/5 males and marked in 1/5 males of the dose group and minimal, slight or moderate in 1 each of 5 recovery group males. Follicular atrophy of the ovaries was moderate in 2/5, marked in 1/5 and massive in 1/5 females of the dose group and slight in 1/5, marked in 3/5, and massive in 1/5 animals of the recovery group. Persistent corpora lutea were reported in 4/5 females of the dose group (3/5 marked, 1/5 moderate) and 5/5 animals of the recovery group. Two of the recovery group females died after 14 and 16 days of treatment.

In the spleen lymphoid atrophy (minimal 1/5, slight 1/5, moderate 1/5, marked 1/5) was observed in 5/5 males and 4/5 females (1/5 minimal, 1/5 slight, 2/5 marked) of the dose group and the 2/5 females that died premature in the recovery group. None of the animals that survived the recovery period had lymphoid atrophy in the spleen.

The changes in the kidneys and the gonads persisted after the 4-week recovery period (100 mg/kg).

Again, only in the two highest doses, there was a reduction of all cell lines in the bone marrow, which correlated with the white blood cell reduction seen in the haematology. The high dose animals showed occasional maturation disorders, vacuolisation and abnormal mitoses in the bone marrow cells. The changes in the bone marrow, thymus or spleen were reversible after the recovery period.

Some animals of the high dose animals had mild focal hyper- and parakeratosis of the forestomach or mild erosions and haemorrhages in the glandular stomach attributed to the local irritant property of EPTAC. The small intestine of these animals had villous atrophy and crypt necrosis. The changes in the stomach and small intestine were reversible.

4.1.2.6.2 Summary of repeated dose toxicity

The most sensitive organ appears to be the kidney in which minimal changes in morphology could already be seen at an oral dose of 3.16 mg/kg. In the two highest dose groups, testes and ovaries showed focal atrophy that persisted through the recovery period. Moreover, the uterus was atrophic and morphologically in anoestrus in several of the female of these dose groups. The NOAEL for effects on the gonads is thus 10 mg/kg bw. Again in the high dose groups, red blood cells, haemoglobin and haematocrit values were slightly increased in both sexes. The high dose males also had increase in segmented neutrophils. These blood cell changes

correlated with the findings of abnormal maturation and mitoses and vacuolisation seen in the bone marrow. The aminotransferases of the liver were increased during the treatment period in the high dose animals. However, these and most of the other clinical chemistry parameters were reversible after the recovery period. These changes may have been due to adaptive processes of the liver.

Based on the effects on the kidney proximal convoluted tubules (vacuolisation, necrosis, hyperplasia) already seen as minimal at 3.16 mg/kg but evident at 10 mg/kg in the kidney a **LOAEL of 3.16 mg/kg** can be set. Classification and labelling working group has agreed to classify EPTAC Xn; R48/22.

4.1.2.7 Mutagenicity

4.1.2.7.1 Studies in vitro

The mutagenicity of EPTAC has been tested extensively in microbes. Most of the data are non-guideline publications that have tested EPTAC's mutation capacity in different bacterial systems. There is, however, one reverse mutation assay that has been conducted in compliance with the method set by 79/831/EC Annex V, No. 431 and OECD GLP principles (Degussa, 1984). The tests in microbial organisms are presented in the following table. If dose dependency was reported, it is given in the result column.

Table 4.8 Microbial mutagenicity tests with EPTAC.

Test system	Concentrations (vehicle in parenthesis)	Lowest effective dose, (S9 in parenthesis)	Result	Reference
S. typhimurium TA 1538	0.2, 2, 20, 100, 500, 2000 µg/plate +/- S9 (aq.)	n/a	negative	(Dean et al., 1978), (Dean et al., 1985)
S. typhimurium TA 1535, 1537, 1538, 98, 100, rfa-, uvrB- (reverse mutation)	0, 1.58, 5, 15.8,50, 158, 500, 1580, 5000 µg/plate +/- S9 (aq.)	n/a	Positive	(Degussa, 1984)
S. typhimurium TA 100, 1535, 1537, 97, 98	0, 5, 10, 10, 50, 100 µg/plate, +/- S9 (aq.)	5 µg/plate (5 µg/plate)	TA100 and 1535 positive at all concentrations with and without S9, (dose dependent)	(Vleminckx et al., 1987), (von der Hude et al., 1990b)
S. typhimurium TA 1535, 1537, 1538, 98, 100	0, 2, 10, 50, 250, 1250, 6250 µg/plate, +/- S9 (DMSO)	50 µg/plate (250 µg/plate)	TA 1535, 1537 (dose dependent) and 100 (two highest doses) and with and without S9 positive (Doses not cytotoxic)	(Toxicol Laboratories, 1982)
Klebsiella pneumoniae (Luria Delbrück fluctuation test)	0 , 2, 5, 10 mmol/l +/- S9 (DMSO)	2 mmol/l (S9 n/a)	Mutation rate incr. with increasing conc: 0, 0, 2.6, 4.4, 7.4	(Voogd et al., 1981)
E. coli WP2, E. Coli WP2 uvrA, S. typhimurium, S. cerevisiae	0, 2, 20, 100, 500, 2000 µg/plate +/- S9 (aq.)	20 µg/plate (*uvrA*), (20 µg/plate (*uvrA*))	Positive in both strains of *E. Coli* with and without S9	(Dean et al., 1978), (Dean et al., 1985)
E. coli PQ37 SOS-chromotest	0, 3.3, 10.0, 100.0 mmol/l, +/- S9 (aq.)	SOS inducing potency ~0.5	Positive	(von der Hude et al., 1990b)
S. cerevisiae JD1 induction of gene conversion (trp & his locus)	0, 0.1, 0.5, 1.0, 5.0, 10.0 µg/ml for 1h @ 37 °C + 16h @ 29°C, +/- S9 (aq.)	0.5 mg/ml (his), (0.5 mg/ml), 1 mg/ml (trp), (1 mg/ml)	Positive with and without S9	(Dean et al., 1978), (Dean et al., 1985)
S. cerevisiae D7 induction of gene	0, 0.01, 0.05, 0.10, 0.50, 1.00, 5.00 mg/ml for 1h	0.5 mg/ml (0.5 mg/ml)	Positive: Gene conversion increased	(Vleminckx et al., 1987)

conversion (trp locus)	@ 37 °C + 3 days @ 30°C, +/- S9		dose dependently	

EPTAC was positive in different microbial systems. Positive response, although slighter, was also seen when liver microsomal fraction (S9) was present. The results in bacteria indicate that EPTAC acts in a similar way to other aliphatic epoxides, direct-acting base pair substitution. When a the genotoxic potency of EPTAC was evaluated along with a series of 51 other epoxides in a SOS test with *E. Coli* PQ37, the results showed that EPTAC has mutagenic potency.

Unscheduled DNA synthesis

The ability of EPTAC to induce mutations in mammalian cells was investigated in a non-guideline primary rat hepatocyte (PRH) unscheduled DNA synthesis (von der Hude et al., 1990a). No metabolic activation was used and no reasoning was given for dose selection. Primary rat hepatocytes were seeded onto coverslips left to attach for 2 h. Unattached cells were removed and attached cells were incubated with the test compound and methyl-3H-thymidine for 20 hours. Two experimental series were made: 1 and 5 µCi/ml concentration. The coverslips were processed by a hypotonic solution, mounted with photographic emulsion and left to develop. On each slide, twenty cells per slide and three slides per dose were counted. Doses used were 2, 20 and 200 µmol/l. The percentage of positives was in the experiment with 1 µCi/ml: 0% (ctrl), 19% (2), 65% (20), 100% (200). None of the doses was reported toxic. EPTAC produced a dose dependently increasing number of nuclear grains.

Sister chromatid exchange

In a study of 58 epoxides, Chinese hamster V79 cells were seeded into flasks and left to grow for 18 hours after which EPTAC was added to growth medium in concentrations of 0, 0.125, 0.25, 0,5, 1.0, 2.0 mmol/l (von der Hude et al., 1989). The study was not conducted following formal OECD or EU guideline, but the methodology and reporting conformed in most parts to the OECD guideline requirements. The growth medium with the test substance was replaced with a fresh one containing 10-5 M 5-bromo-2'-deoxyuridine. Use of metabolic activation was not reported. Mitotic cells were harvested after 28-hour incubation with 2 x 10-7 M Colcemid. The cells were fixed on slides and stained. In all, 50 metaphases, or 25 metaphases from two independent tests, were scored for each dose level. The results showed that EPTAC caused a dose related increase of sister chromatid exchanges, which was statistically different from the control at doses higher than 0.125 mmol/l. All epoxides were tested up to cytotoxic concentrations detected by delay in the replication index.

Chromosome aberration test

One-day-old triplicate cultures of Chinese hamster ovary (CHO) cells were exposed to 0, 5, 10, 20, 50 and 100 µg/ml of EPTAC for 18 hours. Water was used as the negative control and mitomycin C as the positive control (Vleminckx et al., 1987). No metabolic activation was used in the test system. After the treatment, cultures were used to make cytotoxicity measurement and to prepare metaphase spreads. For the determination of mitotic index 1000-2000 cells were scored. The first 50 randomly selected metaphases were used to analyse numerical aberrations. The percentage of aneuploid/polyploid metaphases in treated cells was compared to that of control cells. For each dose level, 50-100 metaphases were analysed for structural aberrations. The scoring of chromosomal aberrations was done according to OECD guidelines. The results showed that both the frequency of aberrations, with or without gaps,

per cell and the percentage of cells with all aberrations increased with the dose. At the same time mitotic index and survival index decreased with the dose. The results were significant starting at 50 µg/ml. The predominant types of aberration were chromatid gaps, interchanges and chromosome breaks. EPTAC induced also chromosome condensation and shattered metaphases. No increase in the number of numerical aberration was noted. The total aberration figures and figures excluding gaps were: 0 µg/ml (0.09) [0.03], 5 µg/ml (0.17) [0.12], 10 µg/ml (0.22) [0.11], 20 µg/ml (0.29) [0.11], 50 µg/ml (0.59*) [0.21], 100 µg/ml (0.70*) [0.32], Mitomycin 0.02 µg/ml (0.40*) [0.28], Mitomycin 0.10 µg/ml (1.76*) [0.74]. The number of chromosome breaks is given in square brackets and ones marked with a star were statistically significant at p=0.001-0.01 or p<0.001. EPTAC was about 1000 less cytotoxic than Mitomycin C. The survival indices were from control to high dose: 100% (ctrl), 87% (5), 86% (10), 70% (20), 57% (50), 56% (100), 78% (0.02 MMC), 62% (0.10 MMC). The mitotic indices were: 10.4% (0), 7.7% (5), 8.3% (10), 6.5% (20), 6.0% (50), 3.1% (100, 5.5% (0.02 MMC), 2.8 (0.01 MMC).

RL1 chromosome assay

Slide cultures of RL1 cells (rat liver) were exposed to medium containing 0, 10, 20, 40 and 80 µg/ml EPTAC for 24 hours. After exposure, cultures were processed for chromosome analysis and 100 cells were analysed from each of the four cultures per dose (Dean et al., 1978), (Dean et al., 1985). The incidence of chromatid aberrations increased with the dose. The most significant changes included increases of exchange figures cells, single chromatid gaps at lower doses and multiple chromatid gaps at higher doses. At 80 µg/ml almost all cells were affected, and in 55 % of the cells, some or all chromosomes had a beaded appearance due to the large number of gaps.

Table 4.9 Mutagenicity tests with EPTAC in mammalian cells *in vitro*

Test system	Concentrations	Result	Reference
PRIMARY RAT HEPATOCYTE UDS	0, 2, 20, 200 µMOL/L, FOR 20H @ 37 °C	POSITIVE CELL COUNT VARIED FROM 15 TO 100 % IN THE TREATED CELLS. AT 20 µMOL EPTAC WAS UDS POSITIVE (>50% POS. CELLS + NET GRAIN COUNT HIGHER THAN 2X SD OF CONTROL)	(von der Hude et al., 1990a)
CHINESE HAMSTER OVARY (CHO) CELLS	0, 5, 10, 20, 50 AND 100 µG/ML OF EPTAC FOR 18 HOURS	FREQUENCY OF ABERRATIONS, WITH OR WITHOUT GAPS, PER CELL AND THE PERCENTAGE OF CELLS WITH ALL ABERRATIONS INCREASED WITH THE DOSE	(Vleminckx et al., 1987)
SCE IN CHINESE HAMSTER V79	0, 0.125, 0.25, 0,5, 1.0, 2.0 MMOL/L	POSITIVE STARTING FROM 0.25 MMOL/L, DOSE DEPENDENT INCREASE, R=0.87, S=7.1	(von der Hude et al., 1991)
CHROMOSOME ASSAY IN RL1 CELL LINE	0, 10, 0, 40, 80 µG/ML	POSITIVE: DOSE RELATED INCREASE OF CHROMATID GAPS	(Dean et al., 1978), (Dean et al., 1985)

4.1.2.7.2 Studies in vivo

Mouse micronucleus test

In a study conducted following GLP and OECD guideline 407, three groups of 18 five-weeks-old mice (BOR:NMRI) each were administered a single 10 ml/kg intraperitoneal injection of

either EPTAC, physiological saline or cyclophosphamide (Degussa, 1992). The test material dose corresponded to 82.5 mg/kg and the positive control dose was 51.1 mg/kg. Twenty-four, 48 and 72 h after the injection, six mice per sex and per control group and seven mice of the groups treated with EPTAC were killed and the bone marrow was removed for erythrocyte analysis. For each sampling, five mice per sex and per group were used and 1000 polychromatic erythrocytes (PCE) were counted per animal. The ratio of polychromatic to normochromatic (PCE/NCE) was used to assess the toxicity of the substance. The PCE indices with micronuclei were statistically analysed by using a Poisson test on each treatment group, sex and both sexes combined. Good Laboratory Practise regulations and OECD guideline 474 were followed.

In clinical examination, toxic symptoms, manifested as slight to moderate clonic convulsions, were observed in the EPTAC treated animals. At 72 h there is a significant increase in the PCE/NCE in males. However, the authors of the report stated that the control values were exceptionally low based on intralaboratory and literature reported historical control incidences. The positive result of the males also caused a significant increase when both sexes were combined. On the other hand, at 24 h, there was a clear, statistically significant increase of micronucleated PCE in females. In males of this sampling time, the number of PCEs was double the size than in respective negative controls with p-value of 0.076. The increase remained significant even when both sexes were evaluated as one group.

Table 4.9 PCEs with micronuclei scored in 1000 PCEs with PCE/NCE in control animals

PCE and PCE/NCE / animal 82.5 mg/kg EPTAC (i.p.)	24h				48h				72h			
	PCE (M)	PCE/ NCE (M)	PCE (F)	PCE/ NCE (F)	PCE (M)	PCE/ NCE (M)	PCE (F)	PCE/ NCE (F)	PCE (M)	PCE/ NCE (M)	PCE (F)	PCE/ NCE (F)
1	3	2.05	1	1.77	1	1.40	1	2.13	0	2.55	0	2.41
2	0	1.71	1	1.97	2	2.04	2	1.86	1	4.05	0	3.33
3	1	1.93	2	1.67	0	2.09	1	1.72	1	2.70	1	2.70
4	2	2.45	2	1.67	0	1.20	2	1.57	0	2.80	1	2.80
5	2	1.89	1	1.96	0	1.75	2	1.42	0	3.41	1	3.41
Mean	1.6		1.4		0.6		1.6		0.4		0.6	

Table 4.10 PCEs with micronuclei scored in 1000 PCEs with PCE/NCE in EPTAC treated animals

PCE and PCE/NCE / animal 82.5 mg/kg EPTAC (i.p.)	24h				48h				72h			
	PCE (M)	PCE/ NCE (M)	PCE (F)	PCE/ NCE (F)	PCE (M)	PCE/ NCE (M)	PCE (F)	PCE/ NCE (F)	PCE (M)	PCE/ NCE (M)	PCE (F)	PCE/ NCE (F)
1	2	1.99	8	2.10	2	1.08	1	1.71	2	1.70	0	1.81
2	1	0.98	4	1.17	3	0.96	1	2.01	2	1.22	0	2.58
3	1	2.40	10	1.08	3	1.08	1	1.40	3	2.97	2	1.78
4	9	2.40	8	1.21	0	1.82	2	1.06	4	1.55	0	2.89
5	3	2.29	6	1.11	0	1.17	3	1.34	0	1.98	0	2.91
Mean	3.2		7.2		1.6		1.6		2.2		0.4	

Table 4.11 Statistical evaluation of mouse micronucleus test

PCE with micronuclei/Group	24h		48h		72h	
	M	F	M	F	M	F
EPTAC	16	36	8	8	11	2
Negative control	8	7	3	8	2	3
F	1.7778	4.5000	2.000	0.8889	3.6667	0.5000
p-value	0.076	0.000	0.113	0.589	0.011	0.812
Positive control	154	138	94	29	35	19
Negative control	8	7	3	8	2	3

F	17.1111	17.2500	23.5000	3.2222	11.6667	4.7500
p-value	0.000	0.000	0.000	0.000	0.000	0.000

4.1.2.7.3 Summary of mutagenicity

EPTAC causes mutations in *E. coli* WP2 and S. typhimurium 1535, 1537 and 100 but not in 1538 or 98. These mutations did not require metabolic activation to occur. The evidence from the bacterial mutagenicity tests suggests that EPTAC act as a direct point mutagen by base pair substitution but not frame shift mutation. In addition, tests in two yeast strains have demonstrated that EPTAC can cause gene conversion in two different gene loci. The positive response in the liver UDS test gives indications of increased DNA damage in mammalian cells as well. In addition, a well-correlated dose-related increase of sister chromatid exchanges in the Chinese hamster V79 cells was seen.

Damage to chromosomes has been shown to occur in mammalian test systems *in vitro* and *in vivo*. The results of the in vitro chromosome aberration tests in both rat liver cells and Hamster ovary cells showed that both the frequency of aberrations per cell, with or without gaps, and the percentage of cells with all aberrations increased with the dose. In vivo, there was also a clear statistically significant increase of micronucleated PCE in females 24 hours after the administration in both sexes.

Positive results in vitro and in vivo show that in addition to causing point mutations in bacterial systems, EPTAC has clastogenic or aneugenic potential in mammalian cells as well. Moreover, microscopic examination in the 28-day test showed that there were abnormal mitosis and polyploid nuclei in the kidney proximal tubule cells at doses 10 mg/kg or higher, which could be indicative of a genotoxic event. In addition, atrophy of testes and especially of ovaries was seen at 31.6 mg/kg after 28-day of exposure increasing the possibility that EPTAC is also a germ cell mutagen.

EPTAC is a mutagen in somatic cells *in vivo*. Based on the evidence seen in a 28 day study, EPTAC also reaches the gonads, thus making it likely that EPTAC is also a germ cell mutagen. Classification and labelling working group has agreed to classify EPTAC Muta. Cat. 3; R68.

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

<u>In vivo studies</u>

Dermal

In a two-year cancer study, EPTAC was applied on CF1 mouse skin (Doak, 1983). The test substance was dissolved in ethanol at concentrations 0.1, 0.3 and 1.0% (w/v) (1% was a non-irritant concentration in a pre-test). Each dose level had 50 male and 50 female mice, except the solvent (ethanol/nonident) which had 100 mice per group and sex. A concentration of 10 mg/ml beta-propiolactone was used to act as the positive control. The test and control substances were applied twice weekly, 0.2 ml at a time, and the treatment continued for up to

104 weeks. Expressed as weight the doses are 0.2, 0.6, 2.0 mg/animal/application. In the absence of data on average animal weight during the exposure (no weight records were available and there is no mention that these data was collected), we use an average weight TGD default assumption of 40 g. Using this assumption, the doses are 5, 15 and 50 mg/kg/application or 10, 30 and 100 mg/kg/week. Based on the in vitro absorption assay with mouse skin, 22.6 to 43.6 % of CHPTAC passed through the skin at this concentration. The clinical observations were made twice daily and detailed records of skin lesions and site were kept. In necropsy, a macroscopical examination was performed and when gross abnormalities were found the organ was sectioned for microscopical preparation. In addition, histological samples were prepared from the adrenals, brain at 3 levels, cervix, eyes and lachrymal glands, gonads, heart, kidneys, liver, lungs, lymph nodes, pancreas, pituitary, salivary gland, skin, spleen, stomach, thymus, thyroid, urinary bladder and uterus. The location of cutaneous tumour suspects was mapped and the time of appearance and growth rate was recorded. The minimum level of detection for a cutaneous tumour was 1 mm. At histological examination, a distinction between malignant and benign tumours was made and the tumours were grouped as either originating from the treated site or from an untreated area.

Female survival was significantly affected by exposure to 1 % EPTAC ($p<0.001$). Pair wise comparisons between control and other treated groups revealed no significant differences using a two-by-two contingency table analysis. Though the male survival in 1 % group was lower than in control group, the contingency table analysis showed that none of the differences between control and treated groups were significant.

Table 4.12: Survival of the mice during the experiment was the following after 104 weeks

	Males %	Females %
Control	27	31
1 % beta-propiolactone	18	20
0.1 % EPTAC	34	26
0.3 % EPTAC	28	22
1.0 % EPTAC	16	2

In all groups, deaths were mainly caused by neoplasia (139 males and 139 females). Compared to negative control group, survival to the 2-year scheduled necropsy was reduced in both, after exposure to 1% EPTAC and the positive control substance (beta-propiolactone). This difference was statistically significant in the females of the 1% EPTAC group. In all mice, the majority of the tumour-related deaths were caused by primary systemic neoplasia (233), mainly of haematopoietic tissues and lungs. In males, there was no evidence of the deaths being treatment related, but in the 1% EPTAC female dose group, there was a slightly higher incidence of tumour related mortality compared with solvent controls. Mammary gland tumours caused 6 deaths of 50 females in the 1.0 % EPTAC, one death in the negative control group and 0 deaths in all the other groups. Cutaneous neoplasia caused 13 deaths in the 1% group, 5 in the positive controls one in the negative control animals and none in all the other groups. The non-neoplastic causes of deaths were mainly those caused by suppurative lesions, renal failures (females) or urethral obstruction. The only significant effect on the aetiology of death or terminal illness was seen in the 1.0 % where there was an increase in mortality due to cutaneous neoplasia and mammary gland neoplasms in the female mice. Other clinical signs were discolouration, epilation and flaking, which were noted in the treated site in the 1.0 % EPTAC and beta-propiolactone groups. In the treated site of the 0.3 and 1.0 % EPTAC and the beta-propiolactone groups, cutaneous nodules and lumps (at least 2 mm in diameter and persisted for at least 2 weeks) were noted. Lumps were present also in the untreated sites of skin in the 1.0 % mice.

Table 4.13 Aetiology of death in CF1 mice treated with EPTAC

	Incidence									
Aetiology	Males					females				
	Solv.	B-Pl	0.1%	0.3%	1.0%	Solv.	B-Pl	0.1%	0.3%	1.0%
Skin neoplasia	1	11	-	-	7	1	5	-	-	13
Mammary neoplasia (adenomacarcinoma)	-	-	-	-	-	1				6
Systemic neoplasia	47	13	20	19	21	37	10	22	20	24
Chronic/ obstructive renal failure	9	9	8	7	5	12	7	5	9	3
Inflammatory conditions	6	2	3	4	2	12	12	6	5	2
Other	10	6	2	6	7	6	6	4	5	1

In macroscopic pathology observations, an increase in the number of multifocal nodules in the lungs and multifocal or solitary skin masses was noted in both sexes. There was also a significant increase of mammary masses in the females of the highest dose group. With the exception of cutaneous ulceration and pre-neoplastic skin lesions in both 1.0 % EPTAC and beta-propiolactone groups, no treatment related histopathological organ changes with regard to non-tumour endpoints were observed. An extensive examination of the sex organs revealed no treatment-related effects.

Tumours of the integument

No dermal or epidermal tumours were found in males or females of the 0.1 % EPTAC dose group. In the mice that were administered 0.3 % EPTAC, 2/50 female mice developed cutaneous tumours, one being malignant basal cell carcinoma and the other a benign sloughed tumour in the treated site. In the negative control male mice group 1/100 had dermal fibrosarcoma. One malignant subcutaneous dermal fibrosarcoma was found in the female control mice in the treated site. In the positive control mice, 26/50 of the males and 15/50 females developed cutaneous tumours (not tabled). In the 1% dose group, the 27/50 of the male and 25/50 female mice developed a total of 140 skin tumours. Most of these tumours were epidermal and malignant squamous cell carcinomas, with the exception of three dermal and one subcutaneous tumour (malignant fibrosarcoma) in female mice. The most typical malignant tumours were of squamous-cell carcinoma.

Table 4.14 Skin tumours at treated site in male and female mice

Tumour	Control M (100)	Control F (100)	0.1 % M (50)	0.1 % F (50)	0.3 % M (50)	0.3 % F (50)	1.0 % M (50)	1.0 % F (50)
Squamous cell carcinoma (M)							24(53)	20(49)
Sloughed tumour (B)						1(1)	5(8)	4(4)
Squamous cell papilloma (B)							4(4)	2(2)
Basal cell carcinoma (M)						1(1)	5(5)	1(3)
Anaplastic carcinoma (M)							1(1)	
Sebaceous gland adenoma (B)							1(1)	2(2)
Basal cell papilloma (B)							3(3)	1(1)
Dermal fibrosarcoma (M)		1 (1)						1(1)
Dermal haemangioma (B)								1(1)
Dermal lymphangioma (B)								1(1)
Fibrosarcoma (subcutis) (M)	1(1)							1(1)

Numbers in parenthesis represent the total number of this tumour type; M malignant, B benign

Table 4.15 Summary of tumour data: treated skin and subcutis of male and female mice

Tumour	Control M	Control F	0.1 % M	0.1 % F	0.3 % M	0.3 % F	1.0 % M	1.0 % F

	(100)	(100)	(50)	(50)	(50)	(50)	(50)	(50)
Number and % of animals with tumours	1 (1%)	1 (1%)	-	-	-	2 (4%)	27 (54%)	25 (50%)
Number and % of animals with single tumours	1 (1%)	1 (1%)	-	-	-	2 (4%)	9 (18%)	9 (18%)
Number and % of animals with multiple tumours	-	-	-	-	-		18 (36%)	16 (32%)
Number and % of animals with benign tumours	-	-	-	-	-	1 (2%)	10 (20%)	10 (20%)
Number and % of animals with malignant tumours	1 (1%)	1 (1%)	-	-	-	1 (2%)	25 (50%)	22 (44%)
Number and % of animals with metastatic tumours	1 (1%)		-	-	-		4 (8%)	6 (12%)
Total number of tumours	1	1	-	-	-	2	75	65
Total number of benign tumours	-	-	-	-	-	1	16	11
Total number of malignant tumours	1	1	-	-	-	1	59	54
Total number of metastatic tumours	1		-	-	-	-	4	6

Systemic tumours

In the incidence of systemic tumours, male mice had a significant increase of thymic lymphosarcomata in the highest dose group. The earliest death where the aetiology was lymphosarcoma occurred at 119 days and the latest at 483 days, on average 268 days. No other significant increases of systemic tumours were seen in males. In females, both, the 0.3 % and 1.0 % dose groups had more lachrymal gland tumours than the control group. The tumours were benign solitary and were seen only in 12/600 mice. Moreover, there was no evidence of dose response since the 1.0 % dose group had a lower tumour incidence than the 0.3 % group. The cutaneous treatment with EPTAC also increased significantly the incidence of lung tumours in the female 1.0 % dose group when compared to the control group. Untreated CF-1 mice have 45-60 % lung tumour incidence with both sexes. The statistical analysis confirmed the dose-related increase of pulmonary tumours in female mice. However, the authors sited literature, which has shown that strains of mice with a high, inherited incidence of spontaneous tumours usually respond to treatment with carcinogens by yielding a high incidence of induced pulmonary tumours, usually adenomata. Therefore, in the authors' opinion, this does not provide conclusive evidence of EPTAC's pulmonary carcinogenic potential. The authors further discussed that the reticulum cell sarcomata in high dose females and the thymic lymphosarcomata in high dose males could be associated with oncornaviruses. The types B and C of this virus are known to make mice carrying them more susceptible to lymphoreticular or haematopoietic neoplasms. The type C virus can be transferred vertically from mother to offspring. The investigators again questioned the statistically significant increase seen in the incidence of mammary adenocarcinomata in high dose females. Citing literature from Nandi and McGrath (1973) the authors speculated that the presence of the mammary neoplasia might be associated with the oncornavirus. The possible mode of action, they say, could be a co-carcinogenic action of the virus with hormonal and genetic factors and the application of EPTAC.

Table 4.16: Statistical analysis of the increases in systemic neoplasia in male mice

Tumour category	Solvent		0.1 %		0.3 %		1.0 %		T
	O	O:E	O	O:E	O	O:E	O	O:E	
Thymic lymphosarcoma	5	0.81	1	0.33	2	0.65	7	2.53	2.62**

Table 4.17: Statistical analysis of the increases in systemic neoplasia in female mice

Tumour category	Solvent	0.1 %	0.3 %	1.0 %	T

	O	O:E	O	O:E	O	O:E	O	O:E	
Reticulum cell sarcoma	21	0.79	11	0.98	9	0.87	11	2.73	3.65**
Lachrymal gland	1	0.29	0	-	4	3.07	2	2.48	2.43**
Lungs	51	0.87	22	0.84	27	0.98	36	1.53	3.86**
Mammary gland	2	0.33	0	-	1	0.35	12	4.15	5.90**

T = Test statistic distributed N (0,1) under the hypothesis that risk of tumour development does not increase with increasing dose
O = Observed number of mice with given tumour, O:E = Ratio of observed to expected, ** = P < 0.01 Significance of value of test statistic

Discussion

There was an increase in the incidence of integumentary tumours at the treatment site when 1.0 % EPTAC was administered. The doses were estimated as 4, 15 and 41 mg/kg/day or 8, 30 and 82 mg/kg/week. Based on the in vitro absorption assay with mouse skin, 22.6 to 43.6 % of CHPTAC passed through the skin at this concentration. However, it must be noted that based on this study, for human skin the internal dose is likely to be up to 60 times lower than in mouse. Twenty-seven of 50 male mice and 25 of 50 female mice developed a total of 140 cutaneous tumours with the shortest latency period being 50 weeks; 75 epidermal tumours were induced in males and 65 tumours (61 epidermal, 3 dermal and 1 subcutaneous) in females. Beta-propiolactone, known for its carcinogenic activity, produced tumours at the treatment site in 71/100 mice with the shortest latency period being only 20 weeks. In contrast, only two tumours developed on the treatment site of the mice in the 0.3 % treatment group. Judging from the high incidence of the cutaneous tumours seen at 1.0 % dose group, it is evident that 2,3-epoxypropyltrimethyl ammonium chloride has cutaneous carcinogenic potential.

In male mice, the only significant effect observed was the increase of thymic lymphosarcomata in the 1.0% group. In female mice, statistical analysis of systemic tumours showed significant results with evidence of increasing risk with increasing dose for the number of mice with lung tumours, reticulum cell sarcomata, tumours of the mammary gland and tumours of the lachrymal gland. However, the mice of 0.3% group were in more risk of developing the lachrymal gland tumours than the 1.0 % mice, thus giving no evidence of dose-response. The lung tumours were mostly adenoma. Although this mouse strain has a tendency for high incidence spontaneous lung tumours a dose response was confirmed by a statistical analysis. Viral origin was discussed by the authors for the reticulum and thymic cell sarcomata and the mammary tumours, but no real evidence for these modes of action could be presented.

In order to define a benchmark dose for a possible, although questionable systemic tumourigenicity of EPTAC the systemic dose can be calculated by using the results of the skin absorption study in mice with CHPTAC and the total amount absorbed at the different concentration levels. The external dose levels were estimated to be 5, 15, and 50 mg/kg/application. The total absorption rate at 0.1 % of 45 % can be used for the low and mid dose group (0.1 and 0.3% were dosed) and the total absorption rate of 29.2% for the 1% solution in the high dose group. This would result in dose levels of 2.3, 6.8, and 14.6 mg/kg bw per application. With a twice per week application this would amount to 4.6, 13.6 and 29.2 mg/kg bw per week corresponding to 0.9, 2.7 and 5.8 mg/kg day (5 days exposure) or 0.7, 1.9, and 4.9 mg/kg day for a 7 day per week exposure.

4.1.2.8.2 Summary of carcinogenicity

EPTAC is a local carcinogen when applied on mouse skin at 1 % concentration (estimated dose applied on the skin: ~50 mg/kg/application). There is some indication that EPTAC could also cause some systemic tumours (e.g. lung or mammary tumours) when applied to mouse skin as a 1 % solution. However, the relevance of these tumours to the treatment is uncertain. Moreover, it is possible that oral intake could have occurred during the experiment. Based on in vitro skin absorption data from CHPTAC, the dermal penetration property of EPTAC is ca. 45 % or 29% in mouse skin at a concentration of 0.1% and 1% respectively, while in human skin it is less than 6%. Regardless of this, it is difficult to completely disregard the relevance of the systemic tumours. Furthermore, as EPTAC has direct mutagenic potential, which does not seem to be inactivated by mammalian metabolising systems, carcinogenic properties could be expected. Classification and labelling working group has agreed to classify EPTAC Carc. Cat 2; R45.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Effects on fertility

Studies in animals

There are no studies conducted on toxicity to fertility or developmental toxicity. Some information of the effect on the morphology of the gonads can be obtained from the 28-day test conducted with Wistar rats. The rats were administered by oral gavage 0, 3.16, 10.0, 31.6 or 100 mg/kg EPTAC (72.6 %) for 28 days (Degussa, 1990). The control and high dose group had 10 males and 10 female and the low- and mid-dose groups had five rats of each sex. Five high dose and five control group animals were submitted to a 4-week post-exposure observation period. The study was conducted under GLP regulations and OECD guideline 407 was followed as the study protocol. Urinalysis was performed in weeks 4 and 8 (recovery groups). Samples for histopathological evaluation were prepared of adrenal glands, bone marrow from sternum, bone marrow smear, brain, various sections of the intestine, heart, kidneys, liver, lungs, ovaries, spleen, stomach, ovaries, testes and thymus. Haematology and clinical chemistry measurements were those recommended in the guideline and they were determined at 4 and 8 weeks. See chapter 4.1.2.6.1 Studies in animals for a more complete description of the study.

Male rats of the highest dose groups had a significant decrease (-35-40%) of the testis weight at week 5, which remained significantly lower in the recovery group at week 9. The female ovaries showed a weight decrease trend at week 5, where the weight difference was significant in the dose groups 31.6 mg/kg and 100 mg/kg. However, at week 9 in the recovery group, there was significant ovary weight decrease (max 60%) in the right ovary only in the 100 mg/kg dose group. Microscopically, males of the 31.6 and 100 mg/dose groups showed a dose-related incidence and severity of focal atrophy of the testes. Females had a dose dependent severity of follicular atrophy and persistent corpora lutea in the 31.6 and 100 mg/kg dose groups. The uterus epithelium was atrophic and morphologically in anoestrus. The changes in the gonads persisted in both sexes through the recovery period. The body weight in the 100 mg/kg group males at day 28 was about 45% lower than the control group and in the 31.6 mg/kg group at that time the mean body weight was about 18% lower and in the 10 mg/kg group a 12 % reduction was noted. The 100 mg/kg dose females had about 38 %

lower mean body weight than the control. No significant difference was noted in other groups or in the recovery group. After the recovery period, the male 100 mg/kg recovery group had still about 29% lower mean body weight, when compared to control.

4.1.2.9.2 Developmental toxicity

There is no data to allow evaluation of developmental toxicity.

4.1.2.9.3 Summary of toxicity for reproduction

Although these results tell little of the effect on the reproductive performance itself they can be used to set an indicative NOAEL based on the rather severe morphological changes in the reproductive organs of both sexes. The 10mg/kg NOAEL obtained from the 28-day repeated dose toxicity study is selected for toxicity to reproduction.

It unlikely that any further information obtained about the possible toxicity to reproduction (fertility or development) by requiring additional testing would enhance the possible risk reduction measures needed by a genotoxic carcinogen. Classification and labelling working group has agreed to classify EPTAC Repro. Cat. 3; R62.

4.1.3 Risk characterisation [5]

4.1.3.1 General aspects

Toxicity

There is no information on toxicokinetics of EPTAC. Inhalation absorption of 75 % is assumed. An assumed oral absorption rate of 50 % will be used in the risk characterisation. An *in vitro* study performed using human and mouse skin samples and a closely related substance, CHPTAC, showed a skin absorption rate of about 6 % in humans, taking into account the deposition to skin after stratum corneum stripping. In mouse, the amount of CHPTAC passing through the skin was 20 to 60 times higher than in humans, but the amount deposited in mouse skin was proportionally lower than in human skin. In acute toxicity test, when administered orally to rats, an LD50 value of about 1500 mg/kg was obtained. Dermal toxicity ranges somewhere between 1500 to 3000 mg/kg. However, the result of the dermal toxicity study is based on a badly reported, non-valid study. A dermal LD50 of 1500 mg/kg is used in the risk characterisation. No reliable information is available for acute inhalation toxicity. In a 7-hour inhalation exposure at a nominal concentration of 8.17 mg/l EPTAC caused no lethality or systemic effects in 4 female rats. This value is used for risk characterisation. EPTAC is classified in the EU for acute toxicity as R21/22 (harmful via skin or ingestion). EPTAC is a strong eye irritant and is classified in the EU as R41 “May cause

[5] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

serious damage to eyes." It causes reddening, swelling damage to iris and clouding of the cornea in the rabbit eye. These effects persist after 21 days. EPTAC is not irritating to skin but it causes a clear sensitisation response in guinea-pigs. These results are supported by positive results from patch tests on workers that were exposed to EPTAC. In repeated dose toxicity study with rat, a 28-day LOAEL of 3.16 mg/kg was found using oral administration. This is based on degenerative kidney effects seen in rat proximal tubule cells. EPTAC is clearly mutagenic in bacterial and mammalian cells in vitro. A positive response was seen in Salmonella strains TA 1535 and TA100. Positive mammalian in vitro tests include an increase in the unscheduled DNA synthesis in rat primary hepatocytes, an increase in sister chromatid exchange in Chinese Hamster V79 cells and an increase in clastogenic activity in Chinese Hamster ovary cells. In vivo, there was also a clear increase in the mouse bone marrow micronucleus 24 hours after the administration in females. EPTAC has been classified as Muta. Cat 3; R68. There was a statistically significant increase of skin tumours when mice where treated topically with 1 % EPTAC (~50 mg/kg/application). In females, there was also a statistically significant increase of lung tumours, mammary gland tumours, lachrymal gland tumours and reticulum cell sarcoma in the 1 % EPTAC treatment group. Of systemic tumours, a statistically significantly increased number of thymic lymphosarcoma in males of the 1 % dose group was reported. Although EPTAC is a genotoxic, the mode of action, which caused the occurrence of the systemic tumours, is somewhat unsure. While authors speculated viral interaction may have been involved, it is also unsure whether EPTAC reaches the body further than the dermis in sufficient quantities to have caused the systemic tumours. EPTAC is classied as Carc. Cat 2; R45. There is no information on toxicity to fertility or foetal development. However, the results of the 28-day test with Wistar rats show that EPTAC causes focal atrophy on testis, atrophy of the ovaries and morphological changes in the uterus epithelium at dose levels of 31.6 mg/kg bw and above. The NOAEL was 10 mg/kg on effects to reproductive organs. Based on these effects, EPTAC is classified as Repro. Tox. Cat 3; R68.

Table 4.18 Summary of effects

Substance name	Inhalation (N(L)OAEL)	Dermal (N(L)OAEL)	Oral (N(L)OAEL)
Acute toxicity	8170 mg/m^3	1500 mg/kg	1500 mg/kg
Irritation / corrositivity	No data.	strong eye irritant	No data.
Sensitization	No data.	sensitiser	No data.
Repeated dose toxicity (systemic)	No data.	No data.	3.16 mg/kg (with 50% assumed absorption: 1.6 mg/kg bw)
Mutagenicity	Positive in vitro and in vivo		
Carcinogenicity	No data.	Causes skin tumours and possibly systemic tumours	No data.
Fertility impairment	No data.	No data.	10 mg/kg* (with 50% assumed absorption: 5 mg/kg bw)
Developmental toxicity	No data.	No data.	No data.

Based on gonads in a 28d study.

Exposure

Worker

In occupational exposure situations, the worker is typically exposed to EPTAC either via skin or via inhalation to residual EPTAC via cationised starch. Respiratory exposure to pure EPTAC is not likely because exposure to pure EPTAC from aerosol is not seen probable. Respiratory exposure would more likely occur to the substance residual in the cationised starch. In the dermal exposure assessment, the data is generated using EASE estimations. For inhalation exposure assessment, measured data was preferred over an EASE estimate whenever available. It should be noted that the EASE estimates could overestimate the true exposure. During loading operations, exposure potentially occurs for a very short time when the pipes are connected. Inhalation exposure is unlikely during loading and unloading due to the technology applied. This is supported by measurements in which EPTAC could not be detected. Detailed instructions how to properly avoid dermal exposure are given and management systems applied.

The biggest exposures are estimated to occur dermally during manufacture, more specifically during formulation, sampling and the handling of the sample in the laboratory. In wet cationising, EPTAC exposure results also from the use of (3-chloro-2-hydroxypropyl)trimethylammonium chloride as the cationising agent since CHPTAC is qualitatively converted with alkaline to EPTAC. Hence, irrespective of the starting substance, the exposure is to EPTAC in the wet cationising process, except in the filling phase where both substances, EPTAC and CHPTAC, are again present. In the selection of residual concentration in the cationised starch, which is the major use of EPTAC, industry survey of residual levels of EPTAC and CHPTAC in commercial cationic starches has been carried out by the industry. The residues were measured in 58 samples. The residual values depend on the type of the product and process parameters. For the worst case calculations in exposure assessment, the values of 90th percentile have been selected. The values are 15 mg/kg for EPTAC. Occupational exposure could occur from other cationised polymers used, e.g., in the cosmetics industry. Cationic polymers are used normally at a concentration of ≤ 0.1-0.2 % in hair and skin care products. Residual EPTAC concentration is usually less than 200 mg/kg polymer. For the calculation of margins of safety, only the worst case exposure figures have been used. In many of the scenarios, typical exposures can be one to two orders of magnitude lower.

Although reasonable worst case values have been used for drawing conclusions, these may present an overestimation of exposure in some cases. According to information received risk reduction measures have already taken place concerning the handling and management of these substances. It is likely that following these measures would lead to lower exposure than what is estimated in the worst case to occur.

Consumers

EPTAC residues are present in cellulose or other cationised macromolecules used in the manufacture of paper or cardboard or as additives in cosmetic products. Exposure figures are estimates, which are based on measurements of EPTAC residue in starch, the amount of starch in cellulose, assumptions of adsorption of EPTAC to paper and degradation of EPTAC in the process. Considering the above variables, it was assessed that a minor consumer exposure could occur through migration of EPTAC to skin from paper used in ordinary copy

paper, newspapers and laminated paper used in children's books or via ingestion of food, which has been contaminated by EPTAC migrated from non-barrier cardboard food packages.

It was estimated that a small amount of EPTAC could migrate from office copy paper and newspapers to skin. The migration from paper to skin can be assumed to occur when the skin surface is moist or wet. However, the figures are based on estimates only since no migration studies are available. The daily skin exposure from copy papers was estimated to be 0.6 µg. In a 70 kg adult, assuming 6 % absorption, this would lead to a daily intake of about 0.0005 µg/kg/d. The exposure from newspapers is expected to be much lower because the amount of residue present in newsprint paper is many folds smaller.

Cationic starch may be used in thin laminated paper outer layer of children cover book to enhance their printing properties. Quantity is typically 0.3 g cationic starch/m^2 laminated paper. When assessing the exposure to children from booklets, the daily dose was estimated using assumptions of booklet size and the migration rates and a study by FDA (2000) according to which, the highest mouthing activity is among children of 6-12 months of age. Using a worst case estimate, EPTAC intake from children's books was estimated assuming a daily exposure of 0.025-0.05 µg/day. A typical weight range of a 6-12 months-old child is 7.5-9.9 kg. Assuming that all is ingested and 50 % is absorbed, a maximum daily intake of 0.0013-0.003 µg/kg/d is reached.

The migration from packages to food is expected to occur only when the food is partly (10 %) moistened. In worst case, up to 0.048 µg/kg EPTAC was expected become ingested in food via migration from packaging. In a 70-kg person with 50 % absorption, this would correspond to a dose of 0.0004 µg/kg bodyweight. This exposure source is considered to be occasional in nature, i.e., less than once a day in frequency. Average long-term exposure would be therefore 2 or 3 orders of magnitude lower that that presented above.

In cosmetics, cationised proteins as well as cationised guar, ginseng and dextran are used in products like shampoos, body wash, shower gel, hair care and skin care products. In all products the concentration of EPTAC is below 0.74 ppm. Using the application amount assumptions given in the revised TGD together with the maximum EPTAC content of 0.74 ppm, the daily dose of EPTAC on the skin is 0.5-20.7 µg, i.e. 0.007-0.29 µg/kg of b.w. Assuming 6 % absorption the actual daily dose would result to 0.0004-0.02 µg/kg. For rinse off products such as shampoos and shower gels, it can be roughly estimated that the dose is 100 times less, 0.004-0.2 ng/kg of b.w.

In conclusion, the highest exposure in consumer scenarios is from the cosmetic products which are left on the skin, 0.02 µg/kg/d.

Indirect exposure via the environment

EUSES modelling is used to calculate the potential indirect human exposure to EPTAC. The estimated concentration of EPTAC in drinking water is relatively high. The respective daily dose is higher than from any consumer product (see the chapter 4.1.1.2). The EUSES modelled estimated daily total dose from all local sources, including drinking water, fish, leaf crops, root crops, meat, milk and air is 2 ug/kg b.w. Assuming 50 % absorption, this results to an oral exposure of about 1 ug/kg b.w. The EUSES modelled estimate for regional exposure was about 30 times lower than the local value at 0.06 X 10^{-5} µg/kg bw/day.

4.1.3.2 Workers

In the work environment, there are three main scenarios, which have been considered: manufacture, loading/unloading and the use of EPTAC.

Table 4.19 Estimated reasonable worst case and typical daily systemic EPTAC doses per scenario

Scenario	Daily Exposure				Estimated Daily Dose (mg/kg)			
	Dermal (mg/d) (RWC)	Dermal (mg/d) (Typical)	Inhalation (mg/m^3) (RWC)	Inhalation (mg/m^3) Typical	Dermal (RWC)	Dermal (Typical)	Inhalation (RWC)	Inhalation (Typical)
Manufacture								
Sampling	150	15	-	-	0.13	0.013	-	-
Laboratory work	300	30	-	-	0.26	0.026	-	-
Maintenance	60	6	-	-	0.05	0.005	-	-
LOADING/ UNLOADING	30	3	0.04	-	0.02	0.002	0.004	-
Use (Wet cationising)								
Sampling	5	0.6	-	-	0.004	$5x10^{-4}$	-	-
			-	-			-	-
Laboratory work	10	1.3	-	-	0.009	0.001	-	-
Maintenance and Clean-up	3	0.3	-	-	0.003	$2.6x10^{-4}$	-	-
Filling	0.0006	$6x10^{-5}$	-	-	$5.1x10^{-6}$	$5.1x10^{-8}$	-	-
Use (Dry cationising or wet cationising with drying)								
Bagging (full shift)	0.01	0.00025	$8x10^{-5}$ ($1.35\ 10^{-5}$)	$6x10^{-5}$	$8.6x10^{-6}$	$2.1x10^{-7}$	$8.6x10^{-6}$ ($1.4x10^{-6}$)	$6.4x10^{-6}$
Clean-up (weekly)	0.01	0.00025	0.0008	$2x10^{-5}$	$8.6x10^{-6}$	$2.1x10^{-7}$	$8.6x10^{-5}$	$2.1x10^{-6}$
Laboratory work	0.006	0.0001	-	-	$5.1x10^{-6}$	$8.6x10^{-8}$	-	-
Sampling	0.003	$6x10^{-5}$	-	-	$2.6x10^{-6}$	$5.1x10^{-9}$	-	-
Maintenance (≤ 4 times per year)	0.01	$2.5x10^{-5}$	0.0008	$2x10^{-5}$	$8.6x10^{-6}$	$2.1x10^{-8}$	$8.6x10^{-5}$	$2.1x10^{-6}$

75 % absorption was assumed via the inhalation, 50 % via oral route and 6 % dermally, 70 kg body weight person, 8 h respiratory volume assumed 10 m^3, *Measured based on total dust, inhalable fraction (in parenthesis) used for dose calculation, ** Measured, as below detection limit value is half detection limit.

4.1.3.2.1 Acute toxicity

Acute toxicity

Only dermal and inhalation routes are relevant. Assuming dermal LD50 value of approximately 1500 mg/kg the resulting MOS for acute toxicity would be relatively high, over 16000 for the scenario with highest exposures, namely maintenance in manufacture. As even the highest daily inhalation dose is very small, acute toxicity via this route is not likely to be a problem. Using the value of 8.17 mg/l, at which no lethality was seen, a MOSs of over 200000 can be calculated for acute inhalation toxicity.

Table 4.20 Occupational risk assessment for acute toxicity

	Inhalation				Dermal			
	Exposure mg/m³	LC50 mg/m³	MOS	Conclusion	Exposure mg/kg/d	LD50 mg/kg	MOS	Conclusion
Production								
Sampling	-	8170	-	ii	0.13	1500	11538	ii
Laboratory work	-	8170	-	ii	0.26	1500	5769	ii
Maintenance	-	8170	-	ii	0.05	1500	30000	ii
Loading/ Unloading and sampling after loading	0.04	8170	204250	ii	0.03	1500	50000	ii
Use Wet cationising								
Sampling	-	8170	-	ii	0.004	1500	$4x10^5$	ii
Laboratory work	-	8170	-	ii	0.009	1500	$2x10^5$	ii
Maintenance	-	8170	-	ii	0.003	1500	$5x10^5$	ii
Filling	-	8170	-	ii	$5.1x10^{-7}$	1500	$3x10^9$	ii
Use Dry cationising or wet cationising with drying								
Bagging	0.00008	8170	$1x10^8$	ii	$8.6x10^{-6}$	1500	$2x10^8$	ii
Clean-up work	$8x10^{-4}$	8170	$1x10^7$	ii	$8.6x10^{-6}$	1500	$2x10^8$	ii
Laboratory work	-	8170	-	ii	$5.1x10^{-6}$	1500	$3x10^8$	ii
Sampling	-	8170	-	ii	$2.6x10^{-6}$	1500	$6x10^8$	ii
Maintenance work	$8x10^{-4}$	8170	$1x10^7$	ii	$8.6x10^{-6}$	1500	$2x10^8$	ii

4.1.3.2.2 Irritation and corrosivity

Eyes

At high concentrations (60-70%) EPTAC causes strong eye irritation in rabbits. The only scenarios where a worker is exposed to such concentrations are during manufacture and loading/unloading operations. In manufacture, the eye can be exposed through splashes when taking samples, laboratory work or maintenance if proper eye protection is not worn. Splashing may be possible also in the loading/unloading procedures. Eye irritation could also occur if a worker passes EPTAC from hands to eyes, e.g., when rubbing eyes. Although there is no information on the eye irritation properties of residual EPTAC in, for example, cationised starch, it is reasonable to assume that the quantity is so small that irritation will not occur. If good hygiene practise is in place and is followed at work place, no irritation is expected to occur. As EPTAC is classified as R41 (serious damage to eyes) leading to a warning label, this is expected to be a sufficient risk reduction measure and justification for no concern.

4.1.3.2.3 Sensitisation

Skin

EPTAC causes sensitisation in guinea-pigs. Human patch tests performed on workers in cationising plants demonstrated that workers who had been exposed to 50-70% EPTAC used in the cationising process had been sensitised. In these cases, contact with non-reacted chemical occurred during process sampling, laboratory work and from various contaminated sites and personal protective equipment in the work place. The patch test studies showed that EPTAC is a potent human sensitiser by skin contact. According to exposure assessment, tasks in EPTAC manufacture and loading and unloading operations in addition to cationising work might cause skin exposure. It has been shown that the proper use of personal protective equipment can effectively reduce dermatitis resulting from handling of EPTAC at the work place. However, if protective equipment is not used properly and conscientiously and appropriate work procedures are not followed, it is likely that sensitisation might be induced in the worker. Although proper personal protection use and work procedure might be in use in most of the plants handling EPTAC, there is no certainty that this is the situation of all plants in the EU. Conclusion iii is drawn in all worker scenarios.

4.1.3.2.4 Repeated dose toxicity

No NOAEL has been determined. The only study available concluded that in rat a LOAEL of 3.16 mg/kg/d was found after oral administration for 28 days, based on the degenerative effects in the kidney proximal tubules. Since the additive contribution of inhalation exposure to dermal dose is small, no separate MOSs are presented for the combined exposures. From the table it is evident that the lowest MOSs are in the manufacture and especially in laboratory work and sample taking. The estimate based on assumed 50% absorption via the oral route would be 1.6 mg/kg bw/day. For inhalation exposure, 75 % absorption is assumed. For the dermal exposure route, 6 % absorption is used. The absorption rate assumption is based on an *in vitro* experiment with CHPTAC using skin from one individual only, which still leaves some uncertainty and possibility for inter-individual variation.

For inhalation and dermal exposure the minimal MOS limit is calculated using a factor 10 for interspecies extrapolation and allometric scaling, factor 3 for intraspecies and a factor of 4 for subacute to chronic extrapolation resulting to a minimal MOS of 120. Based on these assumptions, the MOSs in the dermal exposure are quite low in production and formulation scenarios. Further uncertainty is cast on the margins of safety because they are based on a LOAEL rather than a NOAEL. For production and formulation scenarios, doses and their representative MOSs have been calculated using typical concentrations in addition as predicted by EUSES. Based on the comparison of the measured and EASE estimated exposures, it appears that EASE tends to slightly over estimate the exposure in most cases. Moreover, the fact that maintenance is a task which is incidental in nature, it seems reasonable to assume that repeat dose toxicity would not be a concern for that particular scenario. Equally, exposure during loading and unloading, exposure is likely to occur only shortly during connecting and disconnecting the pipes. Although the minimal MOS of 120 is not reached these two scenarios, due to their incidental nature they are not considered a concern for this end point.

Table 4.21 Occupational risk assessment for repeated dose toxicity

	Inhalation				Dermal			
	Exposure mg/kg/bw/d	LOAEL mg/kg/bw/d	MOS	Conclusion	Exposure mg/kg/d	LOAEL mg/kg/bw/d	MOS	Conclusion
Production								
Sampling	-	1.58	-	ii	0.13 (0.013)	1.58	12 (120)	iii
Laboratory work	-	1.58	-	ii	0.26 (0.026)	1.58	6 (60)	iii
Maintenance	-	1.58	-	ii	0.05 (0.005)	1.58	32 (320)	ii
Loading/ Unloading and sampling after loading	0.001	1.58	1580	ii	0.02 (0.002)	1.58	79 (790)	ii
Use Wet cationising								
Sampling	-	1.58	-	ii	0.004	1.58	395	ii
Laboratory work	-	1.58	-	ii	0.009	1.58	176	ii
Maintenance	-	1.58	-	ii	0.003	1.58	527	ii
Filling	-	1.58	-	ii	5.1×10^{-7}	1.58	3×10^{6}	ii
Use Dry cationising or wet cationising with drying								
Bagging	1.4×10^{-6}	1.58	1.1×10^{-5}	ii	8.6×10^{-6}	1.58	2×10^{5}	ii
Clean-up work	8.6×10^{-5}	1.58	18433	ii	8.6×10^{-6}	1.58	2×10^{5}	ii
Laboratory work	-	1.58	-	ii	5.1×10^{-6}	1.58	3×10^{5}	ii
Sampling	-	1.58	-	ii	2.6×10^{-6}	1.58	6×10^{5}	ii
Maintenance work	8.6×10^{-5}	1.58	18433	ii	8.6×10^{-6}	1.58	2×10^{5}	ii

Oral LOAEL is used for the MOS calculation of inhalation and dermal toxicity with the assumption of 50 % gastro-intestinal absorption. In the calculation of the internal dose entering via inhalation, 75 % i absorption, 70 kg body weight person, 8 h respiratory volume assumed 10 m^3, were assumed.. Figures in parenthesis represent typical concentrations.

4.1.3.2.5 Mutagenicity

EPTAC is mutagenic. No threshold dose can be determined for mutagenic events. Conclusion iii is drawn in all worker scenarios.

4.1.3.2.6 Carcinogenicity

EPTAC caused an increased incidence of skin tumours in mice of both sexes when they where applied topically 1 % solution of the substance (~50 mg/kg/application). There is an indication that EPTAC could also cause some systemic tumours (e.g. lung or mammary tumours) when applied to mouse skin as a 1 % solution, but the relevance of these tumours is uncertain. Because EPTAC is a mutagen, the mode of action of the tumour formation is presumed not to have a threshold. Although not used in the risk characterisation, a calculation using threshold dose is included in Appendix 1. A BMD0.1 (5d) of 9.7 mg/kg bw (malignant and benign tumours combined) can be used to calculate a MOE (Margin of Exposure) based on benchmark dose.

These figures can be used to give an idea of the difference of magnitude of risk between scenarios. From the BMD calculations, it can be seen that, e.g., dry cationising scenarios seem to present a clearly lower risk than others. The most important carcinogenic endpoint is the local skin carcinogenicity. The external dose is compared to the external exposure estimate for the dermal MOE calculation. For a possible systemic tumorigenicity the Benchmark dose derived using the systemic dose calculated with the skin absorption data can be compared with the systemic dose calculated for dermal exposure with the respective "worst case" human dermal absorption of 6%. However, the systemic tumorigenicity of EPTAC is unclear and the evidence is equivocal. The lowest $BMD_{0.1}$ was derived for lung tumours in female rats the BMD was 14 mg/kg bw per week or 2.8 mg/kg bw per day, with 5 days of exposure, or 2 mg/kg bw per day with 7 days of exposure. The corresponding $BMDL_{95}$ values were 10.7 mg/kg bw/week, 2.1 (5 d) or 1.5 (7d) mg/kg bw per day. The relative high AICs and variation between the model, as well as the fact that the predicted tumour rates are very close to the expected rates, is in accordance with the equivocal evidence for an increase in lung tumours. The same is true for mammary tumours in female mice. EPTAC is classified as Carc. Cat 2; R45. Conclusion iii is drawn in all worker scenarios.

Table 4.22 Occupational risk assessment for carcinogenicity

	Inhalation				Dermal			
	Exposure mg/kg/bw/d	LOAEL mg/kg/bw/d (systemic tumour $BMD_{0.1}$ mg/kg/bw/d)	MOE	Conclusion	Exposure mg/kg/d (external)	LOAEL (skin tumor $BMD_{0.1}$ mg/kg/bw/d)	MOE	Conclusion
Production								
Sampling	-	2.8	-	ii	2.1	9.8	*[5]*	iii
Laboratory work	-	2.8	-	ii	4.2	9.8	*[2]*	iii
Maintenance	-	2.8	-	ii	0.9	9.8	*[11]*	iii
Loading/ Unloading and	0.001	2.8	*[2800]*	iii	0.4	9.8	*[25]*	iii

sampling after loading								
Use Wet cationising								
Sampling	-	2.8	-	ii	0.07	9.8	*[140]*	iii
Laboratory work	-	2.8	-	ii	0.14	9.8	*[70]*	iii
Maintenance	-	2.8	-	ii	0.04	9.8	*[245]*	iii
Filling	-	2.8	-	ii	$8.6x10^{-6}$	9.8	*[$1x10^{6}$]*	iii
Use Dry cationising or wet cationising with drying								
Bagging	$1.4x10^{-6}$	2.8	*[$2x10^{6}$]*	iii	$1.4x10^{-4}$	9.8	*[$7x10^{4}$]*	iii
Clean-up work	$8.6x10^{-5}$	2.8	*[32558]*	iii	$1.4x10^{-4}$	9.8	*[$7x10^{4}$]*	iii
Laboratory work	-	2.8	-	ii	$1.4x10^{-5}$	9.8	*[$7x10^{5}$]*	iii
Sampling	-	2.8	-	ii	$4.3x10^{-5}$	9.8	*[$2x10^{5}$]*	iii
Maintenance work	$8.6x10^{-5}$	2.8	*[32558]*	iii	$1.4x10^{-4}$	9.8	*[$7x10^{4}$]*	iii

Table 4.22 continued

	Dermal (systemic)			
	Exposure mg/kg/d (external)	(systemic tumour $BMD_{0.1}$ mg/kg/bw/d	MOE	Conclusion
Production				
Sampling	0.13	2.8	*[22]*	iii
Laboratory work	0.26	2.8	*[11]*	iii
Maintenance	0.05	2.8	*[56]*	iii
Loading/ Unloading and sampling after loading	0.03	2.8	*[93]*	iii
Use Wet cationising				
Sampling	0.004	2.8	*[700]*	iii
Laboratory work	0.009	2.8	*[311]*	iii
Maintenance	0.003	2.8	*[933]*	iii
Filling	$5.1x10^{-6}$	2.8	*[$5x10^{5}$]*	iii
Use Dry cationising or wet cationising with drying				
Bagging	$8.5x10^{-6}$	2.8	*[$3x10^{5}$]*	iii
Clean-up work	$8.5x10^{-6}$	2.8	*[$3x10^{5}$]*	iii
Laboratory work	$5.1x10^{-6}$	2.8	*[$5x10^{5}$]*	iii
Sampling	$2.6x10^{-6}$	2.8	*[$1x10^{6}$]*	iii
Maintenance work	$8.5x10^{-6}$	2.8	*[$3x10^{5}$]*	iii

4.1.3.2.7 Toxicity for reproduction

There are no studies on reproductive toxicity, but the results seen in the 28-day study were used to set a NOAEL of 10 mg/kg on effects to reproductive organs based on morphological changes to the organs at dose of 31.6 mg/kg/d. Assuming 50 % oral absorption an internal NOAEL of 5 mg/kg will be used to compare the exposures from inhalation and dermal route. When compared to the level of exposure in worst case occupational exposure scenario (production: laboratory work), a MOS of 233 is obtained. However, as the NOAEL is based on only on microscopical observations of relatively short study repeated dose toxicity, it can only be indicative of the dose level where toxicity to fertility could occur. Because generalised toxicity was seen already at the lowest dose, it can be difficult to draw conclusion on the specific toxicity to reproduction. This would normally warrant further investigation of EPTAC's properties as a reproductive toxicant. According to the revised TGD there would be a need to further investigate the reproductive toxicity in a 2-generation fertility test and a developmental toxicity test. However, since EPTAC is a genotoxic carcinogen, this property alone is sufficient to lead the strictest measures for risk management in work places. Therefore, *conclusion i on hold* is drawn for all scenarios. EPTAC is classified as Repro. Cat 2; R68.

Effects on fertility

Table 4.23 Occupational risk assessment for reproductive toxicity

	Inhalation				Dermal			
	Exposure mg/kg/bw/d	NOAEL mg/kg/bw/d	MOS	Conclusion	Exposure mg/kg/d	NOAEL mg/kg/bw/d	MOS	Conclusion
Production								
Sampling	-	5.0	-	i on hold	0.13	5.0	38	i on hold
Laboratory work	-	5.0	-	i on hold	0.26	5.0	19	i on hold
Maintenance	-	5.0	-	i on hold	0.05	5.0	100	i on hold
Loading/ Unloading and sampling after loading	0.001	5.0	5000	i on hold	0.02	5.0	250	i on hold
Use Wet cationising								
Sampling	-	5.0	-	i on hold	0.004	5.0	1250	i on hold
Laboratory work	-	5.0	-	i on hold	0.009	5.0	556	i on hold
Maintenance	-	5.0	-	i on hold	0.003	5.0	1667	i on hold
Filling	-	5.0	-	i on hold	5.1×10^{-6}	5.0	1×10^{6}	i on hold
Use Dry cationising or wet cationising with drying								
Bagging	1.4×10^{-6}	5.0	3.6×10^{6}	i on hold	8.6×10^{-6}	5.0	6×10^{5}	i on hold
Clean-up work	8.6×10^{-5}	5.0	58140	i on hold	8.6×10^{-6}	5.0	6×10^{5}	i on hold
Laboratory work	-	5.0	-	i on hold	5.1×10^{-6}	5.0	1×10^{6}	i on hold
Sampling	-	5.0	-	i on hold	2.6×10^{-6}	5.0	2×10^{6}	i on hold
Maintenance work	8.6×10^{-5}	5.0	58140	i on hold	8.6×10^{-6}	5.0	6×10^{5}	i on hold

Oral NOAEL is used for inhalation with the assumption of 50 % absorption by the oral route.

Developmental toxicity

No data is available for the evaluation of developmental toxicity. Conclusion i on hold is drawn.

4.1.3.2.8 Summary of risk characterisation for workers

Table 4.24 Overview of the conclusions with respect to occupational risk characterisation

		Acute toxicity		Sensitisation	Repeated dose toxicity Systemic		Muta genicity	Carcinogenicity (MOE skin)	Reproductive toxicity
		Dermal	Inhalation		Dermal	Inhalation			
Production									
Sampling	MOS	11538	-	-	12	-	-	*[5]*	38
	Concl.		ii	iii	iii	ii	iii	iii	i on hold
Laboratory work	MOS	5769	-	-	6	-	-	*[2]*	19
	Concl.		ii	iii	iii	ii	iii	iii	i on hold
Maintenance	MOS	30000	-	-	32	-	-	*[11]*	100
	Concl.		ii	iii	ii	ii	iii	iii	i on hold
Loading/ Unloading and sampling after loading	MOS	50000	204250	-	79	1580	-	*[25]*	167
	Concl.	ii	ii	iii	ii	ii	iii	iii	i on hold
Use: Wet cationising									
Sampling	MOS	$4x10^5$	-	-	395	-	-	*[140]*	1250
	Concl.	ii	ii	iii	ii	ii	iii	iii	i on hold
Laboratory work	MOS	2x105	-	-	176	-	-	*[70]*	556
	Concl.	ii	ii	iii	ii	ii	iii	iii	i on hold
Maintenance	MOS	$5x10^5$	-	-	527	-	-	*[245]*	1667
	Concl.	ii	ii	iii	ii	ii	iii	iii	i on hold
Filling	MOS	$3x10^9$	-	-	$3x10^5$	-	-	*[$1x10^6$]*	$1.0x10^6$
	Concl.	ii	ii	iii	ii	ii	iii	iii	i on hold
Use: Dry cationising or wet cationising with drying									
Bagging	MOS	$2x10^8$	$8x10^6$	-	$2x10^5$	14364	-	*[$7x10^4$]*	$6x10^5$
	Concl.	ii	ii	iii	ii	ii	iii	iii	i on hold
Clean-up work	MOS	$2x10^8$	$1x10^7$	-	$2x10^5$	18433	-	*[$7x10^4$]*	$6x10^5$
	Concl.	ii	ii	iii	ii	ii	iii	iii	i on hold
Laboratory work	MOS	$3x10^8$	-	-	$3x10^5$	-	-	*[$7x10^5$]*	$1x10^6$
	Concl.	ii	ii	iii	ii	ii	iii	iii	i on hold
Sampling	MOS	$5x10^8$	-	-	$6x10^5$	-	-	*[$2x10^5$]*	$2x10^6$
	Concl.	ii	ii	iii	ii	ii	iii	iii	i on hold

Maintenance work	MOS	$2x10^8$	$1x10^7$	-	$2x10^5$	18433	-	*[$7x10^4$]*	$6x10^5$
	Concl.	ii	ii	**iii**	ii	ii	**iii**	**iii**	ii

4.1.3.3 Consumers

Exposure is negligible in all consumer scenarios. For this reason, only the scenario with the highest exposure, resulting from the use of cosmetics, which are left on the skin, is considered in the acute section, including irritation, sensitisation and repeat dose and reproductive toxicity. Although conclusion i would be implied for reproductive toxicity, conclusion ii on is drawn due to very negligible exposure.

Table 4.25. Internal consumer exposure to EPTAC

Product	Scenario	Internal dose µg/kg bw
Food packaging	Transfer to product from wet packaging	$6x10^{-7}$
Children's books	Small children chewing a book, which can lead to ingestion or skin exposure.	0.003*
Copy paper and news papers	Skin exposure from paper surface.	$5.4x10^{-4}$
Cosmetics	EPTAC residues in cosmetic products expose skin and scalp. Rinse-off products	$4.2x10^{-4}$-0.017 $4.2x10^{-6}$ – $1.7x10^{-4}$

6% dermal absorption, 50% oral absorption assumed, assumed all is ingested

4.1.3.3.1 Acute toxicity

When compared to the oral and dermal acute toxicity LD50 of 1500000 µg/kg, the daily worst case exposure of approximately 0.017 µg/kg/d is negligible.

4.1.3.3.2 Irritation and corrosivity

Eye

No exposure to eyes is expected in amounts, which would cause eye irritation.

4.1.3.3.3 Sensitisation

Skin

Although setting a threshold for sensitisation is difficult it is probable that sensitisation from the minute residual EPTAC in consumer products would not occur.

4.1.3.3.4 Repeated dose toxicity

Assuming 6 % dermal penetration the exposures via dermal routes are expected to be negligible, considering the very low levels of EPTAC in cationic starch as residues. The worst case consumer exposure was expected to occur to cosmetic products that are left on the skin. With a daily dose 0.017 µg/kg/d and an internal LOAEL of 1580 µg/kg a MOS of about 93000 is obtained.

4.1.3.3.5 Mutagenicity

Exposure caused by food packaging materials and copy paper is assessed to be very low. Consumer is occasionally exposed to a few nanograms of EPTAC per kg of body weight. This is roughly six orders of magnitude less than the effective dose in carcinogenicity study. It is recognised that similar residue levels of mutagenic substances are likely to occur in many consumer products.

4.1.3.3.6 Carcinogenicity

EPTAC is a genotoxic carcinogen for which no NOAEL can be determined. The cancer risk from consumer sources is considered minimal. A LOAEL defined by the $BMD_{0.1}$ for skin tumours (9800 mg/kg/bw/d) or the lowest systemic $BMD_{0.1}$ LOAEL (2800 ug/kg/bw/d) can be used to give a theoretical description of the risk magnitude. See table for MOS values.

4.1.3.3.7 Toxicity for reproduction

Effects on fertility

There are no studies on reproductive toxicity. A NOAEL for gonad toxicity was seen in at an internal NOAEL of 5000 µg/kg/d from the 28-day study with EPTAC, when 50 % oral absorption was assumed. The maximum daily consumer internal dose was estimated at 0.017 µg/kg/d. This leads to a MOS of over 290000. Although a 28-day study cannot be used to draw conclusions about reproductive toxicity itself, it is considered that the level of exposure is negligible to warrant concern.

Although no studies are available, due to currently negligible exposure to the consumers, *conclusion ii on hold* is drawn.

Developmental toxicity

No studies are available to evaluate developmental toxicity. No studies are available to evaluate developmental toxicity. Based on animal welfare reasons, it is not considered necessary to perform further testing for this end-point for purposes of this risk assessment.

Although no studies are available, due to currently negligible exposure to the consumers, *conclusion ii on hold* is drawn.

4.1.3.3.8 Summary of risk characterisation for consumers

Table 4.26. Summary of risk characterisation for consumers

		Acute toxicity		Sensitisation	Repeated dose toxicity Systemic		Mutagenicity	Carcinogenicity	Reproductive toxicity
		Dermal	Inhalation		Dermal	Inhalation			
Food packages	MOS	Acute toxicity is not		-	Lowest MOS found in		-	*[4.6x10^9]*	Lowest

	Concl.	relevant in consumer exposure scenarios due to very low exposure. Conclusion ii in all scenarios.	ii	cosmetics scenario: MOS of 93000. Conclusion ii in all scenarios.	**ii**	**ii**	MOS found in cosmetics scenario: MOS of 290000. Conclusion i on hold in all scenarios.
Children's books	MOS		-		**-**	*[9.3x10^5]*	
	Concl.		ii		**ii**	**ii**	
Copy paper & newspapers	MOS		-		**-**	*[1.8x10^7]*	
	Concl.		ii		**ii**	**ii**	
Cosmetics	MOS		-		**-**	*[5.7x10^5]*	
	Concl.		ii		**ii**	**ii**	

4.1.3.4 Humans exposed via the environment

The local scenario, which refers to processing plants (i.e. cationisation of starch) results in much higher environmental concentrations and daily doses than the regional scenario.

The same end points are considered relevant as for the consumer scenario. The MOSs are presented only in form of a summary table (4.27).

4.1.3.4.1 Exposure via air

Daily external exposure via air is estimated about $2.5x10^{-3}$ ug/kg, which is only a fraction of the total indirect exposure. Contribution from this scenario to the total indirect exposure is considered negligible.

4.1.3.4.2 Exposure via food and water

EUSES was used to calculate the potential indirect human exposure to EPTAC.
Total indirect external exposure to EPTAC is about 2 ug/kg b.w of which leaf crops and drinking water are the major individual sources of exposure. The total regional exposure was estimated to be about $0.06x10^{-5}$ ug/kg. In calculation of internal doses, absorption of 50 % from the gastro-intestinal tract is assumed.

In the summary table 4.27, a total internal exposure of 1 ug/kg b.w. is used to calculate the MOSs for indirect exposure against an internal LOAEL of 1580 ug/kg. For the carcinogenicity MOS, lowest systemic $BMD_{0.1}$ LOAEL (2800 ug/kg/bw/d) was used. For the calculation of MOS for reproductive toxicity, an internal NOAEL of 5000 ug/kg was used, based on the effects seen the rat gonads at after 28-d repeated dose. No MOS figures were calculated for regional values, because the exposure figures are about 1/30th of the local values, which were not considered a concern.

4.1.3.4.3 Summary of risk characterisation for exposure via the environment

Based on the calculations, drinking water appears to be the greatest source of exposure. Although the modelled exposure figure is likely to be an overestimate, risks can not be completely excluded as the substance EPTAC is identified as a non-threshold carcinogen thus Conclusion (iii) is drawn for mutagenicity and carcinogenicity. However, the risk assessment indicates that risks are already very low.

Table 4.27. Summary of risk characterisation for indirect exposure all exposures combined

		Acute toxicity		Sensitisation	Repeated dose toxicity Systemic		Mutagenicity	Carcinogenicity	Reproductive toxicity
		Dermal	Inhalation		Dermal	Inhalation			
Combined indirect exposure	MOS	Acute toxicity is not relevant in indirect exposure scenarios due to very low exposure. Conclusion ii.		-	MOS of 1580		-	*[2800]*	MOS of 5000. Conclusion i on hold.
	Concl.			ii	Conclusion ii in all scenarios.		iii	iii	

4.1.3.5 Combined exposure

Not conducted because of negligible impact on human health from combined exposure.

4.2 HUMAN HEALTH (PHYSICO-CHEMICAL PROPERTIES)

4.2.1 Exposure assessment

See chapter 4.1.

4.2.2 Effects assessment: Hazard identification

4.2.2.1 Explosivity

EPTAC is not explosive.

4.2.2.2 Flammability

EPTAC is highly flammable as a pure powder but is sold in water solution which is not flammable.

4.2.2.3 Oxidizing potential

EPTAC is not oxidising.

4.2.3 Risk characterisation

4.2.3.1 Workers

Flammability is not a concern because EPTAC is normally handled as a 50-70% water solution. Conclusion ii is drawn.

4.2.3.2 Consumers

EPTAC is not sold to consumer. Conclusion ii.

4.2.3.3 Humans exposed via the environment

Not relevant.

5 RESULTS [6]

5.1 ENVIRONMENT

Conclusions for the aquatic compartment (including marine environment):

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies to surface water and sediment from cationisation of starch with wet process (Industrial use scenario 1) at local scale for 5 sites (i.e. sites B4, B9, B10, B23 and B25).

From these five starch cationisation sites, which have risk ratio higher than one, two sites (B4, B25) have monitoring data on EPTAC releases to waste water. The detection limit of EPTAC from waste water effluent (0.7-10 mg/l) is rather high compared to PNEC (0.016 mg/l). Use of lower detection limit might decrease risk from these two sites. For those three sites where no monitoring data is available (B9, B10, B23), releases have been calculated with an actual emission factor from a starch cationisation site with highest release factor (1.32 %). Biodegradation at the WWTP has been assumed to take place at these sites.

The PNEC for water and sediment has been calculated from the chronic NOEC for Daphnia using an assessment factor of 10. Refinement of PNEC is therefore not possible with the dataset currently available.

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to fresh water and sediment from production of EPTAC and cationisation of starch with dry process for seven sites (B6, B11, B12, B13, B15, B22 and B28) and with wet process for seven sites (B3, B5, B14, B16, B17, B18 and B21) (Industrial use 1). Conclusion (ii) also applies to paper and board scenario (Industrial use 2), paper recycling (Industrial use 3), AKD formulation (Industrial use 4) and other uses of CHPTAC and EPTAC (Industrial use 5). Conclusion applies also to waste water treatment plants and marine environment from all scenarios.

Conclusions for atmosphere and terrestrial compartment:

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion applies to production and all use scenarios.

[6] Conclusion (i) There is a need for further information and/or testing.
Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.
Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

5.2.1.1 Workers

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account.

Conclusion (iii) applies all worker exposure scenarios because of concerns for mutagenicity, carcinogenicity and sensitisation.

Conclusion (iii) also applies in relation to concerns from repeat dose toxicity for sampling and laboratory work during production of EPTAC.

Conclusion (i) There is a need for further information and/or testing.

There is a need to further investigate the reproductive toxicity in a 2-generation fertility test and a developmental toxicity test. However, since EPTAC is a genotoxic carcinogen, this property alone is sufficient to lead to the strictest measures for risk management in work places. Therefore, ***conclusion i on hold*** is drawn for all scenarios.

5.2.1.2 Consumers

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all scenarios since exposure to consumers is considered to be negligible.

5.2.1.3 Humans exposed via the environment

Conclusion (iii) There is a need for limiting the risks; risk reduction measures which are already being applied shall be taken into account..

Although the modelled exposure figure is likely to be an over estimate, risks can not be excluded as the substance EPTAC is identified as a non-threshold carcinogen thus Conclusion (iii) is drawn for mutagenicity and carcinogenicity. However, the risk assessment indicates that risks are already very low. This should be taken into account when considering the adequacy of existing controls and the feasibility and practicability of further specific risk reduction measures.

5.2.1.4 Combined exposure

Combined exposure was not assessed because of low additional impact to human health.

5.2.2 Human health (risks from physico-chemical properties)

Conclusion (ii) There is at present no need for further information and/or testing and no need for risk reduction measures beyond those which are being applied already.

Conclusion (ii) applies to all scenarios.

6 REFERENCES

BERQVIST-KARLSSON, A. (1995). Contact allergy to glycidyl trimethyl ammonium chloride. *Contact Dermatitis*, **12,** 61-62.

BRIDIÉ, A.L., WOLFF, C.J.N. & WINTER, M. (1979). Bod and cod of some petrochemicals. *Water Research*, **13,** 627-630.

CEFIC (1997a). 2,3-Epoxypropyltrimethylammonium chloride E97/056, Vapour Pressure. pp. 7. Frankfurt am Main: Hoechst.

CEFIC (2006). (3-chloro-2-hydroxypropyl) trimethylammonium chloride (CHPTAC) Simulation test – Aerobic Sewage Treatment – Porous Pot. : CEFIC QUAS Sector Group Testing Facility: Dr. U. Noack-Laboratorien. Study No. APP100501.

CEFIC (2003). Adsorption of EPTAC on Activated Sludge - Batch Test. Final Report. Test Facility: Institut für Biologische Analytik und Consulting IBACON GmbH, Rossdorf, Germany. Project 17391198. 24 p.CEFIC QUAS Sector Group 2003b. 2,3-Epoxypropyltrimethylammoniumchloride. Determination of the growth inhibition of the green algae Desmodesmus subspicatus. (Alga, Growth Inhibition Test). Test Facility: Infracor Chemistry Services. Final report AW 502. pp. 24. Rossdorf, Germany: Institut für Biologische Analytik und Consulting IBACON GmbH.

CEFIC (1998d). Confidential information on consumption volumes and end-uses of EPTAC and CHPTAC. Confidential letter 1998 ed. Institute, F.E. Helsinki.

CEFIC (2000a). Confidential letter from Rene Montaigne on production, import and export volumes of EPTAC and CHPTAC. Confidential letter 8 August 2000 ed. Institute, F.E. Helsinki.

CEFIC (1998b). Determination of the abiotic Degradation of (3-Chloro-2-hydroxypropyl) trimethylammonium chloride – Hydrolysis as a Function of pH. Test Facility: Clariant GmbH – Werk Cassella-Offenbach, Frankfurt am Main, Germany. In *Report No. B 064/97*. pp. 18: CEFIC European Chemical Industry Council

CEFIC (1997b). Determination of the Explosive Properties of 2,3-Epoxypropyltrimethylammonium chloride in accordance with EEC-Guideline A.14. Test Facility: Clariant GmbH – Werk Cassella-Offenbach, Frankfurt am Main, Germany. pp. 10. Bruxelles: CEFIC.

CEFIC (1997c). Determination of the Flammability of 2,3-Epoxypropyltrimethylammonium chloride in accordance with EEC-Guideline A.10. Test Facility: Clariant GmbH – Werk Cassella-Offenbach, Frankfurt am Main, Germany. pp. 9. Bruxelles: CEFIC.

CEFIC (1997d). Determination of the Melting Point of 2,3-Epoxypropyltrimethylammonium chloride in accordance with EEC-Guideline A.1. Test Facility: Clariant GmbH – Werk Cassella-Offenbach, Frankfurt am Main, Germany. pp. 12. Bruxelles.

CEFIC (1998a). Determination of the Partition Coefficient (Octanol/Water) of 2,3-Epoxypropyltrimethylammonium chloride in accordance with EEC-Guideline A.8. Test Facility: Clariant GmbH – Werk Cassella-Offenbach, Frankfurt am Main, Germany. pp. 14. Bruxelles: CEFIC.

CEFIC (1997e). Determination of the Relative Density of 2,3-Epoxypropyltrimethylammonium chloride in accordance with EEC-Guideline A.3. Test Facility: Clariant GmbH – Werk Cassella-Offenbach, Frankfurt am Main, Germany. pp. 11. Bruxelles: CEFIC.

CEFIC (1997f). Determination of the Self-Ignition Temperature of 2,3-Epoxypropyltrimethylammonium chloride in accordance with EEC-Guideline A.16. Test Facility: Clariant GmbH – Werk Cassella-Offenbach, Frankfurt am Main, Germany. pp. 10. Bruxelles: CEFIC.

CEFIC (1997g). Determination of the Surface Tension of 2,3-Epoxypropyltrimethylammonium chloride in accordance with EEC-Guideline A.5. Test Facility: Clariant GmbH – Werk Cassella-Offenbach, Frankfurt am Main, Germany. pp. 12. Bruxelles: CEFIC.

CEFIC (1997h). Determination of the Water Solubility of 2,3-Epoxypropyltrimethylammonium chloride in accordance with EEC-Guideline A.6. Test Facility: Clariant GmbH – Werk Cassella-Offenbach, Frankfurt am Main, Germany. pp. 11. Bruxelles: CEFIC.

CEFIC (2000b). Risk Assessment. Substance name (3-Chloro-2-hyroxypropyl) trimethylammonium chloride. Includes confidential attachment on PEC local calculations. Draft of 8.5.2000: CEFIC QUAS Sector Group.

CEFIC, Q.S.G. (2002). (3-Chloro-2-hydroxypropyl)trimethylammoniumchloride - Determination of the inhibition of activated sludge respiration. Test Facility: Infracor Chemistry Services. In *Final report BH-02/08*. pp. 16.

CEFIC, -.Q.S.G. (2000). Risk Assessment. Substance name 2,3-Epoxypropyltrimethylammonium chloride. Revised draft of 4.12.2000.

CEFIC, Q.S.G.D. (1998c). Study on the inherent biodegradability of 2,3-Epoxypropyltrimethylammonium chloride according to OECD Guideline 302B (Zahn-Wellens/EMPA Test). Test Facility: Institut Fresenius, Study number IF-97/23704-00. 20.1.1998.: Institut Fresenius.

CEPI (2004). Paper Production and Production Capacity. Annual Statistics 2004

DEAN, B.J. & BROOKS, T.M. (1978). Toxicity studies with glycidyl trimethyl ammonium chloride (GMAC): In vitro mutation studies. London: Shell research limited.

DEAN, B.J., BROOKS, T.M., HODSON-WALKER, G. & HUTSON, D.H. (1985). Genetic toxicology testing of 41 industrial chemicals. *Mutation Research*, **153,** 57-77.

DEGUSSA (1987a). The acute toxicity of QUAB 169 to Brachydanio rerio. In *TNO-report no. R 87/325. Degussa AG - US-IT - nr. 87/0169/DGO*. pp. 17: Degussa AG, Netherlands organization for applied scientific research, TNO Division of Technology for Society.

DEGUSSA (1987b). The acute toxicity of QUAB 169 to Daphnia Magna. pp. 17: Netherlands organization for applied scientific research, TNO Division of Technology for Society.

DEGUSSA (1986a). Akute töxizität - Prüfung der Reizung nach einmaliger Applikation am Auge des Kaninchens. pp. 13. Hanau, Germany: Asta-Werke AG, Chemische Fabrik, Toxikologie Degussa-Asta.

DEGUSSA (1981a). Determination of the acute oral toxicity of glycidyltrimethylammoniumchloride (G.MAC) in rats: TNO, Netherlands organization for applied scientific research.

DEGUSSA (1988c). Determination of the biodegradability of Quab 169 according to OECD 301E (Modified OECD screening test): Degussa AG.

DEGUSSA (1988). Effect of QUAB 151 on the dehydrogenase activity of active sludge (TTC-test). TNO.

DEGUSSA (1988d). The effect of QUAB 169 on the growth of the Bacterium Pseudomonas putida. TNO Division of Technology for Society. pp. 16: Degussa AG.

DEGUSSA (1981b). Flammpunkte vom G-MAC 70 %ig und G-MAC 75 %ig (automatischer flammpunktprüfer). pp. 1: Degussa.

DEGUSSA (1981c). Primary skin irritation test with glycidyltrimethylamoiniumchloride (G-MAC) in albino rabbits: Netherlands organization for applied scientific research (TNO).

DEGUSSA (1991a). "Quab 151" Bestimmung des Kohlenstoffgehaltes (TC, TAC, TOC), des chemischen Sauertoffbedarfs (CSB) und des biochemischen Sauerstoffbedarfs nach 25 Tagen (BSB_{25}): Degussa AG.

DEGUSSA (1990). Quab 151, Evaluation of the 4-week oral toxicity study after repeated daily administration in the rats and a subsequent 4-week recovery period: Degussa AG.

DEGUSSA (1985). Quab 151, Prüfung der Ätz-/Reizwirkung nach einmalinger Applikation an der Haut des Kaninchens (Patch-Test): Degussa AG.

DEGUSSA (1992). Quab 188, Mouse Micronucleus Test (Single Intraperitoneal Administration). pp. 1-29: ASTA Medica AG.

DEGUSSA (1986b). Quab, Bestimmung des TOC, CSB, BSB_5, der biol. Abbaubarkeit und Bakteientoxizität etc.: Degussa AG.

DEGUSSA (1984). Salmonella/mammalian-microsome mutagenicity test with Quab 188: Research & Consulting Company AG.

DEGUSSA (1981d). Sensitization test with glycidyltrimethylammoniumchloride (G-MAC) in guinea pigs: Netherlands organization for applied scientific research.

DEGUSSA, A. (1991b). Algenwachstumshemmtest (Clorella vulgaris) mit QUAB 151 (2,3-epoxypropyl-trimethylammoniumchlorid).

DOAK, S. (1983). A Two Year Cutaneous Cancer Study with G-MAC in CFI Mice. Sittingbourne: Shell Research Ltd.

DOW (1984). 8EHQ-1283-0503 3-chloro -2-hydroxypropyltrimethylammonium chloride: The Dow chemical company.

DOW CHEMICAL COMPANY (1996). Evaluation of the acute toxicity of QUAT 188, QUAT 188 Diol and QUAT 188 epoxide to the daphnid, Daphnia magna straus. In *R & D Report, Health and Environmental Sciences the Dow Chemical Company. File number ES-3143. DR number 0060-5505, 0186-1945.*: Dow Chemical Company.

ELLIOTT, P.H. & SEABER, J.A. (1979). Screening test for delayed contact hypersensitivity with OGT AC-85 (Ref. No. MB 8953 R) in the albino guinea-pig: Huntingdon Research Centre.

ESTLANDER, T., JOLANKI, R. & KANERVA, L. (1997). Occupational allergic contact dermatitis from 2,3-epoxypropyl trimethyl ammonium chloride (EPTMAC) and Kathon^{R} LX in a starch modification factory. In *Contact Dermatitis*. pp. 191-194.

ESTLANDER, T., JOLANKI, R. & KANERVA, L. (1986). Occupational dermatitis to 2,3-epoxypropyl trimethyl ammonium chloride. *Contact Dermatitis*, **14,** 49-52.

HANSEN, O.C. (1993). Ecotoxicological evaluation of Chlormequat-chloride. pp. 102: Danish Technological Institut, Environmental Technology.

HELLWIG, G., BISCHOFF, A. & RUBO, A. (1992). Production of cationic starch ethers using an improved dry process. *Die Stärke*, **44,** 69-74.

JOLANKI, R. (1991). *Occupational skin diseases from epoxy compounds*.

NEIMO, L. (1999). Papermaking science and technology - Book 4: Papermaking chemistry. pp. 329. Helsinki: Fapet Oy, Published in cooperation with the Finnish Paper Engineers' Association and TAPPI.

QUAS (2000a). 2,3-epoxypropyltrimethylammonium chloride risk assessment - exposure questionnaire for users. Compilation of 11 questionnaires received in return.

QUAS (2004c). 2001 Volumes by Derivatives and by End-Uses. Confidential letter on 5 October 2004.

QUAS, Q.O.S.P.A. (2004b). (3-Chloro-2-hydroxypropyl) trimethylammonium chloride (CHPTAC) – Daphnia magna Reproduction Test (semi-static, 21d) according to OECD Guideline 211 for Testing of Chemicals: QUAS (Quaternisation of Starch Producers Association). Dr.U.Noack-Laboratorien (Study no. DRE97211).

QUAS, Q.O.S.P.A. (2004a). 2001 Sales by site. Apparent EU Consumption in 2001, 2002 and 2003. Confidential letter 24.9.2004. ed. Institute, F.E. Helsinki.

QUAS, Q.O.S.P.A. (2002). Confidential letter from Michel De Poortere on consumption volumes and end-uses of EPTAC and CHPTAC. Confidential letter 12.9.2002.

QUAS, S.G. (2003). Confidential letter from Michel de Poortere on residues of EPTAC and CHPTAC in cationised strach samples; information from AAC.

QUAS, S.G. (2000b). Risk assessment of 2,3-epoxypropyltrimethylammonium chloride. Revised draft of 4.12.2000.: CEFIC.

RAISIO CHEMICALS, A.K. (2001). 2,3-epoxypropyltrimethylammonium chloride and 3-chloro-2-hydroxypropyltrimethylammonium chloride residues in copy paper; calculation. Confidential memo 31.1.2001: Raisio Chemicals. QUAS Sector Group.

RAISIO CHEMICALS, A.K. (2000). 2,3-epoxypropyltrimethylammonium chloride and 3-chloro-2-hydroxyprpyltrimethylammonium chloride residues in paper and board; calculation. Confidential memo 11.4.2000.

RAISIO CHEMICALS, A.K. (1999). Degradation of 2,3-epoxypropyltrimethylammonium chloride and 3-chloro-2-hydroxyprpyltrimethylammonium chloride during jet-cooking in different pH. Confidential memo: Raisio Chemicals.

RAISIO CHEMICALS, A.K. (2004). Determination of the abiotic degradation of 2,3-epoxypropyltrimethylammonium chloride at pH 7,8 at 12 ºC. Confidential: Raisio Chemicals Oy.

RAISIO CHEMICALS, A.K. (2004b). EPTAC and CHPTAC commercial products – storage stability. pp. 1: Raisio Chemicals.

RAISIO CHEMICALS, A.K. (2004c). Determination of the abiotic degradation of 3-Chloro-2-hydroxypropyltrimethylammonium chloride at pH 7,0; 7,8 and 8,4 at 12C. Laboratory study - Final Report 8.3.2004. Confidential. pp. 17: RaisioChemicals. QUAS Sector Group.

SHELL OIL COMPANY (1979). The acute toxicity of G-MAC (glycidyl trimethyl ammonium chloride) to rainbow trout (Salmo gairdneri) and Daphnia magna. Tunstall: Shell Toxicology Laboratory, Shell Research Ltd.

SHELL OIL COMPANY (1982). Submission of lists and copies of health and safety studies.

SHELLENGBERGER, T.E. (1962). bis(Dibutyl Phosphonomethane) Disulfide (lot GF 6854-188) Glycidyl Trimethyl Ammonium Chloride (THC 6482-145) Amine RC-94(Dodecahydro-1, 4, 7,9a-tetraazophenylene) Amine RC-180 (Aliphatic Polyamine): Standford research institute.

TNO, C. (2003). In vitro percutanous absorption of 3-chloro-2-hydroxypropyltrimethylammonium chloride using viable mouse and human skin membranes. pp. 48. Zeist, Netherlands: TNO.

TOXICOL LABORATORIES, L. (1982). Bacterial Mutagenicity Tests on Ogtac 85: Toxicol Laboratories Limited.

VLEMINCKX, C., ARANY, J., HENDRICKX, B. & MOENS, W. (1987). Genotoxic effects of glycidyltrimethylammonium chloride. *Mutation Research*, **189,** 387-394.

VON DER HUDE, W., BASLER, A., MATEBLOWSKI, R. & OBE, G. (1989). Genotoxicity of epoxides. II. In vitro investigations with the sister-chromatid exchange (SCE) test and the unscheduled DNA synthesis (USD) test. *Mutagenesis*, **4,** 323-324.

VON DER HUDE, W., CARSTENSEN, S. & OBE, G. (1991). Structure-activity relationships of epoxides: induction of sister-chromatid exchanges in Chinese hamster V79 cells. *Mutation Research*, **249,** 55-70.

VON DER HUDE, W., MATEBLOWSKI, R. & BASLER, A. (1990a). Induction of DNA-repair synthesis in primary rat hepatocytes by epoxides. *Mutation Research*, **245,** 145-150.

VON DER HUDE, W., SEELBACH, A. & BASLER, A. (1990b). Epoxides: comparison of the induction of SOS repair in Eschrichia coli PQ37 and the bacterial mutagenicity in the Ames test. *Mutation Research*, **231,** 205-218.

VOOGD, C.E., VAN DER STEL, J.J. & JACOBS, J.J.J.A.A. (1981). The mutagenic action of aliphatic epoxides. *Mutation Research*, **89,** 269-282.

ABBREVIATIONS

ADI	Acceptable Daily Intake
AF	Assessment Factor
ASTM	American Society for Testing and Materials
ATP	Adaptation to Technical Progress
AUC	Area Under The Curve
B	Bioaccumulation
BBA	Biologische Bundesanstalt für Land- und Forstwirtschaft
BCF	Bioconcentration Factor
BMC	Benchmark Concentration
BMD	Benchmark Dose
BMF	Biomagnification Factor
bw	body weight / *Bw*, *b.w.*
C	Corrosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
CA	Chromosome Aberration
CA	Competent Authority
CAS	Chemical Abstract Services
CEC	Commission of the European Communities
CEN	European Standards Organisation / European Committee for Normalisation
CMR	Carcinogenic, Mutagenic and toxic to Reproduction
CNS	Central Nervous System
COD	Chemical Oxygen Demand
CSTEE	Scientific Committee for Toxicity, Ecotoxicity and the Environment (DG SANCO)
CT_{50}	Clearance Time, elimination or depuration expressed as half-life
d.wt	dry weight / dw
dfi	daily food intake
DG	Directorate General
DIN	Deutsche Industrie Norm (German norm)
DNA	DeoxyriboNucleic Acid
DOC	Dissolved Organic Carbon
DT50	Degradation half-life or period required for 50 percent dissipation / degradation
DT90	Period required for 50 percent dissipation / degradation
E	Explosive (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties [Model]
EbC50	Effect Concentration measured as 50% reduction in biomass growth in algae tests

EC	European Communities
EC10	Effect Concentration measured as 10% effect
EC50	median Effect Concentration
ECB	European Chemicals Bureau
ECETOC	European Centre for Ecotoxicology and Toxicology of Chemicals
ECVAM	European Centre for the Validation of Alternative Methods
EDC	Endocrine Disrupting Chemical
EEC	European Economic Communities
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINCS	European List of New Chemical Substances
EN	European Norm
EPA	Environmental Protection Agency (USA)
ErC50	Effect Concentration measured as 50% reduction in growth rate in algae tests
ESD	Emission Scenario Document
EU	European Union
EUSES	European Union System for the Evaluation of Substances [software tool in support of the Technical Guidance Document on risk assessment]
F(+)	(Highly) flammable (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
FAO	Food and Agriculture Organisation of the United Nations
FELS	Fish Early Life Stage
GLP	Good Laboratory Practice
HEDSET	EC/OECD Harmonised Electronic Data Set (for data collection of existing substances)
HELCOM	Helsinki Commission -Baltic Marine Environment Protection Commission
HPLC	High Pressure Liquid Chromatography
HPVC	High Production Volume Chemical (> 1000 t/a)
IARC	International Agency for Research on Cancer
IC	Industrial Category
IC50	median Immobilisation Concentration or median Inhibitory Concentration
ILO	International Labour Organisation
IPCS	International Programme on Chemical Safety
ISO	International Organisation for Standardisation
IUCLID	International Uniform Chemical Information Database (existing substances)
IUPAC	International Union for Pure and Applied Chemistry
JEFCA	Joint FAO/WHO Expert Committee on Food Additives
JMPR	Joint FAO/WHO Meeting on Pesticide Residues
Koc	organic carbon normalised distribution coefficient
Kow	octanol/water partition coefficient

Kp	solids-water partition coefficient
L(E)C50	median Lethal (Effect) Concentration
LAEL	Lowest Adverse Effect Level
LC50	median Lethal Concentration
LD50	median Lethal Dose
LEV	Local Exhaust Ventilation
LLNA	Local Lymph Node Assay
LOAEL	Lowest Observed Adverse Effect Level
LOEC	Lowest Observed Effect Concentration
LOED	Lowest Observed Effect Dose
LOEL	Lowest Observed Effect Level
MAC	Maximum Allowable Concentration
MATC	Maximum Acceptable Toxic Concentration
MC	Main Category
MITI	Ministry of International Trade and Industry, Japan
MOE	Margin of Exposure
MOS	Margin of Safety
MW	Molecular Weight
N	Dangerous for the environment (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC
NAEL	No Adverse Effect Level
NOAEL	No Observed Adverse Effect Level
NOEL	No Observed Effect Level
NOEC	No Observed Effect Concentration
NTP	National Toxicology Program (USA)
O	Oxidizing (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
OECD	Organisation for Economic Cooperation and Development
OEL	Occupational Exposure Limit
OJ	Official Journal
OSPAR	Oslo and Paris Convention for the protection of the marine environment of the Northeast Atlantic
P	Persistent
PBT	Persistent, Bioaccumulative and Toxic
PBPK	Physiologically Based PharmacoKinetic modelling
PBTK	Physiologically Based ToxicoKinetic modelling
PEC	Predicted Environmental Concentration
pH	logarithm (to the base 10) (of the hydrogen ion concentration $\{H^+\}$

pKa	logarithm (to the base 10) of the acid dissociation constant
pKb	logarithm (to the base 10) of the base dissociation constant
PNEC	Predicted No Effect Concentration
POP	Persistent Organic Pollutant
PPE	Personal Protective Equipment
QSAR	(Quantitative) Structure-Activity Relationship
R phrases	Risk phrases according to Annex III of Directive 67/548/EEC
RAR	Risk Assessment Report
RC	Risk Characterisation
RfC	Reference Concentration
RfD	Reference Dose
RNA	RiboNucleic Acid
RPE	Respiratory Protective Equipment
RWC	Reasonable Worst Case
S phrases	Safety phrases according to Annex III of Directive 67/548/EEC
SAR	Structure-Activity Relationships
SBR	Standardised birth ratio
SCE	Sister Chromatic Exchange
SDS	Safety Data Sheet
SETAC	Society of Environmental Toxicology And Chemistry
SNIF	Summary Notification Interchange Format (new substances)
SSD	Species Sensitivity Distribution
STP	Sewage Treatment Plant
T(+)	(Very) Toxic (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
TDI	Tolerable Daily Intake
TG	Test Guideline
TGD	Technical Guidance Document
TNsG	Technical Notes for Guidance (for Biocides)
TNO	The Netherlands Organisation for Applied Scientific Research
UC	Use Category
UDS	Unscheduled DNA Synthesis
UN	United Nations
UNEP	United Nations Environment Programme
US EPA	Environmental Protection Agency, USA
UV	Ultraviolet Region of Spectrum
UVCB	Unknown or Variable composition, Complex reaction products of Biological material
vB	very Bioaccumulative

vP	very Persistent
vPvB	very Persistent and very Bioaccumulative
v/v	volume per volume ratio
w/w	weight per weight ratio
WHO	World Health Organization
WWTP	Waste Water Treatment Plant
Xn	Harmful (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)
Xi	Irritant (Symbols and indications of danger for dangerous substances and preparations according to Annex III of Directive 67/548/EEC)

Appendix A

BENCHMARK DOSE CALCULATIONS FOR 2,3-EPOXYPROPYL-TRIMETHYLAMMONIUM CHLORIDE, CARCINOGENICITY STUDY, SKIN PAINTING STUDY IN MICE.

Model used: US-EPA Benchmark dose model Version 1.3.2 2003. For description of the algorithms see Help manual

The model offers several algorithms for dichotomous data.
Risk type: extra risk.
As a default the benchmark dose for a 10% increase in tumour incidence is calculated as this reflects the discriminatory power of the standard carcinogenicity assays (BMD0.1).The Benchmark doses and 95% lower confidence limits (BMDL) are tabled for those models. The results of the model calculations are provided in the annexes.

Input data skin tumours

The input data are summarised in table 1

Table 1: Input data

Concentration (%)	Number males or females	No of animals with skin tumours, m	No of animals with skin tumours, f	Number of animals m+f	No. Of animals with skin tumours m+f	Concentration (%)
0	100	1	1	200	2	0
0.1	50	0	0	100	0	0.1
0.3	50	0	2	100	2	0.3
1	50	27	25	100	52	1

Benchmark dose calculations for skin tumours

As there seemed to be no considerable differences between males and females the combined data were used.

The BMD0.1 and the respective 95% lower confidence intervals (BMDL) are summarised in table 2 for the different models. Table 3 gives the analysis of the applicability of the models for the data set according to EPA. Looking at the graphs that are displayed following the table supports the consideration.

Table 2: Skin tumours BMD calculations

Model	Quantal quadratic	Probit	Weibull	Gamma	Log-log	quantal-linear	multistage
BMD0.1	0.4	0.49	0.56	0.52	0.54	0.22	does not give output
BMDL95	0.358	0.4	0.44	0.42	0.42	0.18	

Table 3 Goodness of fit

Model	Chi[2]	P-value	AIC[1]	Residuals[2]
Quantal quadratic	5.53	0.06	192.14	-1.7 to 0.84
Probit	1.01	0.316	188.11	-0.82 to 0.58
Weibull	1.03	0.311	188.17	-0.84 to 0.56
Gamma	1.01	0.315	188.13	-0.83 to 0.57

Log-logistic	1.02	0.312	188.15	-0.84 to 0.56
Multistage	-	-	-	-
Quantal linear	25.81	0	220.88	-3.4 to 0.8

[1] AIC [= -2 × (LL - p), where LL is the log-likelihood at the maximum likelihood estimates, and p is the degrees of freedom of the model; generally everything else being equal, lower AIC values are preferred].
[2]observed value - expected value)/standard error]

The goodness of fit analysis shows that the quantal quadratic and the quantal linear model do not seem to be appropriate while the other models are comparable with regard to chi-square, P AIC and residuals. The Probit model has the lowest AIC and gives the lowest BMD of the models and could therefore be preferred. The graphs show that the Weibull model could present a better curve-fitting estimate. However, as the models give quite comparable results the BMD of 0.49% (4.9 mg/ml) corresponding to a dose of 24.5 mg/kg bw (with 0.2 ml application volume and a default body weight of 40 g for male and female mice combined) and the BMDL of 0.4% corresponding to a dose of 20 mg/kg can be derived. The corresponding daily doses for 5 day application would be 9.8 and 8 mg/kg bw and for a 7 day application 7 and 5.7 mg/kg bw.

Summary

The daily benchmark doses for 10% increase of tumour incidence and their lower bound 95% confidence limits that can be derived for skin tumours malignant and benign combined for males and females that gave the best curve fits are summarised in table 4 for 5 and 7 days of exposure.

Table 4

	Benign and malignant skin tumours (m+f)
$BMD_{0.1}$ (5d) mg/kg bw	9.8
BMDL (5d) mg/kg bw	8.0
$BMD_{0.1}$ (7d) mg/kg bw	7.0
BMDL (7d) mg/kg bw	5.7

These doses could be used as a starting point to estimate potency for local tumours.

Derivation of systemic BMD with skin absorption data

Derivation of a benchmark dose for possible systemic tumours using the internal systemic dose derived with the dermal absorption data for CHPTAC (45% absorption at a concentration of 0.1% and 0.3%; 29.2% absorption at 1%). The systemic tumours that could be relevant and had a certain dose response and a statistical significance were lung tumours and mammary tumours in female animals. As only the female data have some dose dependent significance the dose levels are calculated for female animals using a default body weight of 35 g (TGD, female mice 2 year study)

Input data:

Table 5: input data:

Dose mg/kg bw/wk	Number females	No of animals with mammary tumours, f	No. of females with lung tumours (benign and malignant)
0	100	2	51

5.1	50	0	22
15.4	50	1	27
33.4	50	12	36

Model output

Table 6: Output for mammary tumours:

Model	Quantal quadratic	Probit	Weibull	Gamma	Log-log	quantal-linear	multistage
BMD0.1	23.1	23.8	27.6	26.7	25	21.8	calculation not possible
BMDL95	18.5	19.7	21	20.5	21.2	13.8	-

Table 7 Goodness of fit

Model	Chi[2]	P-value	AIC[1]	Residuals[2]
Quantal quadratic	3.08	0.2148	93	-1.1-0.8 1.9
Probit	3.65	0.1611	93	-0.94-1.37 2.31
Weibull	1.01	0.3146	92	-0.8-0.57 1.37
Gamma	1.01	0.3142	92	-0.82-0.58 1.4
Log-logistic	3.02	02209	92	-0.84-1.3 2.14
Multistage	-	-	-	-
Quantal linear	7.4	0.0247	99	-1.6-1.55 3.15

[1] AIC [= -2 × (LL - p), where LL is the log-likelihood at the maximum likelihood estimates, and p is the degrees of freedom of the model; generally everything else being equal, lower AIC values are preferred].
[2]observed value - expected value)/standard error]

The goodness of fit analysis gives the lowest AIC and residual values with the Weibull, Gamma and Log-logistic models which all give a similar result for the BMD and BMDL. Also from the graphical output the curve fitting seems better in those 3 models. The lowest BMDL of the three models giving the best fit is chosen (log-logistic): $BMD_{0.1}$: 25 mg/kg bw wk, $BMDL_{95}$: 21.2 mg/kg bw wk. This would result in a $BMD_{0.1}$ of 5 mg/kg bw/day for 5 days of exposure ($BMDL_{95}$: 4.2 mg/kg bw/day) or 3.6 mg/kg bw day for a 7 day exposure situation (BMDL 3 mg/kg bw/day).

Output for lung tumours in female mice

Table 8: model output for lung tumours in female mice

Model	Quantal quadratic	Probit	Weibull	Gamma	Log-log	quantal-linear	multistage
BMD0.1	14	7.7	16.5	16.1	7.63	6.9	Calculation not possible
BMDL95	10.7	5.1	4	3.9	4.98	4.04	

Table 9 Goodness of fit

Model	Chi[2]	P-value	AIC[1]	Residuals[2]
Quantal quadratic	0.8	0.6691	340	-0.72-0.53 1.25
Probit	1.93	03807	341	-0.94-0.77 1.71
Weibull	0.73	0.3938	342	-0.72-0.43 1.15
Gamma	0.7	0.439	342	-0.70-0.44 1.14
Log-logistic	1.95	0.3763	341	-0.94-0.77 1.71

Multistage	-	-	-	-
Quantal linear	2.29	0.3175	341	-1.02-0.75 1.75

[1] AIC [= -2 × (LL - p), where LL is the log-likelihood at the maximum likelihood estimates, and p is the degrees of freedom of the model; generally everything else being equal, lower AIC values are preferred].
[2]observed value - expected value)/standard error]

The goodness of fit analysis gives the lowest AIC and residual values with the quantal quadratic (lowest AIC), Weibull and Gamma (lowest residuals) models, which all give a similar result for the BMD and BMDL. Also from the graphical output the curve fitting seems better in those 3 models. The lowest BMDL of the three models giving the best fit is chosen (quantal quadratic): $BMD_{0.1}$: 14, $BMDL_{95}$: 10.7.
The multistage model was unable to calculate a BMD. The relative high AICs and varaiation between the model as well as the fact that the predicted tumour rates are very close to the expected rates is in accordance with the equivocal evidence for an increase in lung tumours.

For lung tumours in female mice the $BMD_{0.1}$ of 14 mg/kg bw per week and a $BMDL_{95}$ of 10.7 mg/kg bw per week is derived. This would result in a $BMD_{0.1}$ of 2.8 mg/kg bw/day for 5 days of exposure ($BMDL_{95}$: 2.1 mg/kg bw/day) or 2 mg/kgbw day for 7 days of exposure ($BMDL_{95}$: 1.5 mg/kg bw/day).

Table 10: Summary of BMD calculations for EPTAC systemic tumours

	Mammary tumours begning and malignant combined (internal dose derived from skin absorption data)	**Lung tumours Benign and malignant combined (internal dose derived from skin absorption data)**
$BMD_{0.1}$ (5d) mg/kg bw	5	2.8
BMDL (5d) mg/kg bw	4.2	2.1
$BMD_{0.1}$ (7d) mg/kg bw	3.6	2
BMDL (7d) mg/kg bw	3	1.5

Summary of BMD calculations for EPTAC:
The outcome of the benchmark dose calculations for local and systemic tumours is summarized in table 11.

Table 11: Results of the BMD calculations

	Benign and malignant skin tumours (m+f) (external dose)	**Mammary tumours begning and malignant combined (internal dose derived from skin absorption data)**	**Lung tumours Benign and malignant combined (internal dose derived from skin absorption data)**
$BMD_{0.1}$ (5d) mg/kg bw	9.8	5	2.8
BMDL (5d) mg/kg bw	8.0	4.2	2.1
$BMD_{0.1}$ (7d) mg/kg bw	7.0	3.6	2
BMDL (7d) mg/kg bw	5.7	3	1.5

The report provides the comprehensive risk assessment of the substance 2,3-Epoxypropyltrimethylammonium chloride (EPTAC) It has been prepared by Finland in the frame of Council Regulation (EEC) No. 793/93 on the evaluation and control of the risks of existing substances, following the principles for assessment of the risks to man and the environment, laid down in Commission Regulation (EC) No. 1488/94.

The evaluation considers the emissions and the resulting exposure to the environment and the human populations in all life cycle steps. Following the exposure assessment, the environmental risk characterisation for each protection goal in the aquatic, terrestrial and atmospheric compartment has been determined.
The environmental risk assessment concludes that there is concern for the aquatic ecosystem (including marine environment) from exposure arising from cationisation of starch with wet process at local scale for five sites. There is no concern for the atmosphere, the terrestrial ecosystem and micro-organisms in the sewage treatment plant.

For human health the scenarios for occupational exposure, consumer exposure and humans exposed via the environment have been examined and the possible risks have been identified.
The human health risk assessment concludes that there is concern for workers with regard to mutagenicity, carcinogenicity and sensitisation from all worker scenarios and with regard to repeated dose toxicity from sampling and laboratory work during production of EPTAC. There is also concern for humans exposed via the environment with regard to carcinogenicity and mutagenicity, however the risks are very low. For consumers and for human health (physico-chemical properties) there is no concern.

The conclusions of this report will lead to risk reduction measures to be proposed by the Commission's committee on risk reduction strategies set up in support of Council Regulation (EEC) N. 793/93.