European Union Risk Assessment Report

(3-CHLORO-2-HYDROXYPROPYL)TRIMETHYLAMMONIUM CHLORIDE

(CHPTAC)

CAS No: 3327-22-8

EINECS No: 222-048-3

RISK ASSESSMENT

FINAL APPROVED VERSION

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RISK ASSESSMENT

Final report 2008

Finland

Rapporteur for the risk assessment of 3-Chloro-2-hydroxypropyl)trimethylammonium chloride 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

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Foreword

We are pleased to present this Risk Assessment Report which is the result of in-depth work carried out by experts in one Member State, working in co-operation with their counterparts in the other Member States, the Commission Services, Industry and public interest groups.
The Risk Assessment was 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.
If a Risk Assessment Report concludes that measures to reduce the risks of exposure to the substances are needed, beyond any measures which may already be in place, the next step in the process is for the "Rapporteur" to develop a proposal for a strategy to limit those risks.
The Risk Assessment Report is also presented to the Organisation for Economic Co-operation and Development as a contribution to the Chapter 19, Agenda 21 goals for evaluating chemicals, agreed at the United Nations Conference on Environment and Development, held in Rio de Janeiro in 1992 and confirmed in the Johannesburg Declaration on Sustainable Development at the World Summit on Sustainable Development, held in Johannesburg, South Africa in 2002.
This Risk Assessment improves our knowledge about the risks to human health and the environment from exposure to chemicals. We hope you will agree that the results of this in-depth study and intensive co-operation will make a worthwhile contribution to the Community objective of reducing the overall risks from exposure to chemicals.

[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: 3327-22-8
EINECS Number: 222-048-3
IUPAC Name: (3-Chloro-2-hydroxypropyl)trimethylammonium 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 for four sites with wet process (Industrial use 1) at the local scale (i.e. sites B9, B10, B23 and B25).

From these four starch cationisation sites, which have risk ratio higher than one, only one site (B25) has monitoring data on CHPTAC releases to waste water. However, the detection limit of CHPTAC from waste water effluent (2 mg/l) has been rather high compared to PNEC (0.051 mg/l l). Use of lower detection limit might decrease risks from this site. For those three sites where no monitoring data is available (B9, B10 and B23), releases have been calculated with an emission factor from a starch cationisation site with highest release factor (2.2 %). 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, cationisation of starch for seven sites with dry process (B6, B11, B12, B13, B15, B22 and B28) and for eight sites with wet process (B3, B4, B5, B14, B16, B17, B18, B21) (Industrial use 1), 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:

[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 (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 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 use scenarios because of concerns for mutagenicity, carcinogenicity and sensitisation.

Conclusion ii is drawn in the CHPTAC production scenario. The theoretical possibility of *in vivo* conversion of EPTAC after CHPTAC exposure is not considered a concern in this scenario due to following reasons.

In CHPTAC production phase, epichlorohydrin is used in the synthesis. Being a category 2 carcinogen, the presence of epichlorohydrin sufficient risk reduction measures need to be in place already during synthesis. These are considered sufficient also for limiting the theoretical risk from CHPTAC exposure during manufacturing phase. In the end product, formation of EPTAC is controlled by pH. Therefore, due to current risk reduction measures in the production phase the risk is foreseen as minor and thus, conclusion ii is drawn.

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

Humans exposed via the 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 (iii) applies to all scenarios.

Combined exposure

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.

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.

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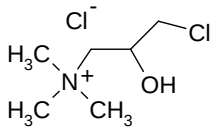
EUSES Calculations can be viewed as part of the report at the website of the European Chemicals Bureau: http://ecb.jrc.it

TABLES

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 3327-22-8
EINECS Number: 222-048-3
IUPAC Name: (3-Chloro-2-hydroxypropyl)trimethylammonium chloride
Molecular formula: $C_6H_{15}ONCl_2$
Structural formula:



Molecular weight: 188.10
Synonyms: CHPTAC, 1-Propanaminium, 3-chloro-2-hydroxy-N,N,N-trimethyl chloride

1.2 PURITY/IMPURITIES, ADDITIVES

The typical concentration of technical CHPTAC is 50-70 % water solution. The solubility of the substance limits higher water concentrations. Main impurities are:

Table 1.0: CHPTAC impurities

CAS No.	Chemical Name	Content
34004-36-9	2,3-dihydroxypropyltrimethylammonium chloride (DIOL)	< 1.5 %
55636-09-4	Bis/trimethylammoniumchloride)-2-hydroxypropane	1.3 - 4 %
106-89-8	Epichlorohydrin	<10 ppm
96-23-1	1,3-dichloro-2-propanol	< 20 ppm, exceptionally < 50 ppm

The pH in the commercial product is slightly acidic, typically 3-5. In such acidic pH CHPTAC is resistant against hydrolysis and does not need any special stabilizing agent (Raisio Chemicals, 2004b).

1.3 PHYSICO-CHEMICAL PROPERTIES

Pure CHPTAC is at 20 °C and 101.3 kPa a solid and water-soluble substance. 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	180.5 °C	DSC method, EEC-guideline 92/69/EEC A.1 (CEFIC, 1997d).
Boiling point	190 °C - 209 °C	At 101.3 kPa. In addition, a sharp exothermal (decomposition) process at 210.3 °C was recorded. Test method: DSC-method, EEC-guideline 92/69/A.2 (CEFIC, 1997a).
Relative density	1.11	At 20 °C for 97.3 % substance. Pycnometer method, EEC-guideline 92/69/EEC A.3(CEFIC, 1997e) 3 (CEFIC, 1997e). Density of 1.16 g/cm3 is reported for 65 % and 1.17 g/cm3 for 69 % CHPTAC at 20 °C (Degussa, 2002b)
Vapour pressure	$< 10^{-3}$ Pa	In the temperature range between 20 °C and 150 °C. Test method: Vapour pressure balance, EEC-guideline 92/69/EEC A.4 (CEFIC, 1997j).
Water solubility	835.2 $\pm$ 9.9 g/l	At 20 °C. The pH-value of the test solution was close to pH 3. At this pH, CHPTAC is probably very stable. Test method: Flask method, EEC-guideline 92/69/EEC A.6 (CEFIC, 1997h).
Partition coefficient n-octanol/water (log value)	$P_{ow} < 0.03$ or log $P_{ow} <$ -1.5	(1-octanol/buffered water phase, pH 4 at 25 $\pm$ 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 CHPTAC in the water phase. The results at neutral pH were not reproducible, and were not used for evaluation. Test method: Shake flask method, EEC-guideline 92/69 EEC A.8 (CEFIC, 1998c).
Granulometry	-	-
Conversion factors	-	-
Flash point	-	-
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).
Flammability	Not highly flammable	In a burning rate test, fire in the pile of CHPTAC went out after 230 seconds at a distance of 40 mm. Therefore CHPTAC is not classified as highly flammable. 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. 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 an Industry statement CHPTAC 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.

Property	Value	Comment
Viscosity	-	-
Henry's constant	< 2.25 · 10^{-7} Pa m^3/mol	Calculated using a vapour pressure of < 0.001 Pa (at 20 °C - 150 °C) and a water solubility of 835 000 mg/l (at 20 °C and at pH 3).
Surface tension	72.8 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).

1.4 CLASSIFICATION

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

The current classification by the manufacturers: Carc. Cat 3, R40

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

1.4.1 Proposal for classification on the 31st ATP

Classification: Carc. Cat 3, R40, R52-53

Labelling: Xn, R:40-52/53

S-phrases: S: 36/37-61

2 GENERAL INFORMATION ON EXPOSURE

2.1.1 Production capacity

CHPTAC was produced at five sites within the EU in 1996 according to information from CEFIC (Table 2.1). Production volumes for the known five producers ranged from 187 to 8360 tons per plant during 1994-1996. In 1998 one plant ceased its production. Total production volume in 1996 was 21 069 t (CEFIC, 1998a) and in 1999 slightly higher i.e. 22 847 tons (CEFIC, 2000a). Total consumption volume including both import and export was 20 960 tons in 1996, 23 087 tons in 1999 and 23 695 tons in 2001 ((CEFIC, 2000a); (QUAS, 2004a)) (Table 2.3).

Table 2.1 CHPTAC producers

Company	Site and country
Degussa AG (production stopped in 1998)	Knapsack, Germany
Raisio Chemicals Oy	Mietoinen, Finland
Roquette Freres SA	Vecquemont, France
SACHEM Europe B.V.	Zaltbommel, Netherlands
Sasol Servo BV	Delden, Netherlands

2.2 USES

CHPTAC is almost totally used for cationisation of starch. From the total volume of 23 695 tons 95 % was used for cationisation of starch in 2001 and 5 % for synthesis of carnitine salts (1-Propanaminium, 3-carboxy-2-hydroxy-N,N,N-trimethyl salts), quaternisation of guar, protein (and/or protein derivatives) and cellulose (modified from (QUAS, 2004a)) (Table 2.2). Cationic 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. 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. Other known applications of CHPTAC are impregnation agent, raw material in the dye industry and synthesis of other chemicals, such as carnitine, which is used in, e.g., nutraceuticals.

Table 2.2 Uses of CHPTAC in 2001**(modified from QUAS 2004a)**

Use category	Quantity used tons	Percentage of total use
Cationisation of starch	22 651	95
Synthesis of carnitine salts and quaternisation of cellulose, protein, guar and other derivatives	1044	5
Total	23 695	100

In 1997 CEFIC sent a questionnaire to all known industrial users of CHPTAC to find out more information on uses and exposure. According to this information there were 13 companies which used CHPTAC in the EU in 1997: 12 sites producing cationised starch and one quaternised guar. The volume covered by these 13 users was 16 800 tons which is about 80 % of the total production volume in 1996. In 1997 there were 11 companies which used EPTAC in the EU: 9 sites producing cationised starch and two quaternized proteins.

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 in 2001, which were not consumed during that year. 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 CHPTAC have been measured in the cationised starch. According to a survey done by industry in 1998, < 50 to 6350 mg/kg CHPTAC was found in the 68 commercial cationic starches available on the European market. A new survey was carried out in 2002, where 90th percentile over 200 samples was 480 mg/kg and 95th percentile 1800 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 CHPTAC concentrations was 450 mg/kg.

2.3 TRENDS

Consumption of CHPTAC (including both import and export) has increased from 20 960 tons in 1996 to 23 695 tons in 2001 (CEFIC, 1998a)(QUAS, 2004a). As the use of EPTAC leads to releases of CHPTAC, consumption of both CHPTAC and EPTAC has been presented in Table 2.3.

Table 2.3 Consumption of CHPTAC and EPTAC between 1996 and 2003 (tons/year). EPTAC volume and total volume is expressed as CHPTAC , where the molecular weight difference (CHPTAC: 188 vs. EPTAC: 151) has been taken into account (modified from QUAS 2004a).

	CHPTAC	EPTAC (as CHPTAC)	Total (as CHPTAC)
1996	20 960	4 813	25 773
1999	23 087	6 524	29 611
2001	23 695	7 661	31 356

2002	27 957	6 520	34 477
2003	27 512	4 902	32 414

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

3.1.1 General discussion

CHPTAC may be released into the environment during its production and industrial use and during use of EPTAC (2,3-epoxypropyltrimethylammonium chloride) (CAS-3033-77-0) .

Six exposure scenarios are assessed at local scale:

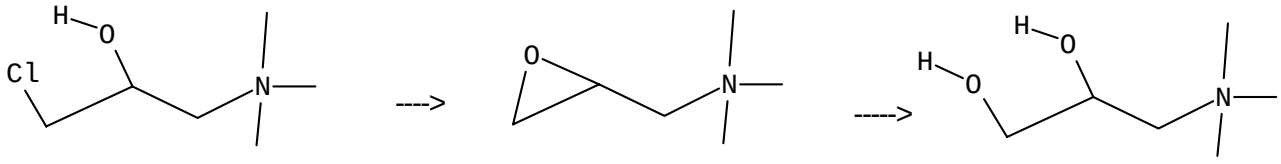
1. Production of CHPTAC
2. Cationisation of starch with CHPTAC and EPTAC (industrial use scenario 1)
3. Use of starch with residual CHPTAC in paper making (industrial use scenario 2)
4. Residual EPTAC and CHPTAC in paper recycling (industrial use scenario 3)
5. Use of starch with residual CHPTAC in production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

During cationisation of starch (industrial use scenario 1) direct CHPTAC emissions are likely from use of 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 starch cationisation 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.

In addition, the conversion of CHPTAC releases to EPTAC in the environment is likely as the conversion half-life is 21 days at pH 7.8 (at 12 ˚C) and this will be considered at the regional scale in the EPTAC Risk Assessment Report.

Conversion of CHPTAC and EPTAC to DIOL (2,3-Dihydroxypropyltrimethyl-ammoniumchloride) (CAS 34004-36-9) is a competitive reaction during the starch cationisation. 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 (CEFIC, 1998a).

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 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 conversion test with CHPTAC (Raisio Chemicals, 2004a) the rate of CHPTAC and EPTAC conversion to DIOL was slow, the mean half-life from EPTAC to DIOL was 138 days at pH 7.8 (12 ˚C). Therefore further conversion to DIOL will not be taken into account in local PEC calculations of CHPTAC.

3.1.2 Environmental releases

3.1.2.1 Release from production

CHPTAC was produced at five sites within the EU in 1996. Production volumes ranged from 187 to 8360 tons per plant during 1994-1996. In 1998 one plant ceased it's production.

CHPTAC is produced in a batch process as an aqueous solution of 50 to 70 %. Due to hazard properties of the starting material epichlorohydrin special care has been taken to keep the process closed. As the synthesis product CHPTAC is not washed with water, there are no releases to water or releases are very low. Site-specific release information from all five production plants are presented in Table 3.1

Table 3.1 Local releases to water from production (for one site releases also from use).

Site	Release to WWTP	Observations
A1	5.2 kg/year	Intermittent release from cleaning 8 times per year
A2	-	Production stopped at this site in 1998.
A3	0	Waste water recycled back to process
A4	0	Waste waters incinerated off-site (includes also waste water from use of CHPTAC)
A5	0	Waste waters recycled back to process

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

3.1.2.2 Release from formulation

There is no real formulation step in the production of CHPTAC, but different concentrations are derived directly from the production process. Manufacturers of CHPTAC produce aqueous solutions (max. < 70 %) at their production plants, which are then sold as such to

customers for use. The pH in the commercial product is slightly acidic, typically 3-5. In such acidic pH CHPTAC is resistant against hydrolysis and does not need any special stabilizing agent (Raisio Chemicals, 2004b). Therefore there is no need to estimate releases from formulation.

3.1.2.3 Release from industrial/professional use

3.1.2.3.1 Cationisation of starch (industrial use scenario1)

In the following section releases of CHPTAC 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 (CEFIC 2004a). EPTAC volume used by these sites was about 7396 tons (as CHPTAC) and CHPTAC volume 21 141 tons i.e. the total volume was 28 537 tons (as CHPTAC) in 2001. In 2001 the total volume for starch cationisation was 30 223 tons (as CHPTAC) (QUAS, 2004a), so the known sites cover 94 % of the total volume. Local releases have been calculated with site-specific volumes from 2001. 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, 2000a). 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 cationised starch or proteins there are 5 plants using dry process and 6 using wet/slurry process (CEFIC, 2000). 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 cationised 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 (CEFIC, 2000).

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 2 EPTAC sites and 7 CHPTAC sites there are measured CHPTAC concentrations available. All these sites have measured releases of both substances (Table 3.2). CHPTAC releases to industrial waste water treatment plants have ranged at these sites from 0.113 t/a to 17.1 t/a, when calculated from the average measured influent concentration. Site-specific emission factors for CHPTAC are as follow: 0.06 %, 0.07 %, 0.071%, 0.23 %, 0.44 %, 0.50 %, 0.72 %, 1.19 % and 2.2 %. For CHPTAC these sites cover 77 % of the 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 CHPTAC and EPTAC from starch cationisation plants to industrial 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
EPTAC users			
B16	**1.15**	**0.6**	Measured CHPTAC and EPTAC concentrations from influent and effluent available. Volume of 2 WWTPs and receiving water known.
B18	**0.387**	**0.173**	Measured CHPTAC and EPTAC concentrations from influent and effluent available. Volume of 2 WWTPs and receiving water known.
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 influent and effluent concentrations available. Volume of WWTP and river flow known.
B5	**0.924(avg) (min. 0.784, max 1.064**)	**7.28 (avg) (min 5.12, max9.44)**	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.
B17	**0.0003**	**0.113**	Measured CHPTAC and EPTAC influent and effluent concentrations 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

Site	Release of EPTAC to industrial WWTP (t/a)	Release of CHPTAC to industrial WWTP (t/a)	Observations
			and receiving water known.
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 two CHPTAC sites and one EPTAC no monitoring of waste water concentrations has been carried out. Thus an emission factor from another existing starch cationisation site will be used for these sites. An emission factor of 2.2 % to water and 300 processing days has been used to calculate releases of CHPTAC (Table 3.3).

There is 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 (7396 + 21 141 = 28 537 t, as CHPTAC) cover 94 % of the total volume used for starch cationisation in 2001 (7572 + 22 651 = 30 223 t).

Table 3.3 Calculated local releases of CHPTAC from cationisation of starch. Emission factor of 2.2 % has been used to calculate releases.

Site	Release of CHPTAC to industrial WWTP (t/a)	Observations
EPTAC users		
B9	13.6	Size of the WWTP known.
CHPTAC users		
B10	8.9	Size of the WWTP and river flow known.
B19	-	This site closed at the end of 2002
B23	50.4	Only volume of effluent and flow of river known.
B26	-	This site is closed in 2004.
Total	72.9	

For five EPTAC sites and two CHPTAC site 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 glycol form 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 water are diluted and sprayed on green fields. Site uses both EPTAC and CHPTAC.
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 0.014 kg/d and 0.265 kg/d (79.5 kg/a).

Regarding site-specific emission data to air industry states that there are 11 sites where no CHPTAC emissions to air exist (CEFIC, 2000c). In addition there are 3 sites using CHPTAC where emissions are estimated to be 0.308 kg/a, 0.648 kg/a and 1.75 kg/a (QUAS, 2003). 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 CHPTAC in paper making (industrial use scenario 2)

Emissions of CHPTAC are likely from the use of starch in the production of paper and board due to residual levels of CHPTAC in the starch. In addition, CHPTAC 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 cationised starch will be added in both sections of the paper machine.

Therefore release estimations from production of three different kinds 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 news paper) (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 in the EU by paper and board industry is around 550 000 tons per year, representing more than quarter of the total starch consumption (CEFIC, 2000a). Concentration of CHPTAC in the cationised starch as a residue will vary due to type of the starch product and process parameters. In the latest survey from 2003 the CHPTAC concentration ranged from < 10 to 3070 mg/kg in the 58 commercial cationic starch available on the European market. For the release calculations value of 90th percentile, 450 mg/kg for CHPTAC, will be used.

Before the cationised starches will be 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 37 % of the CHPTAC was degraded and the degradation was dependent on the pH (at higher pH CHPTAC was converted to EPTAC) (Raisio Chemicals, 1999).

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

Cationised starch is added to the head box of the paper machine with other wet-end solids. The amount of cationised 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 paper and in addition it is assumed that also AKD-wax will be added (0.5 kg/ton), which contains cationic starches. The amount of residual CHPTAC from wet end additive is: 10 kg/ton x 450 mg/kg = 4500 mg/ton and from AKD-wax 0.5kg/ton x 450 mg/kg = 225 mg/ton. After jet-cooking the amounts will be reduced to 2835 mg/ton and 142 mg/ton, respectively. The total CHPTAC volume is thus 2977 mg/ton paper (dry furnish) i.e. roughly 3 g/ton.

Adsorption of CHPTAC to the fibers 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 component (Neimo, 1999). CHPTAC 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 CHPTAC 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.

Cationised starch is used in paper 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 this 2286 tons by the concentration 2.977 g/ton we get the maximum daily release of 6.85 kg/day to WWTP. This corresponds to 2.4 tons per year.

Printing and writing paper (case 2)

For some paper types like printing and writing paper cationised 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 CHPTAC from wet end additive is 3150 mg/ton (7 kg/ton x 450 mg/kg) and from AKD-wax 675 mg/ton (1.5 kg/ton x 450 mg/kg). After jet-cooking the amounts will be reduced to 1985 mg/ton and 425 mg/ton. Total CHPTAC volume from wet end usage is thus 2410 mg/ton paper i.e. roughly 2.4 g/ton.

Adsorption of CHPTAC on fibre is poor, maximum 1 %, so 99 % of the substance is assumed to maintain in the waste water. However, adsorption of cationic starch in the wet end and in 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 2.41 g/ton we get the maximum daily release of 5.165 kg/day to WWTP. This corresponds to 1.8 tons 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 CHPTAC in paper recycling (industrial use scenario 3)

Releases of CHPTAC are possible from paper recycling because of CHPTAC 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, 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 CHPTAC 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 CHPTAC as impurity) is used in printing and writing paper. This gives a starch consumption value of 522 500 t/y for printing and writing paper in EU. 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 the 11.1 million tonnes. Default value of 60 % (from ESD) is used for calculating the fraction which goes to recycling from commercial, 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 CHPTAC in copy paper, 1216 mg/tonne of paper (Raisio Chemicals, 2001), the total amount of CHPTAC which enters to recycling sites each year is 8.64 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 CHPTAC amount which enters to the recycling stream (8.64 t) by the number of recycling sites results the average amount of CHPTAC, 17.28 kg/y, which is used per site. Operation days of 350 is used to get daily input to the site which is 0.049 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 CHPTAC from the paper, hence 0.049 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 CHPTAC 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 CHPTAC from use of AKDs during paper and board production have been considered at the industrial use scenario 2. An attempt to estimate CHPTAC 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 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 production 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. 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.

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 15 t/y. As the CHPTAC residue in cationic starches is 450 mg/kg (90^{th} percentile) this will result an CHPTAC release of 6.75 kg/y. If we further divide this with number of operation days (300 days assumed) we get 22.5 g/d. This will be used further in PEClocal calculations.

An emission factor of 0.25 % to air for can be found for formulation from the TGD for Industrial category 12: Pulp, paper and board Industry. As the volume of CHPTAC 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 CHPTAC and EPTAC (industrial use scenario 5)

In 2001 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. 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 CHPTAC releases are 0.75 tons per year (3.75 kg/d x 200 d) (Table 3.5). .

Furthermore industry has provided data from one site (site 27) where quaternisation of substances other than starch is being carried out with CHPTAC. Based on site specific information there will be no releases to water compartment from this site due to dry

production process (Table 3.5). In addition there are two sites using EPTAC for quaternisation of substances other than starch, where also small CHPTAC releases have been measured (Table 3.5). However, at sites B1 and B2 EPTAC was used fairly seldom, only about 10 days in 2002, which partly explains small releases.

Table 3.5 Releases of EPTAC and CHPTAC from other uses (releases presented in bold are based on measurements or other site-specific information)

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.
B2	**0.005**	**0.08**	Based on influent concentration. Size of municipal WWTP known.
B27	0	**0**	No emissions to water, dry process.
B29	**450**	**750**	Based on influent concentration. Size of 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 have not been estimated from these uses. Regarding site B29 emissions to air according to TGD default emission factor of 0.001 % results 9 kg/a (0.0459 kg/d) emissions to air.

3.1.2.4 Regional and continental releases

Due to CHPTAC conversion half-life of 21 days to EPTAC at environmentally relevant conditions (pH 7.8 and temperature 12 ˚C) (see 3.1.3.1.2) the toxic effects of CHPTAC to aquatic environment will be caused by EPTAC at the regional and continental scale. Toxicity of CHPTAC is lower than toxicity of EPTAC (see 3.2.1.2). Therefore no CHPTAC release estimation at regional and continental scale has been carried out in the risk assessment report on CHPTAC, but will be estimated at the regional and continental scale in the EPTAC Risk Assessment Report.

There is no information of the conversion rate of CHPTAC to EPTAC in the terrestrial environment, but in general it can be assumed to be slower than in water. However, as the adsorption of CHPTAC to sludge is low (see 3.1.3.2.1) and no direct releases to soil exist, the terrestrial releases are low. Therefore regional estimation has not been carried out for CHPTAC in the terrestrial environment.

Regarding air emissions the vapour pressure and the Henry's law constant for CHPTAC are low, $< 10^{-3}$ Pa and $<2.25 \times 10^{-7}$ Pa x m^3/mol respectively. Also according to several starch cationisation plants there are no CHPTAC emissions to air or the emissions are low (see 3.1.2.3.1). Therefore no regional estimation has been carried out for CHPTAC in the atmospheric environment.

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 CHPTAC. 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 7.1 hr. As the substance has low vapour pressure (< 0.001 Pa, tested at 20 – 150°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

Abiotic degradation of CHPTAC has been studied in two tests. In a hydrolysis test carried out according to EC guideline C.7 half-life of CHPTAC was estimated at pH values 4, 7 and 8.7 (CEFIC, 1998b) at temperatures 50 and 35 ˚C. In another study conducted by Raisio Chemicals (Raisio Chemicals, 2004a) abiotic degradation was studied at pH values 7.0, 7.8 and 8.4 at 12˚C. Additional information on hydrolysis rate of CHPTAC can be found from a adsorption test to sludge and from a chronic Daphnia test. Degradation of CHPTAC to EPTAC is not a clear hydrolysis reaction but more a conversion reaction. Therefore the hydrolysis will be referred later as conversion.

In a test carried out with EC guideline only 1.7 % of the test substance was converted after five days at pH 4 and 50 ˚C. Therefore a half-life of more than a year was estimated for CHPTAC at pH 4 at 25 ˚C (Table 3.6).

At pH 7 half-life was 3.75 days at 35 ˚C, from where half-life of about 27 days at 25 ˚C was estimated. If the temperature correction is made to the extrapolated half-live at 25 ˚C according to revised TGD, corrected half-live at 12 ˚C would be 75.5 days at pH 7 (Table 3.6). However, there are indications that conversion rate in neutral pH might be remarkably higher than reported in hydrolysis test referred here. In the octanol-water partition test measured with Shake Flask Method (OECD 107) the result from test with pH 7 could not be used, because the CHPTAC converted too fast at neutral conditions (see section 3.1.3.2.1 Adsorption).

At pH 8.7 and 50 ˚C CHPTAC converted very rapidly, after 2.4 hours the test substance could not be determined in the solution anymore. Therefore it was estimated that the half-life at 25 ˚C at pH 8.7 is less than one day (Table 3.6).

The tests indicate that conversion reaction is directly influenced by the OH^- -concentration and in alkaline conditions CHPTAC will convert primarily to EPTAC (2,3-epoxypropyl-trimethylammonium chloride).

Table 3.6 Conversion rates of CHPTAC in the EEC C.7 test

	T ½ (35 ˚C)	T ½ (25 ˚C)	T ½ (12 ˚C)
acidic (pH 4)		> 1 year [2]	
neutral (pH 7)	3.75 days [1]	27 days	75.5
alkaline (pH 8.7)		< 1 day [2]	

[1] Measured at 35 ˚C

[2] Estimated from test at 50 ˚C

An additional study was performed in 2004 by Raisio Chemicals on CHPTAC to evaluate the degradation rate at more realistic environmental conditions i.e. at pH values 7.0, 7.8 and 8.4 in 12 ˚C. 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 %). During the tests concentrations of CHPTAC, DIOL and EPTAC was measured by HPLC-method. In the test conditions CHPTAC reacted with OH-ions, which led to formation of EPTAC.

At pH 7.0 (range: 6.86 - 7.04) and 12.0˚C degradation of CHPTAC was slow: in 35 days concentration of CHPTAC degreased only 6.5 %. As a result a half-life of approximately 6700 hours i.e. 279 days has been received (Table 3.7).

At pH 7.8 and 12˚C the test was performed in duplicate and the results differed from each other only slightly. However, the degradation of CHPTAC was clearly faster in pH 7.8 than in pH 7.0: a half-life of 533 hours (22.2 days) and 476 hours (19.8 days) were received in duplicates. The pH dropped during the test to 7.2 which was due to consumption of hydroxyl ions in the conversion reaction. Decreasing pH led to slower degradation rate as well. Therefore the correlation between CHPTAC concentration (ln conc.) and time is not a linear but curved. For the estimation of rate constant at pH 7.8 only those values where pH was 7.8 ± 0.1 was used in calculation. The combined degradation rate from the duplicates was 505 hours i.e. 21 days (Table 3.7). It can be observed that as the CHPTAC concentration decreased, concentration of both EPTAC and DIOL increased. EPTAC concentrations were at the beginning of the test 4.5 and 9.7 mg/l and after 35 days 286 and 290 mg/l. 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. Based on this study further conversion of EPTAC to DIOL seems to be much slower at pH 7.8 that conversion from CHPTAC to EPTAC. An average half-life of 138 days has been calculated for conversion of EPTAC to DIOL (see Risk Assessment Report on EPTAC).

Degradation of CHPTAC was fastest at pH 8.4 (12˚C): half-life was reached within 127 hours (5.3 days). The pH dropped during the test to 8.1 and therefore the correlation between CHPTAC concentration (ln conc.) and time was curved. For the estimation of rate constant at pH 8.4 only those values where pH was 8.4 ± 0.1 was used in calculation. It can be observed that 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. Also at pH 8.4 the conversion of CHPTAC to EPTAC was faster than conversion of EPTAC to DIOL, where average half-life of 98.5 days has been calculated (see Risk Assessment Report on EPTAC).

Table 3.7 Conversion rates of CHPTAC (Raisio Chemicals 2004a)

pH	T ½ (12 ˚C)
7.0	279 days
7.8	21 days

8.4	5.3 days

In the latter study conversion seems to be slower than in the former study. Considering that in the former study half-lives at 25 ˚C were calculated from 35 ˚C or even 50 ˚C this may cause substantial uncertainties in the extrapolation. In two other tests, namely sludge adsorption test and chronic Daphnia test fairly rapid conversion of CHPTAC can also be observed. In the sludge test the abiotic removal of CHPTAC in the abiotic and sterile controls was 22-27 % in 3 days. In the 21 day semi-static Daphnia test both substances were measured, and the percentile of EPTAC conversed from CHPTAC was approximately 30 % of the total sum after 2 days. The pH range based on measurements once per week was 7.85 at 0 hour to 8.94 at 2 days. Test solutions were renewed 3 times in a week. The temperature range was from 20.6 to 21.6 ˚C.

Based on the European GEMS database 50-percentile value for the pH of the European surface water is about 7.8. Therefore the half-life of 21 days at pH 7.8 is used for the calculation of CHPTAC concentrations at regional and continental scale. In addition, as the degradation product EPTAC is more toxic than CHPTAC, all CHPTAC releases at regional and continental scale will be converted to EPTAC and taken into account in the regional and continental assessment in EPTAC Risk Assessment Report.

Biotic

Biodegradation of CHPTAC was tested in a modified Sturm test (OECD 301B), but using pre-adapted inoculum (Table 3.8, test no 1). Test was conducted with two concentrations, 20 and 10 mg/l, and the CHPTAC was found to be more rapidly degraded with higher concentration than with lower concentration, 42 % and 9 % respectively. Test pH's were 5.1 and 5.4. Test duration was 27 days, preceded by 19 days of acclimatisation. Test was conducted under GLP, except for the stability of the test substance (no further information has been given in the test report to what this GLP statement means).

In 2006 an STP simulation test (Porous pot test) was conducted for CHPTAC according to OECD 303A (Table 3.8, test number 2). Test period was 135 days, where DOC elimination of the organic medium reached a degradation rate of > 80 % after 13 days and test item application started on day 40. Once the DOC results indicated removal of CHPTAC, the specific analysis of CHPTAC, EPTAC and DIOL were carried out via LC-MS/MS. Influent and effluent concentrations and adsorption on the activated sludge were determined for selected samples. Influent concentration of CHPTAC was 78.4 mg/l, which is in the range of measured influent concentrations at starch cationisation sites. The primary degradation of CHPTAC was in the range of 5 – 49 %. No clear degradation tendency was observed and no plateau was reached. Mean primary degradation was calculated from 14 (out of total 23) measurements which were done on days 100 – 113, corresponding to days 61 – 74 of test item application. The mean primary degradation of CHPTAC was 28 ± 14.3 %. As the sludge retention time was 6 hours, an average half-life of 10.7 hours can be calculated. This can be translated to a rate constant of 0.0648 h-1, which according to TGD is lower than for substance which is inherently biodegradable. Applying this rate constant a degradation of 30.6 % at STP can be calculated with EUSES (Simple Treat).

In test 3 (Table 3.8) measuring oxygen consumption degradation of 22 % was observed after 20 days with mixture of CHPTAC (51 % i.e. 1000 mg/l), 1,3-bis(trimethylammonium)-2-hydroxypropane dichloride (9%) and water (40%). Sludge used was probably non-adapted. No data on dilution water, concentration of the inoculum, pH or temperature. No data on how evolved carbon dioxide has been treated. No reference compound in the test.

In test 4 (Table 3.8) biodegradation of CHPTAC was studied in batch and continuous cultures by monitoring the removal of dissolved organic carbon (DOC). Batch cultures were inoculated with biological sludge from the starch industry (presumably adapted) and incubated under a) aerobic, b) anaerobic ($NaNO_3$ present, but no oxygen) and c) anoxic conditions at 30 °C. Concentrations of organic matter in the sludges were 0.2 g/l, 0.5 g/l and 3 g/l, respectively, which are much higher than typically used in ready tests. A blank sample, a sterile control sample and a toxicity control sample were incubated at the same time. pH of the mineral medium was 7, but pH's in batch cultures were not recorded. There is no data on reference substance. Under aerobic conditions (test 4a) 90 % removal of DOC was observed after three days using CHPTAC concentration of 563 mg/l (3 mM). No further degradation was observed from day three till day 10. In the sterile control sample no DOC removal was observed.

Under anaerobic conditions (test 4b) decrease of DOC was observed after 17 days: between day 17 and 38 the DOC concentration decreased 44 % when starting concentration of CHPTAC was 508 mg/l (2.7 mM). In addition, formation of chloride (i.e. dechlorination) occurred at the same rate in the sterile control as in the bottle with microbes, so the dechlorination was not caused by micro-organisms. No DOC was removed under anoxic conditions (test 4c) in 43 days when the starting concentration was 470 mg/l (2.5 mM).

In a modified semi-static test (test 4d) 12.5 mM CHPTAC-C (2.1 mM = 395 mg/l CHPTAC) and 10 mM acetate-C (as alternative source of carbon) were introduced in the effluent containing adapted sludge (volume of sludge 100 ml). pH was between 6.5 and 7.3 during the test. Unlike in the OECD 302A SCAS-test (modified semi-continuous activated sludge method) with daily fill-and-draw procedure, filling in this test was done twice, on day one and on day 14 and the duration of test was 25 days. DOC concentration in the effluent increased to 6.7 mM C on day 2 and stayed relatively constant till day 5. From day 5 onwards the DOC concentration slowly decreased up to 2.7 mM (at day 14). On day 14 a new bottle of medium was connected to the culture which caused an increase of DOC to 5.2 mM. From day 23 onwards a stable DOC concentration of 1.4 mM C was measured. The author of the test concludes that this corresponds to a removal efficiency of 97 %. It is not clear how the author has calculated this result. If we calculate the removal by separating the two additions, we get about 60 % removal at the first addition and 73 % removal at second. In a reference/similar test, but without acetate as an alternative carbon source, the concentration of DOC and chloride were virtually the same.

Table 3.8 Biodegradation test results for CHPTAC

No.	Type of test	Detection	Deg.	Period	Method	Conc.	Conc. of inoculum	Reference
1	Ready, but adapted sludge	CO_2	9 % 42 %	27 d 27 d	OECD 301B	10 mg/l 20 mg/l	$200x10^7$ cells/ml	(Chemishe Fabriek Zaltbommel, 1989)
2	STP simulation	DOC CHPTAC EPTAC	28 ± 14.3 % in 6	135 d	OECD 303A	78.4 mg/l	2.5 g/l	(CEFIC, 2006)

No.	Type of test	Detection	Deg.	Period	Method	Conc.	Conc. of inoculum	Reference
		DIOL	hours					
3	Inherent	O_2 consumption	22 %	20 d	Other	1000 mg/l	No data	(Dow Chemical (U.S.A.), 1978), (DOW Chemical Company, 1993)
4a	Inherent, aerobic	DOC	90 %	3 d	Other	563 mg/l	0.2 g/l of organic matter	(De Jong et al., 1996)
4b	Inherent, anaerobic	DOC	44 %	38 d	Other	508 mg/l	0.5 g/l of organic matter	(De Jong et al., 1996)
4c	Inherent, anoxic	DOC	0 %	43 d	Other	470 mg/l	3 g/l of organic matter	(De Jong et al., 1996)
4d	Inherent, semi-continuous	DOC	60 % 73 %	14 d 10 d	Similar to modified SCAS test (OECD 302A)	395 mg/l no data	No data (100 ml sludge)	(De Jong et al., 1996)

Conclusion on aquatic biodegradation

From the two guideline studies (modified Sturm test (OECD 301B) and STP simulation test (OECD 303A)) it can be concluded that CHPTAC is not readily biodegradable. However, the removal rate constant received from the STP simulation test (0.065 h^{-1}) is close to removal rate for inherently degradable substance, which fulfils the criteria set in the TGD (0.1 h^{-1}).

In other, non-standard tests some removal of CHPTAC have been observed: in test 3 with possibly non-adapted sludge degradation of 22 % was observed. In tests 4a-c sludge from the starch industry, presumably adapted, was used. Test 4d was similar to modified SCAS test (OECD 302A), but according to TGD a rate constant of 0 hr^{-1}(i.e. not biodegradable) should be used for SCAS test result. According to TGD, usually more than 70 % biodegradation within 28 days indicates that the substance is inherently biodegradable. So the only test where higher than 70 % degradation was observed was test 4 a, but the test conditions (adapted sludge and high temperature) were more favourable for biodegradation than in inherent tests in general.

Furthermore nine starch cationisation sites have provided measured CHPTAC influent and effluent concentrations (3.1.4.1.2, Table 3.12). For most of the sites concentration in untreated waste water at WWTP is higher than measured concentration in the effluent i.e. removal of 36, 50, 58, 73, 88, 89 and 93 % of CHPTAC can be seen. This decrease could be partly due to biodegradation, but also due to conversion 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 40 to 360, with majority between 100 to 262 days. Therefore the exposure of CHPTAC to microbes at WWTP may not be constant at all cationisation sites, and thus microbes may not be adapted to degrade CHPTAC 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 CHPTAC can be regarded as inherently biodegradable, but not fulfilling the criteria set in the TGD. As a consequence the CHPTAC half-lives will in STP be 10.7 hours, in surface water 150 days and in sediment 300 d. However, it needs to be kept in mind that degradation of CHPTAC will result formation of more toxic EPTAC i.e. degradation percentage of CHPTAC does not mean mineralisation, but mainly primary degradation.

Biodegradability of the EPTAC(/CHPTAC) hydrolysis product

Biodegradability of the hydrolysis product of EPTAC(/CHPTAC), 2,3-dihydroxypropyltrimethylammonium chloride (DIOL) 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. A 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 dihydroxypropyltrimethylammonium chloride may be regarded as readily biodegradable.

3.1.3.1.3 Degradation in soil

No degradation studies have been carried out for CHPTAC 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 CHPTAC 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 CHPTAC will partition to water almost totally (100 %) and distribution to other compartments is negligible (soil 8.86 x 10^{-5} %, sediment 1.97 x 10^{-6} % and air 4.54 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 4 (CEFIC, 1998c). As the CHPTAC could not be detected in the 1-octanol phase, the partition coefficient has been calculated with the detection limit of CHPTAC in the 1-octanol phase (<50 mg/l) and with the concentration of CHPTAC in water, which ranged from 1583 to 1634 mg/l. This gives an average Pow of < 0.03 or log Pow of < -1.5. The result from test with pH 7 could not be used, because the CHPTAC hydrolysed too fast at neutral conditions.

Determination of a Koc from log Pow is not realistic, because the common calculation method for Koc in the TGD is not suitable for ionic (cationic) organic substances like epoxide or CHPTAC. 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 CHPTAC. However, in a new adsorption test on activated sludge only very slight or no adsorption could be observed. In a 72 h test with ISO 18749 test guideline the removal of CHPTAC from water was 22 %, but also at the abiotic control (without the sludge) and sterile control (with sterile sludge) the removals were almost the same, 22 % and 27 % respectively (CEFIC, 2003). As the concentration of CHPTAC in the sludge was not measured at the end of test it is not possible to estimate the partition coefficient (Kd) to sludge.

From new STP degradation simulation test (conducted according to OECD 303A) it was possible to estimate a partition coefficient to sludge. 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 CHPTAC in activated sludge ranged between 0.388 mg/g – 3.9 mg/g (average 1.71 mg/g) and in the aqueous phase between 33.7 mg/l – 68.1 mg/l (average 49.7 mg/l) (CEFIC, 2006) . Adsorption to sludge can be calculated as follows: Kp_{sludge} = conc. in sludge/conc. in water =1710 mg kg^{-1} / 49.7 mg l^{-1} = 34.4 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 68.8 l/kg. This Koc-value will be used in further calculations.

In addition, at one starch cationisation plant concentration of CHPTAC and EPTAC has been measured from the sludge. The CHPTAC concentrations range from < 1 mg/kg to 5 mg/kg (90^{th} percentile 4.4 mg/kg) in the sludge. The CHPTAC influent and effluent concentrations (90^{th} percentile) were at the same time 63.2 (influent) and 4 mg/l (effluent). These sludge concentrations are 1000 times lower compared to concentrations in degradation simulation study above.

Adsorption of CHPTAC to soil or sediment may differ from adsorption to sludge due to higher content of clay/minerals in soil and sediment.

<u>Adsorption of a similar kind of quaternary ammonium compound to soil and sediment</u>

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 100ml 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-trimethyl-ammonium-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 CHPTAC to soil, sediment or suspended matter are not available, the calculated value for the chlormequat-chloride could serve as a realistic surrogate value for CHPTAC (with known limitations). Like the chlormequat-chloride also positively charged quaternary nitrogen group in CHPTAC 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 CHPTAC 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 CHPTAC 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 CHPTAC to soil. However, as there is information on CHPTAC adsorption to STP sludge, an Koc value has been derived for CHPTAC from this study. This Koc (68.8 l/kg) can be used to estimate Kp values for CHPTAC in soil, suspended matter and sediment. Partitioning coefficients (Kp) based on the measured log Pow (-1.5) and estimated from a measured Koc have been presented in Table 3.9. Partition coefficients estimated from the measured Koc for soil, suspended matter and sediment will be used in further calculations.

3.9 Partition coefficients for CHPTAC.

	Calculated (from log Pow)	Calculated (from measured Koc)	Definition
Koc	0.077 l/kg	68.8 l/kg	Partition coefficient organic carbon-water
Kp_{soil}	1.54 x 10^{-3} l/kg	1.38 l/kg	Partition coefficient solid-water in soil
Kp_{susp}	7.68 x 10^{-3} l/kg	6.88 l/kg	Partition coefficient solid–water in suspended matter

Kp_{sed}	3.84 x 10^{-3} l/kg	3.44 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.

3.10 Partition coefficients for CHPTAC (dimensionless)

	Calculated (from log Pow)	Calculated (from measured Koc)	Definition
$K_{soil-water}$	0.202 m^3/m^3	2.26 m^3/m^3	Partition coefficient soil-water
$K_{susp-water}$	0.902 m^3/m^3	2.62 m^3/m^3	Partition coefficient suspended matter-water
$K_{sed-water}$	0.802 m^3/m^3	2.52 m^3/m^3	Partition coefficient sediment-water

3.1.3.2.2 Precipitation

No information is available regarding precipitation of CHPTAC. Since the substance is non volatile and emissions to air are negligible, no precipitation is assumed nor measured.

3.1.3.2.3 Volatilisation

A Henry's law constant of < $2.25 \cdot 10^{-7}$ Pa m^3/mol can be calculated using a vapour pressure of < 0.001 Pa (at 20 °C - 150 °C) and a water solubility of 835 000 mg/l (at 20 °C and at pH 3). This indicates that CHPTAC does not volatise from water to air.

3.1.3.2.4 Distribution in wastewater treatment plants

Based on the test data available, 30.6 % of CHPTAC will be degraded and 0.779 % will adsorb to sewage sludge at the wastewater treatment plant when estimated with EUSES. As the CHPTAC does not volatilize, 68.6 % 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 CHPTAC 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 CHPTAC log Kow < -1.5). 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} = 3.36 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})

The local concentration of CHPTAC 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 (0.686 i.e. 68.6 %)
Kp_{susp} = solids-water partitioning coefficient of suspended matter (6.88 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 30.6 % biodegradation and 0.779 % adsorption to sludge at WTTP will be taken into account. It is assumed that 68.6 % of the CHPTAC will be distributed from WWTP to water. Adsorption to the suspended matter 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.

3.1.4.1.1 Calculation of PEC_{local} for production

Based on site-specific information there are 3 sites where no emissions to waste water treatment plant exist. The production at site A2 was ceased in 1998. For the remaining production plant A1, small releases to waste water will occur. Biodegradation (30.6%) and adsorption (0.8 %) have been taken into account at the municipal WWTP. Local concentrations of CHPTAC in the surface water from the production plant has been presented in Table 3.11.

Table 3.11. Concentration of CHPTAC in surface water from the production plants.

Site	Release to municipal WWTP	WWTP $Clocal_{influent}$ (mg/l)	WWTP $Clocal_{effluent}$ (mg/l)	WTTP effluent flow (m^3/d)	Dilution	Clocal = PEC_{local} (µg/l)
A1	0.65 kg/d	0.009	0.006	72 000	10	0.619
A2 *	0	- 0	- 0	-	- 0	- 0
A3	0	-	-	-	-	0

Site	Release to municipal WWTP	WWTP $Clocal_{linfluent}$ (mg/l)	WWTP $Clocal_{effluent}$ (mg/l)	WTTP effluent flow (m^3/d)	Dilution	Clocal = PEC_{local} (µg/l)
A4	0	-	-	-	-	0
A5	0	-	-	-	-	0

* Production has stopped at this site

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

Cationisation of starches (industrial use scenario1)

In Table 3.12 monitoring data on CHPTAC has been used to calculate CHPTAC 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 - 10mg/l) the local PECs will be high compared to PNEC (51 µg/l i.e. 0.051 mg/l).

From monitoring data in Table 3.12 it can be seen that the removal of CHPTAC will take place in WWTP at most of the starch cationisation plants. For 7 sites removal ranges between 36-93 % as for two sites (B17 and B18) 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.

In the absence of monitoring data PECs in Table 3.13 have been calculated by using the release factor of 2.2 %, which is from a another starch cationisation plant. In addition 30.6 % biodegradation and 0.8 % adsorption has 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. As presented in 3.1.4.1. the effect of adsorption to surface water PECs seems to be so minor that it has not been taken into account in the calculations for PECs in Table 3.13.

Table 3.12 Concentration of CHPTAC in water from starch cationisation with EPTAC or CHPTAC – based on effluent monitoring data (bold= measured). If municipal WWTP available, the removal of 31.4 % taken into account.

Site	Concentration in water from the starch cationisation plant, partial stream (mg/l)	Concentration in industrial WWTP effluent $Clocal_{effluent}$ (mg/l)	Removal at industrial WWTP (%)	Industrial 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 = PEC_{local} (µg/l)
	CHPTAC users							
B 3	**32** (highest concentr.)	**< 3** (detection limit)	89	2400	<7.2	< 0.235	206.7	< 1.14
B4	**100**	**<10** (detection limit)	58	800	(<8.0)	(< 10)	596	< 16.8
B5	**80.4** (min), **100.0** (avg.) and **150.0** (max) (90^{th} percentile)	**4.57** (90^{th} percentile)	73	2760	12.6	0.024	3.22	7.5
B14	**63.2** (90^{th} percentile)	**4** (90^{th} percentile)	36	6900	(27.6)	(4)	1000	4
B17	**12** (90^{th}percentile)	**< 0.7** (detection limit)	0	8570	<1.80	**< 0.06** (detection limit)	7.17	< 8.37
B21	**102.5** (90^{th} percentile)	LOQ **= <2** (90^{th} percentile), will be divided by 2 => 1	88	3192	3.19	0.081	5.8	14
B25	**30** (90^{th} percentile)	LOQ= **< 2** (90^{th} percentile), will be divided with 2 => 1	50	7500	(7.5)	(1)	11	90.9
	EPTAC users							
B16	**53.60** (highest concentr.)	**< 3.6** (detection limit)	93	300	< 1.08	< 0.114	16	< 7.12
B18	< **3.6** (detection limit)	**< 3.6** (detection limit)	0-	160	< 0.576	< 0.0395	1000	< 0.04
B19[1)]	-	-	-	-	-	-	-	-
Total					69.55			

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

Table 3.13 Concentration of CHPTAC in water from starch cationisation with CHPTAC and EPTAC – based on calculated release factor of 2.2 % (biodegradation of 30.6 % and 0.8 % adsorption at the WWTP is assumed).

Site	Release to industrial WWTP (kg/d)	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 receiving water (kg/d)	Dilution	Clocal = PEC_{local} (µg/l)
	CHPTAC users						
B10	29.69	8.48	5.82	3500	20.4	23.22	251
B23	152.6	22.4	15.4	6800	104.7	2.04	7 549
B26[1)]	-	-	-	-		-	-
	EPTAC users						
B9	45.43	13.0	8.9	3500	31.2	23.22	383

1) This site has been closed in 2004

In addition, there are 4 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 CHPTAC in paper making (industrial use scenario 2)

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

Releases due to residual levels of CHPTAC in the cationised starch used in the production of paper and board have been estimated to be 6.85 kg/day from the wet-end use at plant which produces 800 000 tons board per year. 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 0.160 mg/l . When we take further biodegradation (30.6 %), adsorption (0.8 %) and dilution to the receiving water into account by using a default factor of 10, this will result a local concentration of 0.0110 mg/l (i.e. 11.0 µg/l) in the surface water.

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 lower releases per day i.e. 5.77 kg/day (i.e.1938 ton/d x 2.977 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, 0.361 mg/l, than in the previous bigger mill. Further biodegradation (30.6 %), adsorption (0.8 %) and dilution by a factor of 10 would result a local concentration of 0.0248mg/l (i.e. 24.8µg/l) in the surface water. This case is presented in EUSES.

<u>Printing and writing paper (case 2)</u>

CHPTAC releases from production of printing and writing paper have been estimated to be 5.165 kg/day. If the average production of waste water is 15 m^3/ton at plant which produces

750 000 tons paper per year, this means 42 855 m^3waste water per day. Then the concentration in the WWTP would be 0.121 mg/l. When we take further biodegradation (30.6 %), adsorption (0.8 %) and dilution to the receiving water into account by using a default factor of 10, this will result a local concentration of 0.0083mg/l (i.e. 8.3µg/l) in the surface water.

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. 4.67 kg/day (i.e.1938 ton/d x 2.41 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, 0.29 mg/l, than in the previous bigger mill. Further biodegradation (30.6 %), adsorption (0.8 %) and dilution (by a factor of 10) would result a local concentration of 0.0199 mg/l (i.e. 19.9µg/l) in the surface water. This case is presented in EUSES.

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.

Recycling of printing and writing paper with residual CHPTAC (industrial use scenario 3)

Releases due to residual levels of CHPTAC in recovered printing and writing paper material used in recycling plant (incl. deinking process) have been estimated to be 0.049 kg/day. Adsorption of CHPTAC to sludge is low, only 0.8 % is calculated (EUSES) to adsorb to sludge. Taking adsorption and further biodegradation (30.6 %) into account 68.6 % of CHPTAC i.e. 0.0336 kg/d is emitted to water. If the average production of waste water is 2880 m^3/d, the CHPTAC concentration in water is then 0.0117 mg/l. Further dilution by a factor of 10 to the receiving water will result the concentration of 1.2 µg/l in the surface water.

Use of starch with residual CHPTAC 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 CHPTAC residue in cationic starches is 450 mg/kg (90^{th} percentile) this will result an CHPTAC release of 6.75 kg/y. If we further divide this with number of operation days (300 days assumed) we get 22.5 g/d.

Biodegradation of 30.6 % and adsorption of 0.8 % at the municipal WWTP (2000 m^3/d, TGD default) is expected. This results a concentration of 0.0077 mg/l at the WWTP. Taking further dilution to receiving water into account (10, TGD default), the concentration of CHPTAC in the receiving water will be 0.77 µg/l.

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

Majority of the volume in this scenario is used by one site (B29), which has provided site-specific information on releases. According to monitoring data from waste at industrial site a local PEC for surface water from this site will be 9.67 µg/l (Table 3.14). In addition site-specific data on CHPTAC concentrations have been provided by two smaller sites, where

quaternisation of substances other than starch is being carried out with CHPTAC or EPTAC (Table 3.12). Estimations are based on measured influent concentrations at industrial sites and dilution factor of 100 has been used as the releases are to estuary. At sites B1 and B2 EPTAC was used fairly seldom, only about 10 days in 2002, which partly explains small releases of CHPTAC.

Table 3.14 Monitoring data on concentration of CHPTAC 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 = PEC_{local} (µg/l)
B1	0.0045	0.0031	2960	(9.18×10^{-3})	(0.0031)	100	0.031
B2	**16.7**	**16.7** 0.00026	0.8	0.0134	0.00017	100	0.0017
B27	0						0
B29	**25**	**20**	150	3.0	0.051	5.32	9.67

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 (2.62 m^3/m^3)
RHO_{susp} = bulk density of suspended matter (1150 kg/m^3)

In this equation partition between water and suspended matter has been estimated according to a similar kind of substance (see 3.1.3.2.1) as no data is available on CHPTAC. PEC's for different scenarios have been calculated using highest site-specific fresh water releases within the scenario (Table 3.15) .

Table 3.15 Local PECs in sediment.

Life cycle step	**PEC in sediment (**mg/kg wwt)

Life cycle step	**PEC in sediment (**mg/kg wwt)
Industrial use 1 (starch cationisation)	
B3	< 2.59E-03
B4	< 0.0382
B5	0.017
B9	0.875
B10	0.572
B14	9.11E-03
B16	< 0.016
B17	< 0.0191
B18	< 9E-05
B21	0.0318
B23	17.2
B25	0.207
Industrial use 2 (case 1, board production)	0.025 (0.0563)*
Industrial use 2 (case 2, paper production)	0.019 (0.0456)*
Industrial use 3 (paper recycling)	
Industrial use 4 (AKD formulation)	1.76E-03
Industrial use 5 (other uses)	
B1	7.06E-05 Marine
B2	3.91E-06 Marine
B29	0.022

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

$PEC_{sediment}$ of 0.00141 mg/kg has been calculated for EPTAC production site A1 from site-specific $PEC_{surface\ water}$.

3.1.5 Terrestrial compartment

3.1.5.1 Calculation of PEC_{local}

The EUSES model (1.0) takes into account both the application of STP sludge on agricultural soil and the deposition from air for the calculation of CHPTAC concentrations in the terrestrial compartment. Table 3.16 gives the terrestrial PECs at a local scale (i.e. the concentration measured 30 days after sludge application).

PEC's for different scenarios have been calculated using highest site-specific fresh water releases within the scenario.

Table 3.16 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	
B3	< 0.0134
B4	< 1.7E-05
B5	1.37E-03
B9	7.65E-06
B10	5.01E-06
B14	2.29E-05
B16	< 6.5E-03
B17	< 3.42E-03
B18	< 2.26E-03
B21	4.62E-03
B23	2.83E-05
B25	4.35E-05
Industrial use 2 (case 1, board production)	0.0141
Industrial use 2 (case 2, paper production)	0.0114
Industrial use 3 (paper recycling)	6.68E-04
Industrial use 4 (AKD formulation)	4.39E-04
Industrial use 5 (other uses)	
B1	9.75E-06
B2	9.79E-06
B29	2.94E-03

3.1.6 Atmosphere

3.1.6.1 Calculation of PEC_{local}

Annual average CHPTAC concentrations in air (100 m from point source) estimated according to EUSES 2.0.3 are presented in Table 3.17. 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 3.17 Local PECs in air.

Life cycle step	Annual average local PEC in air (mg/m^3)
Industrial use 1 (starch cationisation)	3.08×10^{-6} - 7.06×10^{-5}
Industrial use 2 (board and paper production)	-

Life cycle step	Annual average local PEC in air (mg/m^3)
Industrial use scenario 3 (paper recycling)	-
Industrial use 3 (AKD formulation)	Negligible
Industrial use 4 (other uses – B29)	6.99 x 10^{-6}

According to site-specific information there are 3 user sites (Industrial use 1), where emissions to air have been estimated. Concentrations in the exhaust stream in the stack at two sites have been 2.1 x 10^{-4} mg/m^3 and < 8 x 10^{-4} mg/m^3. Average air flows have ranged from 3.6 x 10^6 m^3/d to 4.1 x 10^6 m^3/d. 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. CHPTAC 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. According to low adsorptivity of CHPTAC in the sludge adsorption test, bioaccumulation is not likely. The lack of high adsorptive capacity (log Kp < 3) is an additional evidence of low bioaccumulation potential.

It seems likely, that CHPTAC would not bioconcentrate in high degree. CHPTAC is not classified as Toxic (T) or Very Toxic (T+), but it is classified as harmful (Xn) without R48, 60, 61 or 62 phrases on the basis of mammalian data. Therefore no assessment of secondary poisoning is necessary.

3.1.8 Calculation of $PEC_{regional}$

Regional PECs have not been calculated as the risks posed by CHPTAC are assumed to be due to degradation product EPTAC at the regional scale. This will be considered in the risk assessment of EPTAC.

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 short term toxicity studies on fish, Daphnia and algae available for CHPTAC. In addition there is an acute toxicity test on bacteria and one chronic Daphnia reproduction test available. Due to the nominal concentrations used and the lack of chemical analyses of the

substance in the short term tests it is probable that part of the CHPTAC in test conditions has been hydrolysed to EPTAC. According to conversion tests CHPTAC was moderately stable at pH 7 (T ½ 279 d), but converted more rapidly in pH 7.8 (T ½ 21 d) and pH 8.4 (T ½ 5.3 d) at 12 ˚C (see 3.1.3.1.2). In the chronic semi-static test the concentrations of CHPTAC and its conversion product EPTAC were determined. Only studies that are considered valid are cited in the following tables.

Some of the studies were performed with aqueous solution of CHPTAC (65-69 %) and also results in the study reports were expressed as diluted CHPTAC. Therefore results from the test reports have been corrected as 100 % CHPTAC.

3.2.1.1.1 Fish

The CHPTAC is very slightly toxic to fish. In a short-term toxicity study the nominal LC_{50} value for fish is 4128 mg/l (Table 3.1.8). The pH ranged from 6.5 to 8.0, and pH lower than 7.0 was observed with the highest test CHPTAC concentration (10 000 mg/l, nominal). Two other studies are rejected due to poor documentation, missing information and unclear interpretation of the test results.

Table 3.18 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*	4128 (2094)	96 h	OECD 203	65.4 % CHPTAC	(Degussa, 1988a)

3.2.1.1.2 Aquatic invertebrates

The CHPTAC short-term toxicity studies for aquatic invertebrates are summarised in Table 3.19.

Table 3.19 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*	240.2 (36.6)	24 h	OECD 202	65.4 % CHPTAC	(Degussa, 1988b)
Static	*Daphnia magna*	164 (62.5)	48 h	OECD 202, EC method C.2, EPA OTS 7979.1300	99.5 % CHPTAC	(DOW Chemical Company, 1996)

There are two valid studies on Daphnia magna where acute nominal EC_{50} -values ranged from 164 mg/l to 240.2 mg/l. In the Degussa study aqueous solution of CHPTAC has been used (65.44 %) and therefore results from the test report have been corrected as 100 % CHPTAC. In the Degussa study pH values ranged at the beginning of the test from 7.7 to 8.0 and in the end of the test from 7.3 to 8.0. In the Dow study pH values ranged at the beginning of the test from 7.5 to 7.8 and in the end of the test from 7.0 to 7.6. Lowest pH values could be seen with highest test concentrations in both studies.

Results from the chronic (21 day) Daphnia reproduction test are presented in Table 3.20. The chronic study on Daphnia magna was semi-static, the test solutions being renewed 3 times per week. During the test concentrations of CHPTAC and its conversion product EPTAC were determined in all test concentrations (0.17, 0.51, 1.52, 4.56 and 13.7 mg/l) and in controls. The CHPTAC concentrations decreased within 48 hours, whereas increasing concentrations of the conversion product EPTAC were found. The average percentage of EPTAC was around 30 % of the total measured sum of CHPTAC and EPTAC as CHPTAC after two days. The recovery rate based on the sum of the active ingredient CHPTAC and the conversion product EPTAC (calculated as CHPTAC) was ≥ 80 %. The results are based on the nominal concentrations of the active ingredient i.e. CHPTAC. The 21 day NOEC for reproduction rate is 0.51 mg/l. The LOEC for reproduction rate is 1.52 mg/l and EC_{50} is between 1.52 and 4.56 mg/l. The EC_{50} based on immobilisation was lower (1.03 mg/l) than the EC_{50} based on reproduction.

Table 3.20 Chronic toxicity data for aquatic invertebrates.

Type of test	Species	Endpoint NOEC reproduction (LOEC) mg/l nominal	Exposure period	Method	Test substance	Reference
Semistatic	*Daphnia magna*	0.51 (1.52)	21 days	OECD 211	65.2 % CHPTAC	(QUAS, 2004b)

3.2.1.1.3 Algae

The CHPTAC toxicity study for algae is presented in Table 3.21.

Table 3.21 Toxicity data for algae.

Type of test	Species	Endpoint ErC_{50} (mg/l)	Exposure period	Method	Test substance	Reference
Growth inhibition test	*Scenedesmus subspicatus*	10 000 (>10 000)	72 h	OECD 201	69.4 % CHPTAC	(CEFIC, 1997i)

The only algae study was carried out according to OECD Guideline 201, except of a few deviations from the guideline. The deviations were following: in the algal medium the concentration of $NaHCO_3$ was twice that indicated in the Guideline and the quantification of the test substance was performed using DOC/TOC determination method. The DOC/TOC method measures total organic carbon and it can not distinguish CHPTAC and its main degradation product EPTAC (at alkaline conditions) from each others. Since the pH has been fairly alkaline (above 9) at the end of test in the lowest test concentration some portion of the CHPTAC must have been converted to EPTAC. In the highest concentrations pH-values have been lower (around 8 or less). Therefore the test concentrations can be regarded as nominal only.

EC_{50}- and EC_{10}-values based on algae growth rate were >10 000 mg/l and 3200 mg/l. However, it is unclear from the test report are the results presented as pure substance or not,

since according to test report the degree of purity of the test substance was 69.4 %. No corrections to the reported EC-values have been made.

3.2.1.1.4 Micro-organisms

CHPTAC 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 3.22). In the test report EC_{20}-, EC_{50}- and EC_{80}-values higher than 2000 mg/l have been reported, and in the addendum to the test report an EC_{10}-value has been estimated to be 1032 mg/l. Therefore this concentration will be used for the PNEC derivation.

Table 3.22 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	69.4 % CHPTAC	(CEFIC, 2002)

The effect of CHPTAC on the dehydrogenase activity of active sludge has been tested (Degussa, 1979a). 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.

In addition there is an experiment from 1978, where it was tested if the addition of cationic wastewater to the non-CHPTAC-adapted wastewater treatment plant is harmful for the biological treatment. It was a fill and draw test with six basin where each basin had different exposure of cationic water and/or CHPTAC. No dose-response has been presented in the report regarding CHPTAC concentration in the waste water, and therefore the study has not been considered relevant for the risk assessment purposes.

3.2.1.1.5 Toxicity of the degradation product of CHPTAC and 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 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 CHPTAC. Daphnids seem to be clearly more sensitive to CHPTAC 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 CHPTAC 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.

This is further supported by results from a similar kind of substance. Pesticide chlormequat-chloride (2-chloroethyltrimethylammonium chloride; CAS N:o 999-81-5) has similar kind of structure with CHPTAC and therefore it can be assumed that the effects in an aquatic organism might be similar. For chlormequat-chloride there are fish, Daphnia, algae and Lemna studies available, including both acute and chronic tests. Chronic NOEC for fish is 43.1 mg/l, chronic NOEC for Daphnia 2.4 mg/l and chronic result for higher plants 5.3 mg/l. Based on these tests Daphnia is the most sensitive organism also for chlormequat-chloride.

Accordingly the PNEC will be derived from the 21 day Daphnia reproduction rate NOEC of 0.51 mg/l with an assessment factor of 10.

$AF_{aquatic} = 10$

This results a **PNEC of 51 µg/l** for the fresh water organisms. This will be used in the risk characterisation on CHPTAC.

According to the TGD an assessment factor of 100 could be use to derive PNEC when emission takes place only a few times a year i.e. an intermittent release. This may happen as a result of batch process. In extrapolating to such a PNEC only short-term effects need to be considered. Thus, PNEC will be derived using the lowest acute EC50 164 mg/l and the assessment factor of 100.

This results a **$PNEC_{aquatic}$ of 1640 µg/l** for intermittent use.

CHPTAC will hydrolyse primarily to EPTAC fairly rapidly when moving from neutral to alkaline conditions in the environment (see section 3.1.3.1.2) and this will be taken into account in the risk assessment of EPTAC at the regional scale.

PNEC for micro-organisms can be derived from the recent activated sludge respiration inhibition test. As no EC_{50}-value could be found in the test with the highest concentration tested, a test concentration of 1032 mg/l, where 10 % inhibition was observed, will be used as EC_{10}-value for the PNEC derivation. 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 103 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 CHPTAC.

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

As there are 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 (2.62 m^3/m^3),
RHO_{susp} = bulk density of suspended matter **(**1150 kg/m^3) and
$PNEC_{aquatic}$ = 0.051 mg/l for CHPTAC

$PNEC_{sediment}$ will be **0.116** mg/kg**,** when using fresh water toxicity data for CHPTAC and the 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 (2.26 m^3/m^3),
RHO_{soil} = bulk density of wet soil (1700 kg/m^3) and
$PNEC_{aquatic}$ = 0.051 mg/l

$PNEC_{soil}$ will be **0.068** mg/kg**,** when using fresh water toxicity data for CHPTAC and a soil-water partition coefficient.

3.2.3 Atmosphere

There is no toxicity data available on CHPTAC via atmospheric exposure. Concerning abiotic effects CHPTAC 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 $2.25 \cdot 10^{-7}$ 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 CHPTAC. However, as CHPTAC has low vapour pressure and small Henry's law constant, it is not expected that CHPTAC could have effect on global warming.

3.3 MARINE ASSESSMENT

The main goals in the marine risk assessment 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. No actual marine assessment has been carried out for CHPTAC as the CHPTAC transforms in sea water in short period of time (t½ = days) to a more persistent EPTAC. Industry associations (CEFIC/QUAS) were asked to identify sites that discharge directly into the sea. In the year 2004 none of the CHPTAC (or EPTAC) production plants or starch cationizing sites 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 cationisation) and which are discharging to an estuary.

For simplicity, the marine assessment of EPTAC tries to fully take into account direct and indirect emission of CHPTAC and EPTAC into marine environment (see chapter 3.3 in

EPTAC RAR). Therefore in the marine regional PEC calculation, the use and emissions of CHPTAC are converted to EPTAC.

3.3.1.1 Partitioning and Degradation in Sea Environment

The conversion rate of CHPTAC to EPTAC is highly dependent on the alkalinity conditions. At pH 8.4 conversion is fast (T ½ 5.3 days) and at pH 7.8 (T ½ 21 days). At sea water alkalinity (ca. pH 8) the conversion is relatively fast. Long term effects are therefore associated mainly to effects of EPTAC.

3.3.1.2 Exposure assessment for the local marine environment

PEC's in Table 3.23 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 3.23). According to information provided by CEFIC QUAS known CHPTAC production or cationising sites do not distribute waste waters to the sea. Therefore no PEC marine has been calculated for those scenarios.

Table 3.23 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.)	5.77	350		3.46E-03	8.22E-03
Industrial Use 2 (paper manuf.)			3.61E-03	2.8E-03	6.65E-03
		350	2.92E-03		
	4.67				
Industrial use 3 (paper recycling)	0.0494	350	1.18E-04	1.13E-04	2.68E-04
Industrial Use 4 (AKD production)	0.0225	300	1.12E-04	9.25E-05	2.56E-04
Industrial Use 5 (other uses)					
B1					
B2	9.18E-03	12	3.1E-05	5.1E-07	7.06E05
	0.013	6	1.71E-06	2.82E-08	3.91E-06

3.3.1.3 Effects assessment for the marine environment

There are three acute test results from three trophic levels available and two long term NOECs for algae and Daphnia. The $PNEC_{marinewater}$ will be derived from the 21 day Daphnia reproduction rate NOEC of 0.510 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 CHPTAC acute test results showed Daphnids to be clearly the most sensitive species and therefore lowering of assessment factor was justified. Therefore an assessment factor of 100 was chosen for the marine environment.

This results a **$PNEC_{marinewater}$ = 5.1 µg/l**

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

$PNEC_{marinesediment}$ = 11.6 µg/kg

3.3.2 PBT-assessment

3.3.2.1 Conclusion for the PBT-assessment

According to existing data and assessment of inherent PBT -properties it can be concluded that CHPTAC can not be regarded as a PBT-substance nor vPvB –substance since it does not meet the B criterion. CHPTAC is considered potentially persistent, thus meeting the screening P-criterion. Also T-criterion can be seen fulfilled regarding human toxicity endpoints due to toxicity of the degradation product of CHPTAC.

Conclusion for the PBT-assessment has been drawn from the following facts:

3.3.2.2 Persistence-criterion

According to existing biodegradation study results CHPTAC is not readily biodegradable. There are two guideline tests available: one regarding ready biodegradability and the other on STP degradation simulation. In a 27 day ready test degradation of 42 % and 9 % was observed at two different test concentrations.In a 135 day STP simulation test 28 ± 14.3 % primary degradation was observed in 6 hours (sludge retention time 6 hours). Although CHPTAC is moderately biodegradable, it is concluded that the screening level P criterion is met.

Conversion rate of CHPTAC to EPTAC is highly dependent on the acidity conditions. At pH 8.4 conversion is fast (T ½ 5.3 days), but at pH 7.8 and pH 7.0 (12 ˚C) slower (T ½ 21 days and 279 days, respectively) at 12 ˚C. Hydrolysis of EPTAC to readily biodegradable product DIOL (Dihydroxy-2,3-propyltrimethylammonium chloride) at neutral conditions (pH 7.0) takes approximately T ½= 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 neutral and acidic aquatic environmental conditions CHPTAC is considered potentially persistent, meeting the screening P criterion. Under alkaline conditions in marine water, CHPTAC is rapidly converted to EPTAC (i.e. within a few days). EPTAC is classified as a potential persistent substance meeting the screening level P criterion (see RAR on EPTAC). Hence also in the marine water compartment CHPTAC is a potentially persistent compound.

3.3.2.3 Bioaccumulation-criterion

There are no bioaccumulation study results available for CHPTAC. 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 CHPTAC does not meet the B-criterion (> 2000) for bioaccumulation.

3.3.2.4 Toxicity-criterion

The lowest aquatic chronic test shows a NOEC of 0.51mg/l. This is slightly higher than the T-criterion of 0.01mg/l. Hence CHPTAC does not meet the T criterion concerning the tested ecotoxicological endpoints. Based on the human health classification: Carc. Cat 3, R40, CHPTAC might fulfill the T-criterion. According to the TGD a Carc. Cat 3 classification is regarded as a borderline case and needs case by case evaluation. Since CHPTAC can convert in the environment to more toxic EPTAC having a more severe Carc Cat 2 classification, the T criterion can be seen fulfilled.

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

Local risk characterisation

PNEC for fresh water organism is 51 µg/l for CHPTAC and this will be used for comparison with predicted environmental concentrations of CHPTAC at the local scale. When emission to waste water takes place only few times per year, PNEC for intermittent release, 1640 µg/l has been used. This concerns one production plant. $PNEC_{sediment}$ has been calculated from $PNEC_{aquatic}$ and is 0.116 mg/kg.

There are PECs based on monitoring data available from production, cationisation of starch and other uses of CHPTAC and EPTAC. PEC/PNEC ratios to surface water from production are presented in Table 3.24. Based on site-specific information there is no local risk to surface water from any of the production sites.

Table 3.24 Site-specific PEC/PNEC ratios in surface water and sediment from production

Site	PEC_{local} (µg/l)	$PEC_{sediment}$ (mg/kg)	PEC/PNEC $_{aquatic\ (\&\ sediment)}$
A1	0.619	1.41E-03	0.0004
A2	-	-	-*
A3	0		
A4	0		
A5	0		

* Production has stopped at this site

Site-specific PEC/PNEC ratios to surface water and sediment from cationisation of starch have been presented in Table 3.25. PECs for sediment have been derived from PECs for water by using equilibrium partitioning method. PEC/PNEC ratios for surface water and sediment are higher than one for 1 site (out of 9), where CHPTAC has been measured from the waste water at the site. For sites, where CHPTAC has not been measured, releases are estimated according to a release factor of 2.2 % from another cationisation site. PEC/PNEC ratios are higher than one for all sites (Table 3.26).

Sites presented in Tables 3.25 and 3.26 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 3 sites with wet process but without releases to water (Table 3.27). As there are no releases of CHPTAC to water from these sites, the risk ratios from these sites to aquatic environment are zero.

Table 3.25 : Site-specific PECs in surface water and sediment (based on measured CHPTAC effluent conc.) and corresponding PEC/PNEC ratios from starch cationisation.

Site	PEC_{local} (µg/l)	$PEC_{sediment}$ (mg/kg)	$PEC/PNEC_{aquatic\ (\&\ sediment)}$
CHPTAC users			
B3	< 1.14	< 2.59E-03	< 0.023
B4	< 16.8	< 0.0382	< 0.329
B5	7.5	0.017	0.146
B14	4	9.11E-03	0.078
B17	< 8.37	< 0.0191	< 0.16
B21	14	0.0318	0.274
B25	90.9	0.207	1.78
EPTAC users			
B16	< 7.12	< 0.0162	< 0.14
B 18	< 3.95E-05	< 9E-05	< 7.75E-04
B 19	-	-	- *

* This site has been closed at the end of 2002

Table 3.26: Site-specific PECs in surface water and sediment and corresponding PEC/PNECratios from starch cationisation. At these sites CHPTAC have not been measured from the waste water, but there are other site-specific information available.

Site	PEC_{local} (µg/l)	$PEC_{sediment}$ (mg/kg)	$PEC/PNEC_{aquatic\ (\&\ sediment)}$
CHPTAC users			
B10	251	0.572	4.92
B23	7549	17.2	148
B26 [1)]	-	-	-
EPTAC users			
B9	383	0.875	7.53

[1)] This site has been closed in 2004.

Table 3.27 Risk ratios from starch cationisation sites with dry process or with wet process, but no releases to water.

Site	$PEC/PNEC_{aquatic}$	Justification
EPTAC users		
B6	0	No waste water from normal process. Spillages 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 (spillages) 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 3.28. PECs for sediment have been derived from PECs for water by using equilibrium partitioning method. PEC/PNEC ratios are lower than one for all scenarios.

Table 3.28 PECs in surface water and 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 CHPTAC (Industrial use 2) * high grade board (case 1) *printing and writing paper (case 2)	11 (24.8) * 8.3 (19.9) *	0.025 (0.0563) 0.019 (0.0456)	0.22 (0.486)* 0.16 (0.392)*
Paper recycling (Industrial use 3)	1.2	2.68E-03	0.024
AKD formulation (Industrial use 4)	0.77	1.76E08	0.0151
Other uses of CHPTAC and EPTAC (Industrial use 5) * site B1 * site B2 * site 27 * site B29	0.031 (marine) 0.0017 (marine) 0 9.67	7.06E-05 3.91E-06 0.022	0.0061 0.0003 0 0.19

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

Regional risk characterisation

Regional risk characterisation has not been carried out as the risks posed by CHPTAC at the regional scale will be considered in the risk assessment of EPTAC.

3.4.1.2 Wastewater treatment plant

PNEC for micro-organisms is 103 mg/l for CHPTAC.

Site-specific PEC/PNEC ratios for micro-organisms at WWTP from cationisation of starch (industrial use 1) have been presented in Table 3.29. For all starch cationisation sites PEC/PNEC ratios are lower than one, and therefore there is no risk to micro-organisms.

For CHPTAC production sites the PEC/PNEC ratios are lower than one.

Table 3.29 Site-specific PECs and corresponding PEC/PNEC ratios at WWTP from cationisation of starch (bold= measured) .

Site	Concentration in untreated waste water $Clocal_{influent}$ (mg/l)	PEC/PNEC
CHPTAC users		
B3	**< 0.235**	< 2.28E-03
B4	**< 10**	< 0.10
B5	**0.024**	2.33E-04
B10	5.83	0.06
B14	**4**	0.04
B17	0.06	< 5.81E-04
B21	**0.081**	7.85E-04
B23	14.4	0.14
B25	**1**	0.010
B26[1)]	-	-
EPTAC users		
B9	8.91	0.09
B16	**< 0.114**	< 1.1E-03
B 18	**< 0.0395**	< 3.83E-04
B 19[2)]	**-**	-

1) This site has been closed in 2004.

2) This site has been closed at the end of 2002.

PEC/PNEC ratios for micro-organisms at WWTP from industrial uses 2, 3, 4, and 5 have been presented in Table 3.30. All risk ratios are lower than one.

Table 3.30 PEC/PNEC ratios at WWTP for industrial use scenarios 2, 3, 4 and 5.

Life cycle step	PEC in WTTP (mg/l)	PEC/PNEC

Life cycle step	PEC in WTTP (mg/l)	PEC/PNEC
Use of starch with residual CHPTAC (Industrial use 2) * high grade board (case 1) *printing and writing paper(case 2)	 0.11 (0.248)* 0.083 (0.199) *	 0.002 0.002
Paper recycling (Industrial use 3)	0.0118	1.14E-04
AKD formulation (Industrial use 4)	0.0077	7.48E-05
Other uses of EPTAC and CHPTAC (Industrial use 5) * site B1 * site B2 * site B29	 3.1E-03 1.71E-04 0.0514	 3.0E-05 1.66E-06 4.98E-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 for four sites with wet process (Industrial use 1) at the local scale (i.e. sites B9, B10, B23 and B25).

From these four starch cationisation sites, which have risk ratio higher than one, only one site (B25) has monitoring data on CHPTAC releases to waste water. However, the detection limit of CHPTAC from waste water effluent (2 mg/l) has been rather high compared to PNEC (0.051 mg/l l). Use of lower detection limit might decrease risks from this site. For those three sites where no monitoring data is available (B9, B10 and B23), releases have been calculated with an actual emission factor from a starch cationisation site with highest release factor (2.2 %). 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, cationisation of starch for seven sites with dry process (B6, B11, B12, B13, B15, B22 and B28) and for eight sites with wet process (B3, B4, B5, B14, B16, B17, B18, B21) (Industrial use 1), 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

Local risk characterisation

For the estimation of PNEC a partition coefficient and $PNEC_{aquatic}$ of CHPTAC is used. $PNEC_{soil}$ will be **0.068** mg/kg. Local CHPTAC concentration and PEC/PNEC ratios are presented in Table 3.32. Risk ratio is lower than one for all use scenarios.

Table 3.32 PEC/PNEC ratios for soil.

Life cycle step	**PEC_{local} terrestrial** (mg/kg wwt)	**PEC/PNEC**
Industrial use 1 (starch cationisation)		
B3	< 0.0134	< 0.197
B4	< 1.7E-05	< 2.5E-04
B5	1.37E-03	0.0202
B9	7.65E-06	1.13E-04
B10	5.01E-06	7.37E-05
B14	2.29E-05	3.38E-04
B16	< 6.5E-03	< 0.096
B17	< 3.42E-03	< 0.05
B18	< 2.26E-03	< 0.033
B21	4.62E-03	0.068
B23	2.83E-05	4.17E-04
B25	4.35E-05	6.41E-04
Industrial use 2 (case 1, board production)	0.0141	0.207
Industrial use 2 (case 2, paper production)	0.0114	0.168
Industrial use 3 (paper recycling)	6.68E-04	9.84E-03
Industrial use 4 (AKD formulation)	4.39E-04	6.46E-03
Industrial use 5 (other uses)		
B1	9.75E-06	1.44E-04
B2	9.79E-06	1.44E-04
B29	2.94E-03	0.0432

Conclusions to the risk assessment for the terrestrial compartment:

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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 CHPTAC no significant exposure to the atmosphere is expected. CHPTAC 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 CHPTAC 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

None of the CHPTAC production sites was situated by the sea in 2004. For industrial uses (scenarios 2-5) local risk characterisation ratios to sea water and sediment have been presented in Table 3.33. For use scenario 1 (starch cationisation) no local estimation has been carried out as no sites were located by the sea (in year 2004). The $PNEC_{marine}$ is 5.1 µg/l and $PNEC_{marinesediment}$ is 11.6 µg/l.

Table 3.33 Marine Risk Characterisation for Industrial Use Scenarios

Emission scenario	PEClocal marine water (µg/l)	PEClocal marine sediment (µg/kg)	PEC/PNEC marine water (& sediment)
Industrial Use 2 (board manufacturing)	3.61	8.22	0.707
Industrial Use 2 (paper manufacturing)	2.92	6.65	0.572
Indusrtial Use 3 (paper recycling)	0.118	0.268	0.0231
Industrial Use 4, AKD-wax production	0.112	0.256	0.0221
Industrial Use 5 (other uses)			
B1	3.1E-05	7.06E-02	6.08E-03
B2	1.71E-03	3.91E-03	3.36E-04

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 (ii) 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

3-chloro-2-hydroxypropyl)trimethylammonium chloride (CHPTAC) is a non-volatile organic salt, which is handled as a water solution in concentrations of 50-70%. The vapour pressure for this chemical is below 0.001 Pa at temperatures 22-150°C with decomposition beginning at 160°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 CHPTAC may arise from working processes and indirectly via food and the environment. Consumer exposure may take place through the residual amounts of CHPTAC in the final products, paper and board, manufactured from cationised starches.

During use of the chemical, the exposure assessment of (3-chloro-2-hydroxypropyl)trimethylammonium chloride (CHPTAC) is very much related to exposure assessment of 2,3-epoxypropyltrimethylammonium chloride (EPTAC) 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 converted with the addition of alkaline. So 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 concentrations of EPTAC, because of its health effects. In this exposure assessment document of CHPTAC the chapters related to uses are the same as in the document of EPTAC.

4.1.1.2 Occupational exposure

The present data concerning occupational exposure to CHPTAC 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. CHPTAC 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. Exposure was evaluated with the EASE (Estimation and Assessment of Substance Exposure) model (EASE for Windows Version 2.0, August 1997). Information from the industry and related information on the manufacture and use of EPTAC was used in the exposure assessment.

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 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 CHPTAC (or EPTAC).

Occupational exposure limits for CHPTAC have not been established.

4.1.1.2.1 Occupational exposure from production

CHPTAC is produced by reaction of trimethylamine, epichlorohydrin, hydrochloric acid and water. Sodium hydroxide is used to catalyse the reaction. Unreacted epichlorohydrin and trimethylammonium chloride is removed by steam distillation. The product is an aqueous solution with CHPTAC content of 50% to 70% (mainly 65%).

The process was described by producers as an automated or semi-automated closed process with batchwise or campaign production.

The total number of workers with the production of this chemical can be estimated to be around one hundred. There are four production plants for CHPTAC. Intermitted work was reported for 11 to 20 people at two sites and up to 10 people at one site. At two sites no females were working in the process, two other sites report 1 to 4 females with intermittent work.

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

Personal protective equipment (PPE) used in manufacture is according to the industry gloves, goggles, respirator or overall protection depending on the situations. 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 from the process and from storage tanks. The concentration of the chemical in the samples is 70% at the maximum. Sampling is performed by the process worker by opening the manual valve in order to partially fill a small flask. Samples from production are

taken every five hours. The process worker must wear goggles and gloves during the sampling operation. Taking a sample and analysing it shortly at the site is considered to last few minutes. Exposure to CHPTAC 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 CHPTAC is 0.1-1 mg/cm2/day. If the concentration of CHPTAC in the sample is about 70 %, the predicted dermal exposure is 0.07-0.7 mg/cm2/day. Considering an exposed area of 210 cm2 (fingers and palm) the exposure level amounts to 15-150 mg/person/day. Because the exposure time in sampling is only few 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 under hood with a window protection. The technician wears goggles as protective equipment. In the production plants, time spent with analysing varies, but the laboratory technician may spend about half of her working day handling samples containing CHPTAC about 70%. 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 CHPTAC is 0.1-1 mg/cm^2/day. Because the concentration of this chemical in the sample is about 70 %, the predicted dermal exposure is 0.07-0.7 mg/cm2/day. Considering an exposed area of 420 cm^2 (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 is taken care 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 and incidental contact (1 per shift).

The predicted dermal exposure to liquid containing CHPTAC is 0-0.1 mg/cm2/day. Because the concentration of this chemical in the sample is about 70 %, the predicted dermal exposure is 0-0.07 mg/cm2/day. Considering an exposed area of 840 cm^2 (hands) the exposure level amounts to 0-60 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. It is estimated that a reasonable worst case, RWC (deposition to the skin) would be 60 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

CHPTAC is transported to the users by road tankers.

The production worker does the loading with the driver assisting. Loading can be done by pumping via the top or the bottom valves of the tank. Personal protective equipment worn includes gloves, goggles and protective suit.

Driver does the unloading 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.

Inhalation exposure is unlikely during loading and unloading due to the technology applied. 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 contaminating the work sites too. The maintenance of gloves to keep them clean is therefore of importance for driver's safety; however this may not be guaranteed as each driver keeps his gloves in the tanker.

Inhalation exposure

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, vp-value 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 70%, the estimated exposure is 0-0.042 mg/m3 (0-0.07 ppm).

Summary/statement of the exposure level

The inhalation exposure during loading was estimated to be 0.04 mg/m3.

Dermal exposure

Modelled data

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

The predicted dermal exposure to liquid containing CHPTAC is 0-0.1 mg/cm2/day. Because the concentration of this chemical in the sample is about 70 %, the predicted dermal exposure is 0-0.07 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 were hand is first contaminated or gloves contaminated inside are used. For that kind of 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 producers CHPTAC is mainly used in cationisation of starch (96.7 %), in synthesis of d,l-carnitinamide hydrochloride (3.1%) and quartenisation of protein and cellulose (0.2%).

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.

According to the industry, 201 workers (6 females) were reported to be continuously working, and 99 workers (8 females) were intermittently working in the use process. The number of users of CHPTAC was 13.

The processes were described as batch, semiautomated, closed in six cases; batch, automated, closed processes in seven cases; and continuous, automated, closed processes in three cases. Two companies had two different kinds of processes.

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 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 CHPTAC is added through closed pipes and dosing systems from the storage facilities. With diluted sodium hydroxide solution CHPTAC is activated to EPTAC and 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 industry has given the information of the temperatures of the processes. The temperatures of reactions vary from 20ºC, 35 to 45ºC, 50ºC and 70ºC.

Because CHPTAC is converted in the cationising process to EPTAC, the exposure assessment deals qualitatively with EPTAC in this scenario. When the reaction is completed, starch is neutralised and then the final product contains both of these chemicals.

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. 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 210 cm2 (fingers and palm) 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. Gloves are in some cases worn. 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 cause an exposure risk. Pump leaks may incidentally occur causing the spread of the reaction product on the factory floor. The maintenance is usually cared for 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 worn 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 concentration of EPTAC and CHPTAC in this kind of dry cationic starch dust is expected to be in the same range as in dry cationised starch.

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, calcium hydroxide) are intensively mixed in a high shear force mixer and subsequently CHPTAC is sprayed onto the mixture. The operation is performed in a closed reactor. The mixture is intensively homogenised within seconds (continuous mixer) or some minutes (batch type mixers). The process takes place in a closed reactor. The mixture is then either discharged into silos or to heat jacketed mixing systems 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

Filling

A few workplace measurements were reported by the industry (CEFIC, 2000). 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 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). Another 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 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. 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. For CHPTAC the estimated air concentration would be 0.02 mg/m3 (with 450 mg/kg residual concentration).

Bagging

Dry cationised starch is filled into big bags or transferred to storage silos. Workers in this area may be exposed by inhalation to 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 of cationised starch. According to the industry, filling operations were in most cases reported to either be fully contained or segregated. General or local ventilation was additionally reported in 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

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 and 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 and palm) 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 RWC 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 and intermittent contact

Dermal exposure to cationised starch during filling 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 and bagging. The reasonable worst case was 0.01 mg/person/day.

Occupational exposure during other possible uses

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

CHPTAC can be used to manufacture cationic polymers for cosmetic industry. These 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.

CHPTAC 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.

Occupational exposure during use of products with residual EPTAC and CHPTAC

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 papergrade 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 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 were found in the Exposure Measurement Database of FIOH. 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.

4.1.1.2.4 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 CHPTAC is a non-volatile organic salt handled in water solutions, inhalation exposure to this chemical does not occur. In loading operations where 70% water solution of this chemical is handled, EASE estimation for exposure is 0-0.04 mg/m3 (0-0.07 ppm).

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 CHPTAC manufacturing process is a closed 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 60 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 0.5-5 mg/person/day in sampling and 1 to 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 CHPTAC 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.

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										
Loading/Unloading (CHPTAC conc. 70%)	Daily	2	-	-	-	-	0.04[3]	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 EASE estimate in bagging and lower estimate of EASE in maintenance and clean-up

Table 4.1B: 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 (CHPTAC conc. 70%)										
Sampling	Daily	0.5	Intermittent	0.07-0.7	210	-	-	150	15[b]	EASE
Laboratory work	Daily	4	Intermittent	0.07-0.7	420	-	-	300	30[b]	EASE
Maintenance and clean-up	Weekly	4	Incidental	0-0.07	840	-	-	60	6[b]	EASE
Loading/Unloading	Daily	2	Incidental	0-0.07	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-prod. 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 15 mg/kg, CHPTAC conc. 450 mg/kg for RWC; EPTAC conc. 3 mg/kg, CHPTAC conc. 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	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 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

(3-chloro-2-hydroxypropyl)trimethylammonium chloride (CHPTAC) is not intentionally used for products which are directly marketed as consumer products. Possible exposure to the substance may occur via 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 may contain CHPTAC 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 (isotonic drinks).

This exposure assessment has be prepared keeping in mind that a substantial part of CHPTAC is converted to 2,3-epoxypropyltrimethylammonium chloride (EPTAC) in the reaction with starch. For example, in the relevant food contact regulations, EPTAC is listed. Since the two compounds occur simultaneously, the regulations are also presented in this risk assessment report.

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, 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, 58 analyses of CHPTAC in cationised starch were reported. Samples were provided by cationised starch producers 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 (QUAS, 2003). All samples were analysed with the same analytical method by the same external laboratory. The 95th percentile was 611 mg/kg. This percentile could be used for estimation of reasonable worst case exposures according to the draft TGD (21.2.2002). 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 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 the residual level in the end-products:

- Residual levels of CHPTAC in cationised starches; average (156 mg/kg) and reasonable worst case (611 mg/kg) concentration (QUAS, 2003), 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 the 95th percentile of the measured levels, i.e. 611 mg/kg of CHPTAC in 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 they are not directly applicable for the paper and board materials. So far, no specific data on migration rate are available.

Dose

Transfer rate and duration of the skin contact and on the other hand, ingested amount will be used to calculate the dose. EPTAC is a carcinogen and a sensitizer, and CHPTAC is partly converted to EPTAC in the end-products. Since these endpoints of relevance may be regarded as non-threshold effects, the calculation of safe levels will be complicated.

4.1.1.3.1 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, VGB 2001, 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, BfR	Maximum nitrogen content in starch ethers: 4 %, epichlorohydrin max. 1 mg/kg	BfR, 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, 2003, § 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 flour with EPTAC is approved by the German BfR (epichlorohydrin max. 1 mg/kg) and cationising of guar gum with EPTAC max. 25 % is approved by 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 it is in contact with fatty of aqueous food, and therefore, migration of CHPTAC 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. 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. When the weight of the package is 5-20 g, the respective weight of starch is 0.05-0.2 g and the concentration of CHPTAC in starch is 611 mg/kg, the amount of CHPTAC, which could migrate, is 3.1-12.2 µg. Since CHPTAC is easily soluble in water, it is assessed that the entire 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 is consumed (e.g. by children) and when the package is discarded, skin contact to migrated CHPTAC could occur. Therefore, it is assumed that in the worst case, 10% of this, i.e. 0.31-1.22 µg could actually be either ingested or become in contact with the skin. 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 0.00003 µg/kg bw).

Skin absorption rate of CHPTAC in human is low. Furthermore, 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.

Summary/statement of the exposure level

The reasonable worst case exposure is 0.00003 µg/kg bw.

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 CHPTAC residues in the surface of the booklet paper 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 penetrate, moisten and ingest some of the booklet paper.

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/m^2, typically 80 g/m^2) 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/m^2 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) each, total 0.066 m^2, the amount of cationic starch in such a book is 0.02 g (0.3 g/m^2 * 0.066 m^2). Using the 95th percentile of the measured residues levels in the starch (i.e. 611 ppm), is calculated that a booklet may contain up to 12 µg of CHPTAC. If 5-10 % of the total amount would be ingested or would expose the skin, the maximum daily exposure via these routes is 0.6-1.2 µg. The weight of a child at the age of 6-12 months is 7.5-9.9 kg and thus the daily dose 0.06-0.16 µg/kg of b.w.

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

Summary/statement of the exposure level

The reasonable worst case exposure is a daily dose of 0.16 µg/kg of b.w.

Copy paper and newspapers

One of the QUAS members has estimated that the concentration of CHPTAC in the copy paper is about 1200 µg/kg (Raisio 2001a). 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 CHPTAC. Assuming that 1 % of the surface of copy papers is touched and that 10% of the CHPTAC 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 skin absorption rate of CHPTAC is low, the exposure in this scenario appears negligible.

In a newsprint, the residue of CHPTAC was estimated to be much lower (i.e. 40 µg/kg), than in copy paper (Raisio Chemicals, 2001). Also the daily dermal exposure to CHPTAC in this scenario is considerably lower than that given above for copy paper.

Summary/statement of the exposure level

The reasonable worst case exposure is a daily dermal dose of 0.6 µg/day.

Cosmetic products

Colipa has collected data on the use of relevant raw materials, i.e. cationised proteins, which contain (QUAS, 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 CHPTAC 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 CHPTAC 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 CHPTAC 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.

Summary/statement of the consumer exposure level

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 4.2b. Consumer exposure to CHPTAC

Product	Scenario	Total exposure
Food packaging	Transfer to product from wet packaging	0.00003 µg/kg bw
Children's books	Small children chewing a book, which can lead to ingestion or skin exposure.	0.06-0.16 µg/kg bw
Copy paper and news papers	Skin exposure from paper surface.	0.6 µg/day
Cosmetics	CHPTAC residues in cosmetic products used on skin and scalp. Rinse-off products	0.007-0.29 µg/kg bw 0.07-2.9 ng/kg b.w

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 CHPTAC in the surface water (PEClocal) near to starch cationisation plants are given in table 3.12. These concentrations were calculated from the measured WWTP concentrations which were available for nine sites. CHPTAC concentrations in the environment ranged between 0.04-90.9 µg/l (16.65 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 CHPTAC was estimated using EUSES based on the release factor 2.2 % and assumed biodegradation and adsorption figures. The range of calculated PEClocal was 251 - 7549 µg/l (table 3.13).

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 16.65 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 CHPTAC may take place in the drinking water processing, but no data is available on the possible removal efficiency of CHPTAC 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 0.0006 mg/kg of b.w. is derived (table 4.1).

Using EUSES, the average (local) concentration of CHPTAC in fish is estimated to be 0.0223 mg/kg in wet weight. The average (RWC) human daily intake via fish is 0.000036 mg/kg of b.w. These averages have been calculated using EUSES estimates for nine monitored sites (table 4.1).

Average 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 CHPTAC is used. In the addition, estimate of intake from leaf crops might represent unlikely exposure.

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

Table 4.2c Indirect human exposure to CHPTAC, averages based on the EUSES estimations (local scenario) for nine monitored sites.

Source of exposure and concentration	**Daily dose (mg/kg of b.w)**
Drinking water, 18.8 µg/l (average of nine sites)	0.0006 (nine sites)
Fish, 0.0223 mg/kg	0.000036 mg/kg
Leaf crops	0.00164
Root crops	$1.33E^{-5}$
Meat	$2.51E^{-8}$
Milk	$3.37E^{-7}$
Air	$3.09E^{-6}$
Total	**0.00229 mg/kg**

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

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 tests were conducted using four concentrations: 0.1, 1, 20 and 65% CHPTAC in water. 14^C-testosterone was used as the reference compound. The amount of CHPTAC content in the receptor fluid and the residual CHPTAC 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 cm^2 for the test substance, which was applied 10 ul/cm^2. 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, which was sampled only at 24 and 48 hours, and the controls, which 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 $DC_{Tx-Ty}/(x-y)$, 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^{-2}x 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 4.3 for mouse skin and in table 4.3b for human skin.

Table 4.3 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 absorption (% of the radioactivity present in the receptor fluid, the receptor compartment wash and the skin (excluding tape strips)	13	44.9	29.2	45.0
Mean total absorption (% 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 4.3b Results of the skin permeation study in human skin

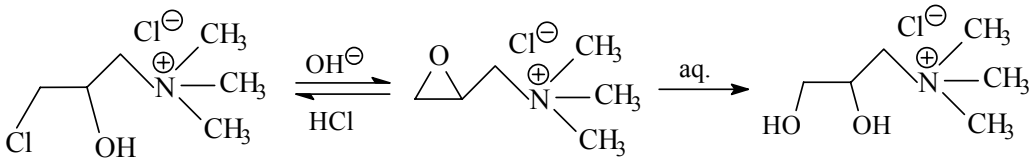
Concentration of CHPTAC	65%	20%	1%	0.1 %
Kp-values [cm h^{-1}]	0.0005 x 10^{-3}	0.0009 x 10^{-3}	0.0015 x 10^{-3}	0.0022 x 10^{-3}
Flux constants µg cm^{-2} h^{-1}	0.36	0.18	0.014	0.002
Relative absorption (% in receptor fluid)	0.053	0.148	0.534	0.685
Mean total absorption (% of the radioactivity present in the receptor fluid, the receptor compartment wash and the skin (excluding tape strips)	0.46	0.46	3.74	5.79
Mean total absorption (% 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. The amount found in stratum corneum was between 1.1 to 21 times higher than what was found in the receptor fluid. In mouse skin, the amount of radioactivity in skin after tape stripping 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.

Determination of abiotic degradation of CHPTAC

The purpose of this study was to evaluate the abiotic degradation of CHPTAC in neutral to slightly alkaline pH, at 40 °C, which correspond to the temperature of *in vitro* mutagenicity tests (Raisio Chemicals, 2004a). The purpose was to determine the possible formation of 2,3-epoxypropyltrimethylammoniumchloride under the incubation conditions, the systems with a relatively high buffer concentration and temperature conditions used *in in vitro* genotoxicity tests.

The reaction of CHPTAC to EPTAC is an non-catalyzed reaction with hydroxyl ions. EPTAC can further react with water and hydrolyze to the corresponding DIOL. The degradation rate constant of CHPTAC (k_{obs}) and the half-life ($t_{1/2}$) were determined. Due to presence of sodium chloride in the test solution, the concentration of the formed DIOLcould not be measured because of limitations in the analytical method.



Conversion of CHPTAC to EPTAC and the corresponding DIOL

A HPLC-method was used. Due to the method being confidential it is not described in detail in this report. The test substance was purified (recrystallised) 3-chloro-2-hydroxypropyltrimethylammonium chloride. The solid test substance was specially prepared for this analysis and is not as such commercially available. A solution of 100 ml was made in a volumetric flask for the test point. The start concentrations of CHPTAC and EPTAC were measured and the test solution flask was stored in water bath at target temperature of 40 °C. CHPTAC and EPTAC concentrations were measured by HPLC without dilution.

Results

Logarithm of CHPTAC-concentration (ln(c)) was plotted against time for approximation of reaction kinetics. The rate constant, k_{obs} was calculated from degradation results. Calculated constants and ln (c) vs. time –plot are presented in the following table.

Table 4.3c Ln © CHPTAC Vs. time

Degradation time	Conc. of CHPTAC	ln (conc.)	k_{obs}	Degradation of CHPTAC	pH
(h)	mg/l		(h^{-1})	%	
0	91,8	4,5194		0	7,4
4	83,9	4,4300	0,022	8,6	7,4
5	79,3	4,3734	0,029	13,6	7,4
10	74,7	4,3128	0,021	18,7	7,4
12	74,7	4,3135	0,017	18,6	7,4
15	68,4	4,2260	0,020	25,4	7,4
23	48,5	3,8807	0,028	47,2	7,4

The ln(c) vs. time plot of CHPTAC is straight line in pH 7,4. The reaction thus follows pseudo first order kinetics. The rate constant k_{obs}, average value is 2.3 x $10^{-2}h^{-1}$.The half-life of CHPTAC under test conditions (pH 7.0; t: 40 °C) is approximately 30 h.

The decrease in the concentration of CHPTAC+EPTAC at 23 h could be indicative of a further degradation of EPTAC to the corresponding DIOL.

4.1.2.1.1 Other information

Basic physico-chemical characteristics are available, which can be used to estimate toxicokinetic behaviour. CHPTAC resembles the endogenous carnitine, which is used as a carrier molecule in mitochondrial fatty acid transport (the terminal chlorine is replaced by an acetyl group). The molecular size of CHPTAC is moderately small (MW 188 g/mol), which can be facilitate the absorption through membranes. Data from toxicological tests shows that some absorption occurs via the gastro-intestinal (G-I) tract and skin. Being a small molecule, it is possible that CHPTAC pass through G-I tract membranes by passive penetration through aqueous pores at the tight junction. Due to the low fat solubility and the ionic nature of the substance penetration rate through the skin is not expected to be very rapid. The finding of very low mean flux rate seen in the *in vitro* study also supports this assumption. It is also notable that CHPTAC penetration in mouse viable skin membrane was 43-117 times higher than in humans. However, the integrity of stratum corneum can be affected due to various reasons, such as hydratation by occlusion or solvents. This could play significant role in increasing the passage of CHPTAC through skin. Inhalation exposure to CHPTAC is mainly expected to occur via the residual content in cationised starch. Theoretically CHPTAC could enter the lungs also as aerosolised water solution (~60 %). Depending on the particle size, the starch dust can enter various parts of the respiratory system. The majority of big dust particles would probably stay in the nasopharyngeal mucous membranes. There, the residual CHPTAC 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 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.
The passage of CHPTAC from the vascular space to extracellular or intracellular compartment could be envisaged although it is probably slow due to the poor membrane passing quality. Entrance into fat is expected to be slow because of the low lipid/water partition coefficient.
At pH 7.4, which is the pH of most *in vitro* test systems, about up to 50 % of CHPTAC is could be converted to 2,3-epoxypropyltrimethylammonium chloride (EPTAC) (Mendrala, 1984a), (Raisio Chemicals, 2004a). In acidic conditions, e.g., at pH <4, there is practically no conversion to the epoxy form. This raises the question whether part of the CHPTAC entering the body would spontaneously convert to EPTAC on entrance to the small intestine (pH 6), the respiratory tract or the vascular compartment (pH 7.4). While this scenario is probable, the toxicological significance of it is unknown. In addition, conversion to other molecules, such as DIOLs, cannot be ruled out. Being a comparatively non-reactive and a molecule with low fat solubility, it is probable that CHPTAC is excreted by the kidneys as such or as a conjugate formed by the phase 2 enzymatic reactions.

Summary

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. Based on the findings of the abiotic degradations test, it is assumed that up to almost 50 % of CHPTAC could be converted to EPTAC in 24 hours in pH 7.4. However, it should be kept in mind that the conversion is a reaction affected by a multitude of factors and that no direct conclusion can be drawn from it to in regards CHPTAC's behaviour to biological systems.

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 12.05 mg/l CHPTAC caused no deaths or changes in appearance, demeanour or food consumption in 4 rats. No other information was available. (Source: USEPA Chemical Hazard Information Profile).

Dermal

A test performed according to the 79/831/EEC Annex V guideline investigated the acute dermal toxicity CHPTAC in five female and five male CD rats (Gardner, 1987). A 65 % aqueous solution of CHPTAC was applied to a shaved dorso-lumbar area corresponding to about 10 % of total body area. The site of application was immediately covered with a gauze held in place by an occlusive dressing. Since the test was a limit test, only 2000 mg/kg dose was used. After the 24 h exposure period the skin area was washed with water. Post-exposure observation period was 14 days. In post mortem examination, the macroscopic appearance of abnormal organs was recorded.

There were no deaths or clinical signs observed during the whole observation period. There were no abnormal autopsy findings. The acute lethal dermal dose to rats was found to be greater than 2000 mg/kg.

Another limit test conducted with Wistar rats gave a dose of 2.0 ml/kg 65 % CHPTAC (1174 mg/ml [density of the 65 % CHPTAC] x 2.0 ml/kg = 2348 mg/kg) to five female and five male rats (Degussa, 1986). The substance was applied to dorsal area of about 30 cm2 and covered with an occlusive patch for 24 h after which the site was washed. The animals were observed for 14 days after the application for symptoms of toxicity. Weight was recorded on days 0, 7 and 14. At the end of the observation period, surviving animals were killed and autopsied and the organs were subjected to macroscopic examination. The dermal LD50 value was found to be over 2348 mg/kg which corresponds to 1526 mg/kg of pure CHPTAC. No deaths or other signs of toxicity were noted at this dose level. No signs or symptoms of intoxication and no local irritation reactions were reported. Terminal autopsy findings did not reveal any substance related macroscopic organ changes.

Oral

Ten female and ten male Sprague-Dawley rats/group were administered undiluted CHPTAC (QUAB 60 %) by gavage at doses 3.16 ml/kg (3.67 g/kg), 3.83 ml/kg (4.44 g/kg), 4.64 ml/kg (5.17 g/kg) and 5.62 ml/kg (6.52 g/kg) (Degussa, 1977). No control group was used. Feeding had been ceased 15-16 hours before the administration of the test substance. LD50 values were calculated for 24 hours and 7 days using Litchfield-Wilcoxon method. The animals were observed for 4 weeks after the administration during which animals were observed for clinical signs, feed consumption and body weight development. Animals that died during the experiment were subjected to post mortem macroscopic examination and necropsy.
There were no deaths at the lowest dose level and there was no significant change in body weight during the first seven days or other signs of toxicity. At 3.83 ml/kg, four animals of each sex died after 24 hours or 7 days and at 4.64 ml/kg 6 males and 7 females died in 24 hours or 7 days. The two mid dose groups showed 6-12 % decrease in mean body weight development. All animals in the 5.62 ml/kg group died. No pathological findings were reported for any test groups. The toxicological symptoms were described as sedation, myosis, dyspnoea, tremors and cramping. The calculated LD50 for males was 4.15 ml/kg (4.81 g/kg 60 % substance) and for females 4.05 ml/kg (4.70 g/kg). Converted to pure substance the respective LD50 value is approximately 2800 mg/kg.

Five female and five male rats were dosed by gavage six different doses of 20 % CHPTAC in corn oil (total volume not exceeding 40 ml/kg) ranging from 1600, 2500, 3200, 4000, 5000, 6400 mg/kg (Kynoch et al., 1982). Controls were given 32 ml/kg corn oil only. Clinical signs

included at all dosage levels: piloerection, an abnormal body carriage, abnormal gait, lethargy, decreased respiratory rate, pallor of the extremities and increased salivation. Following mortality was seen in males: ctrl: 0/5, 1600:1/5, 2500: 4/5, 3200: 3/5, 4000: 5/5, 5000: 5/5, 6400: 4/5. In females the mortality rates were: ctrl: 0/5, 1600: 0/5, 2500: 4/5, 3200: 4/5, 4000: 5/5, 5000: 4/5, 6400: 5/5. The time of death after dosing was less than one hour in males and between 22 h to less than one hour in females. Autopsy revealed congestion or haemorrhage of the lungs and pallor of the liver, spleen and kidneys. An LD50 value of approximately 2170 mg/kg CHPTAC (95% Confidence limits: 830 to 2940 mg/kg) was obtained.

In another test, five female and five male SPF-bred albino rats were administered undiluted 60 % CHPTAC (Servon XRK) in doses varying between 1.67 (1.92 g/kg), 2.00 (2.30 g/kg), 2.40 (2.40 g/kg), 2.88 (3.31 g/kg) and 3.46 ml/kg (3.98 g/kg) (TNO, 1982). The animals were observed for 14 days post dosing, body weights were recorded on days 0, 7 and 14. After the last weighing, the surviving animals were killed and autopsied. Following mortality rates were seen in the male/female rat groups: ctrl: not given, 1.92 g/kg: 1M/0F, 2.30 g/kg: 0M/1F, 2.76 g/kg: 2M/1F, 3.31 g/kg: 4M/3F and 3.98 g/kg: 4M/2F. The animals showed signs of sedation, ataxia and exophthalmus. Macroscopic examination of the survivors at autopsy did not reveal any treatment-related gross alterations. At the highest doses, convulsion, rough coats and coma were frequently observed. An LD50 of 3.20 ml/kg (95% Confidence limits were 2.66 and 3.84 ml/kg) was calculated. Converted to mg/kg and using the given specific gravity of 1.15 g/kg of 60% solution, an LD50 of 3688 mg/kg (1.15 g/ml x 3.2 ml/kg x 1000 mg/g) with confidence interval of 3059 – 4166 mg/kg is obtained for 60 % solution. When converted to pure CHPTAC, the LD50 is 2213 mg/kg.

4.1.2.2.2 Summary of acute toxicity

For oral acute toxicity, an LD50 of 2170 mg/kg and an LD50 dermal of >2348 mg/kg is taken to the risk characterisation. For dermal toxicity, an LD50 value of over 2000 mg/kg can be derived based on limit tests. Although there is relatively little data on acute toxicity via inhalation, based on available information it appears that toxicity via that route is low enough not to warrant classification. Based on limited data, no signs of toxicity were seen in rats exposed to 12.05 mg/l CHPTAC for seven hours. However, due to the lack of study details, no definite conclusion can be drawn on the acute for the acute toxicity via inhalation route.

4.1.2.3 Irritation

4.1.2.3.1 Skin

Studies in animals

In a study conducted according to EU guideline, three NZW rabbits received a 0.5 ml dose of 65 % CHPTAC in water to a shaved region in the dorso-lumbar area (Liggett et al., 1987a). Using density of 1.16 g/ml, a dose of 580 mg is obtained. The test substance was applied under a 2.5 cm^2. The patch was semi-occluded with an adhesive dressing for 4 hours. After the removal of the semi-occlusive dressing the application area was washed. The skin was

examined 30 minutes after the removal of the patches and on days 2, 3, and 4. The scores were zero on all time points. The substance was not irritating to rabbit skin.

In a patch study conducted with three female albino rabbits, three female albino rabbits were dosed 0.5 ml of 60 % CHPTAC in water to the dorsal area (6.25 cm^2), half of which was scarred (Degussa, 1982). Using density 1.16 g/ml from the study, a dose of 580 mg is obtained. The application sites were covered with patches that were left under occlusion for 4 hours. The skin was scored after 1, 24, 48 and 72 hours according to methods presented by Draize. One half of the clipped area on both the scarred or non-scarred side was not treated but only covered with a patch and occluded to act as a control. The primary irritation score was zero, thus, the substance was found non-irritant in both treated areas.
A skin irritation test was conducted with 6 male and 6 female NZW rabbits. A 0.5 ml volume of CHPTAC (concentration not given) was applied under a gauze patch on the clipped dorso-lumbar area (Leuschner, 1977a). Half of the animals were scarred in the application area (2.5 cm^2). The patch was occluded with an adhesive dressing, which was left on for 24 hours. After the removal of the patch, the site was scored. The treatment area was examined 24 and 72 hours after the removal of the patch and scored 0 to 4 for erythema and oedema. All scores were zero at all time points, scarred or intact.
A skin irritation carried out according to the method of Draize in six NZW with 55% CHPTAC caused very slight skin irritation in two rabbits with intact skin and 2/6 rabbits with abraded skin. The effects disappeared after 72 hours (TNO, 1977). No other information was given.

4.1.2.3.2 Eye

Studies in animals

Six NZW rabbits were applied 0.1 ml of 55 % CHPTAC (116 mg) to one eye each rabbit, the other remaining as a control (TNO, 1977). The eyes were not washed and they were examined at 24, 48, 72 hours and 7 days after the instillation of the test material. The cornea opacity, iris integrity and conjunctivae redness and chemosis were scored using the USFDA scoring scale. All the scores were zero after 24 and 48 hours, except in one animal that had a redness score of 1 on a Draize scale of 0 to 4 at 24 h (TNO). According to FDA standards, CHPTAC was not considered to be an eye irritant.
Three female and three male New Zealand White rabbits per dose were administered 0.1 ml of 50, 25 and 12.5 % CHPTAC in their left eye while the right eye was used as a control (distilled water) (Leuschner, 1977b). One group received the same amount of the test substance at its “original concentration”. Neither the original concentration nor the density of the substance was given. Taking 1.16 g/ml density of 65% CHPTAC in water solution, the respective dose would be 111 mg and the diluted doses 89, 45 and 22 mg. The eyes were examined 5, 15 and 30 minutes and after 1, 2, 4, 24, 48 and 72 hours after instillation of the test substance. Distilled water was instilled in the other, control eye. At the original concentration (65 %), the results showed slight initial erythema, oedema and hypersecretion of the conjunctiva during the initial hours. No effect was seen in the cornea or the iris at any time point. The conjunctiva score was zero after 24 hours. Similar reaction was seen at 50 and 25% concentration but the normalisation took place already after 1 hour. At 12.5%, all scores were zero at all observation points.
An eye irritation study conducted according to the EU guidelines used three New Zealand White rabbits to test the eye irritation properties of 65% CHPTAC (Liggett et al., 1987b). After a pre-examination of the eye, the test substance was instilled to the lower lid of one eye,

while the contralateral eye remained untreated serving as a control. Eyes were examined after 1 hour, 1, 2, 3, 4 and 7 days after instillation. Cornea was scored for density; iris for functional and anatomical abnormalities and conjunctivae redness and chemosis was estimated using the Draize based scoring of 0 to 4. All three animals had conjunctiva redness and chemosis 2 days after the instillation. A temporary corneal opacity was observed in one animal at day 2. The eyes were normal in all animals 4 days after instillation. The following ocular reaction scores were obtained:

Table 4.4. Ocular reactions to CHPTAC (Liggett et al., 1987b)

Rabbit	Eye Region		24h	48h	72h	96h	Mean 24-48-72 h score
1	Cornea		0	0	0	0	0
	Iris		0	0	0	0	0
	Conjunctivae	Redness	2	2	1	0	1.7
		Chemosis	2	1	0	0	1
2	Cornea		0	1	0	0	0.3
	Iris		0	0	0	0	0
	Conjunctivae	Redness	2	2	1	0	1.7
		Chemosis	1	1	1	0	1
3	Cornea		0	0	0	0	0
	Iris		0	0	0	0	0
	Conjunctivae	Redness	1	2	1	0	1.7
		Chemosis	1	1	1	0	1

A volume of 0.1 ml of 60% solution of CHPTAC was instilled in the conjunctival sac of three albino rabbits. The other eye was not treated and served as a control eye (Degussa, 1983). The eyes were clinically examined for cornea density, iris abnormalities and conjunctiva redness and oedema, 1, 24, 48 and 72 hours after instillation using the Draize scoring. The cornea and iris were unaffected by the test substance. The conjunctivae showed redness, swelling and hypersecretion up even after 72 hours after the instillation. However, the authors of the test did not see justification to call CHPTAC an irritant based on the total irritation score. All scores concerning cornea and iris were zero.

Table 4.5: Mean irritation 24, 48, 72 h -scores of 60 % CHPTAC in rabbit eye (Degussa, 1983)

Rabbit	Eye Region		24h	48h	72h	Mean
1	Cornea		0	0	0	0
	Iris		0	0	0	0
	Conjunctivae	Redness	2	2	2	2
		Chemosis	2	1	2	1.7
2	Cornea		0	0	0	0
	Iris		0	0	0	0
	Conjunctivae	Redness	2	2	2	2
		Chemosis	2	1	1	1.3
3	Cornea		0	0	0	0
	Iris		0	0	0	0
	Conjunctivae	Redness	1	1	1	1
		Chemosis	1	1	0	0.7

4.1.2.3.3 Summary of irritation

Skin

CHPTAC is not irritating based on the skin irritation tests described above. CHPTAC did not cause skin irritation.

Eye

CHPTAC caused slight irritation when administered at a maximum concentration of 65 %. The irritation scores are not sufficient to warrant classification according to the criteria. If tests were conducted with pure CHPTAC, higher irritation scores could be expected, possibly warranting classification.

4.1.2.4 Corrosivity

CHPTAC is not corrosive based on the results of irritation tests.

4.1.2.5 Sensitisation

4.1.2.5.1 Studies in animals

Skin

In vivo studies

The ability to cause delayed contact hypersensitivity of CHPTAC has been tested following the OECD guideline 406. Following a preliminary skin irritation investigation, an aqueous solution of 65 % CHPTAC was used to induce 10 female Hartley/Dunkin strain albino guinea pigs. Ten animals were included in the control group. The induction was conducted by saturating a surgical gauze patch with 0.5 ml of the test substance and occluding it on a hair-free area in the shoulder region for 6 hours. The skin area was assessed for erythema and oedema 24 h after the removal of the dressing. The application was repeated in total three times once per week. The control animals were treated in similar fashion, with the exception that the test compound was not present. The animals were challenged to the test substance two weeks after the third induction. The challenge procedure was conducted as with the induction. The challenge site was evaluated 24, 48 and 72 hours after the patch removal. There was no reaction to the test substance during the induction phase. At challenge, there was slight erythema seen in 2/10 animals at 24 hours which had changed to slight localised erythema at 48 and 72 hours. Additionally, one animal had localised erythema only at 24 hours and another at 24, 38 and 72 hours. However, the challenge reactions were considered as "inconclusive" and not sufficient to warrant classification as a skin sensitiser, according to the EU classification criteria (Kynoch et al., 1988).

In another sensitisation study, a maximisation test conducted following the OECD 406 and EU guideline 92/32/EEC (8), 10 female Pirbright White strain guinea pigs were used with two

control groups using 6 animals each (Degussa, 1993). The induction was performed both by an intracutaneous injection and by an epidermal occlusive patch. In the epidermal induction, the applied solution contained CHPTAC at a concentration of 70 %, which had been determined as the maximum concentration not causing irritation. In the first induction phase, six injections were given per animal to the scapular region of the back. The injection volume was 0.1 ml and it consisted of two applications of Freund's Complete Adjuvant (FCA) with saline (1:1), two with test substance solution (0.5 %) and FCA (1:1) and two sites were applied with the test substance alone. In the control groups, identical solutions were applied, except for the test substance. At day 8, undiluted (solubility in water ~70 %) test substance was applied to the scapular area using an occluded patch. The patch was left in place for 48 h and was done only once. The control animals were given 0.9 % saline. The challenge was performed on day 22 of the first induction using an occluded patch with 0.2 ml of 30 % CHPTAC in 0.9 % saline. Right flank was applied with test substance and the left with vehicle. The challenge application lasted for 24 hours. Since the result was a clear negative after the first challenge, the second challenge was not performed.

4.1.2.5.2 Summary of sensitisation

CHPTAC is not a sensitiser.

4.1.2.6 Repeated dose toxicity

4.1.2.6.1 Studies in animals

In vivo studies

Dermal

Groups of 50 NMRI mice of each sex per dose were treated twice a week with dermal doses of 0, 0.018 and 0.18 ml of 65.79% CHPTAC (QUAB 188) corresponding to nominal doses of 0, 13.8, and 138 mg per animal. Taking the average mouse body weight of 48 g during the study doses of 2875 mg/kg for the high dose and 288 mg/kg for the low dose per application are obtained, which amounts to 575 mg/kg or 5750 mg/kg per week. Male mice were treated for 105 weeks and females for 89 weeks. The substance (65.79 % and 32.36 % water) was dissolved in 10 % ethanol, which was applied to 2 cm^2 clipped dorsal skin area in constant volume of 0.2 ml (Degussa, 1997).

There were no significant treatment related differences between the test substance and control group animals. No treatment related changes in food consumption were noted, but there were occasional statistically significant changes in the high dose males, which consumed more food in weeks 3/4, 10/11, 25/26, and 97/98. During week 49/50, these animals had slightly lower food consumption. The low dose group had slightly lower food consumption in week 65/66. The high dose females had marginally higher food consumption in weeks 3/4, 11/12, 13/14, 65/66 to 73/74. Low dose females had slightly increased food consumption in weeks 3/4, 11/12 and 81/82. The overall food consumption was 3.3% higher in low dose females and 6.6 in high dose females. These changes were considered to reflect biological variation since they were marginal, less than 10 % overall. No treatment related body weight changes were observed during the study. The body weight of low dose males was slightly higher during weeks 11 to 21 (max. 6.5 %) 57, to 61 (5.0 %) and in the week 73 (6.1 %). The body weight

of low and high dose females was slightly higher in week 65 (7.4 % in low and 7.7% in high dose). In the pathological examination, a small but statistically significant decrease of left testis absolute (0.223 g control, 0.214 g low dose (-4%) and 0.192 g high dose (-14%)) and organ weight relative to body weight (0.488 control, 0.477 (-2%) low dose and 0.414 high dose (-15%)) was seen in the high dose male mice. The female mice of the high dose group had an increased absolute and relative weight of the liver and adrenals. The absolute weight of the right kidney was increased in the high dose females. In histopathology, the microscopical examination revealed a slight dose-related increase in the incidence of minimal to mild focal acanthosis and hyperkeratosis at the application site.

Oral

An evaluation of the four-week oral toxicity was performed following the OECD limit test guideline and GLP (Degussa, 1990). There were two groups, one control and one treated, which both had five male and five female rats (Bor: WISW). The treated group received a dose of 1085 mg/kg CHPTAC by oral gavage while the control animals were given tap water. The test substance was 69.57 % pure with 28.44 % water, 1.14 % 1,3-bis-trimethylammoniumpropanol-2-dichloride and 0.63 % 2,3-dihydroxypropyl-trimethylammonium chloride. The pH of the substance was 2.5. The dose had been selected based on a previous dose-finding study. Clinical investigations included recording of mortality, body weight, food and drink consumption, reflexes and examination of the eyes, hearing and teeth and recording of general symptoms. The basic erythrocyte and leukocyte parameters were measured. In clinical chemistry, liver transaminases, cholinesterase, creatine kinase, electrolytes, bilirubin, urea and cholesterol, triglycerides and proteins were determined. Urine was analysed for bilirubin, urobilirubin, glucose, haemoglobin, ketones, leukocytes, nitrite, osmolality, protein and pH. After the sacrifice, the organ weight was recorded on adrenals, brain, heart, kidneys, live, ovaries and testes. After the gross necropsy, samples were taken for histopathology from the above organs and in addition from sternum bone and its marrow, caecum, colon, duodenum, ileum, jejunum, rectum, skin, stomach and spleen.

In group 2, which was the only treated group, clinical symptoms included slightly red discoloured salivation, alopecia in the fore legs or neck. One female performed strenuous respiration, tremor and piloerection on day 20. Two females died 10 minutes after the second administration and were replaced by spare animals. However, the authors did not consider this substance related. Neither the food consumption nor the bodyweight development was affected significantly by the treatment. The reflexes, eyes, hearing and teeth had no abnormalities. Haematological parameters of the treated group had no statistically significant changes when compared to the control group. Clinical chemistry showed a slightly but statistically significantly decreased (-26 %) glucose value to control group. The female rats had a decreased creatinine concentration while the creatinine kinase (202 %) and aspartate aminotransferase (ASAT) values were slightly increased but were within the normal range of this strain of rats. The change in ASAT was only slight (22 %) but significant. The creatine kinase values, which are known to vary over a wide range, were within the historical controls. No morphological changes were found to correlate with the increased creatine kinase values. Urinalysis did not produce any substance-related findings. The only statistically significant, although slight, change in organ weights was a decrease of absolute (-16 %) and relative body weight (-14 %) heart weight in males and a 20 % increase of relative kidney weight in males. Females had no statistically significant changes in their organ weights. In the macroscopical examination of the necropsy, focal alopecia of the forepaws (1 male) and neck (1 female) and reddening of the proximal parts of the small intestine or the glandular stomach was seen. The

latter finding was only observed in the animals that died on day 2 of the study for non-substance related reasons. Microscopically, slight or moderate vacuolisation of proximal tubule cells of the inner cortical and outer medullar region of the kidney were seen in 5/10 male animals but not in females. This was not observed in control animals. In addition, this region had minimal tubular hyperplasia (4/5 males, 2/5 females) and minimal or slight hypertrophy (5/5 males 0/5 females). Control animals had no hyperplasia or hypertrophy. The female rat with alopecia was diagnosed to have moderate atrophy of hair glands and sebaceous glands in the affected skin areas. The causes of the two deaths of the female rats in the group 2 were unresolved by the necropsy examination.

4.1.2.6.2 Summary of repeated dose toxicity

Based on an oral 28-day limit study, there were only slight morphological changes seen in the kidney proximal tubules. The microscopical changes in kidneys appear similar to those seen with EPTAC. In addition to the renal histopathological changes, there was a 20% increase in relative kidney weights in male animals. A slight decrease in left testis weight was noted when CHPTAC was administered to mice dermally at a maximum dose of 5750 mg/kg/week. However, since a significant weight change was noted only at top dose in one testicle and there were no histopathological changes found, the toxicological significance of this finding was left unclear, and it was decided not to use this to set the NOAEL for repeated dose toxicity. In addition, the study used an unusual dosing regime, i.e., twice a week. Moreover, the oral study used rat as the test animal, which is preferable species to mice. Due to these facts, the 28-day rat study will be used for the determination of the lowest effect level via oral and inhalation routes. Based on the kidney changes seen in the 28-day study the LOAEL for CHPTAC after oral administration is 1085 mg/kg/day. For inhalation, a systemic LOAEL of 543 mg/kg will be used, based on the assumption that 50 % of the dose is absorbed from the gastro-intestinal tract.

4.1.2.7 Mutagenicity

4.1.2.7.1 Studies in vitro

All Ames tests were performed with and without S9 metabolic activation. The studies by (Degussa, 1984), (Richold et al., 1982b) and (Richold et al., 1982a) were conducted in compliance with GLP. The study by RCC was also done following the EEC Directive 79/831, Annex V, Method 431. Cytotoxicity but no mutagenic activity was reported at all dose levels without S9 in the study (Richold et al., 1982a) and mutagenic activity slight toxicity was also reported by (Richold et al., 1982b) at 5000 µg/ml. In the latter study, mutagenicity was seen at 1500 ug/ml without s9. In the study (Richold et al., 1982a) buffered (pH 4.0 or 5.5) water was used as the vehicle whereas the in the study (Richold et al., 1982b) water only was used. (Hassack et al., 1976), (Degussa., 1982), (Degussa, 1984), or (Mendrala, 1984a) reported no toxicity. The latter studies used technical grade CHPTAC, which was 60-65% pure. The studies that reported toxicity did not report the substance concentration. (Hüls, 1984) or (Degussa, 1979b) did not comment on toxicity. The two latter studies, together with Hassack (1976), used dimethylsulphoxide (DMSO) as the solvent. Only the study by Mendrala (1984a) listed impurities. They used two types of CHPTAC, technical and purified. The technical grade substance contained 2.57% of the mutagenic 2,3-epoxypropyltrimethylammonium chloride (EPTAC). In the purified substance, no EPTAC was detected. In contrast to others,

Mendrala (1984) used only a 3-fold increase in mutations to the background to count for a positive response. All the studies, which showed mutagenicity, also showed a positive dose correlation between the dose and the mutant colony number.

Table 4.6 Microbial mutagenicity tests with CHPTAC

Test system	Concentrations (µg/plate)	Lowest effective dose (LED), (S9 in parenthesis, max LED mutant ratio in square brackets)	Positive strains	Reference
S. typhimurium TA 1535, 100	500, 1500, 5000, 15000 (water buffered to pH 4.0 or 5.5)	- (cytotoxic at all dose levels without S9)	-	(Richold et al., 1982a)
S. typhimurium TA 1535, 1537, 1538, 100, 98	150, 500, 1500, 5000, 15000 (water)	5000 [4.4] (1500, [2.4]) (slightly cytotoxic)	1535, 100	(Richold et al., 1982a)
S. typhimurium TA 1535, 1537, 1538, 100, 98	10, 50, 250, 500, 1000, 2000, 3000, 4000, 5000 (DMSO)	1000 [3.5], (1000, [2.9]) (no data on cytotoxicity)	1535, 100	(Hüls, 1984)
S. typhimurium TA 1535, 1537, 1538, 100, 98	10, 100, 1000, 10000, 50000, 100000	10000 [6.0] (10000. [3.0]) (not cytotoxic)	1535 ((a slight but not two-fold increase in strain 100 at the highest dose)	(Mendrala, 1984a)
S. typhimurium TA 1535, 1537, 1538, 100, 98	5, 50, 500, 5000, 25000, 50000 (purified)	25000 [4.0] (25000, [4.8]) (not cytotoxic)	1535 (a slight but not two-fold increase in strain 100 at the highest dose)	(Mendrala, 1984a)
S. typhimurium TA 1535, 1537, 1538, 100, 98	1.58, 5, 15.8, 50, 158, 500, 1580, 5000	1580 [2.6] (1580, 2.1]) (not cytotoxic)	1537 (2.2, S9 only), 1535 (1.9, 500 ug/kg), 98	(Degussa, 1984)
S. typhimurium TA 1535, 1537, 1538, 100, 98, *E. Coli WP2 uvrA*	400, 1000, 4000, 12000, 41000, 124000	12000 [2.4] (12000, [3.6]) (not cytotoxic)	1535, 100	(Degussa., 1982)
S. typhimurium TA 1535, 1537, 1538, 100, 98	1000, 5000, 10000, 12500, 20000, 25000 (DMSO)	10000 (10000) (no data on cytotoxicity)	1535, 100	(Degussa, 1979b)
S. typhimurium TA 1535, 1537, 1538	100, 1000, 10000, 100000 (DMSO)	10000 [5.6] (10000, [4.0]) (not cytotoxic)	1535	(Hassack et al., 1976)

Lymphocyte chromosome analysis

The clastogenic effects of 60 % CHPTAC were studied in human lymphocytes by subjecting the donor cells to CHPTAC concentrations ranging from 0.016, 0.049, 0.148, 0.444, 1.333, 4.000 12.000 mg/ml in the absence and presence of S9 mix (Wilmer, 1984). The study was conducted in compliance with GLP. After a preliminary incubation of 48 hours, 100 µl of test substance was added to obtain the predetermined concentration in duplicates with negative and positive controls. Two hours before treatment the CO_2 level was raised to 10 % in order to lower the pH and prevent the formation of 2,3-epyxypropyltrimethylammonium chloride as much as possible. The pH was about 6.8 during the treatment. The pH was measured two hours after the addition of the test substance and at the end of the total incubation period. After a total of 70 hours of incubation, the cells were treated 2h with colcemid and processed for chromosome analysis. The cultures that were added S9 mix were centrifuged after 48 hours and transferred to 3.5 ml serum-free medium, to which 100 µl of test or control substance was added together with 1.0 ml of S9 mix. After two hours of incubation, the S9

cells were collected by centrifugation, transferred to fresh medium and incubated for another 22 hours, of which the two last hours were colcemid treatment. The cells were processed for chromosome preparations as with the non-S9-cells. If possible, 100 well-spread metaphases, each containing 46 centromeres, were analysed per each culture (25 /slide). The analysis included structural aberrations, such as gaps, breaks, fragments, dicentrics and exchanges.

The results showed that the test substance showed clastogenic activity in cultured lymphocytes. The aberrations are listed in the table below. Analysis was not possible at the highest dose 12.0 mg/ml due to excessive damage to chromosomes. In the presence of S9-mix, gaps were significantly increased only at the two highest doses and breaks at the highest dose. CHPTAC causes chromosome mutations *in vitro* at high doses.

Table 4.7. Chromosome aberrations in human lymphocytes treated *in vitro*

Dose	Number of cells with aberrations			% of cells with aberrations		Mitotic index
	Gaps	Breaks	Exchanges	+ Gaps	- Gaps	
Control	7	1	0	8	1	7.0
0.016	14	1	0	15	1	6.3
0.049	20**	8*	0	27***	8*	4.5
0.148	17*	12**	1	30***	13**	4.7
0.444	24**	24***	0	39***	24***	3.4
1.333	28***	38***	3	55***	40***	2.7
4.000	65***	66***	5*	88***	66***	2.8
12.000	-	-	-	-	-	2.2
MMS	12	11**	12**	33***	22***	5.5

One hundred metaphases were analysed per each dose, * P<0.05; **P<0.01; ***p<0.001

Liver Unscheduled DNA Synthesis Assay

Primary rat hepatocyte cultures were established by harvesting them in situ with a collagenase solution perfusion. The harvested cells were transferred to Williams E medium with foetal calf serum (Mendrala, 1984c). The study was conducted in compliance with GLP. The protocol was mostly in line with the OECD 482 recommendations. Cultures that contained 0.001, 0.00316, 0.01, 0.0316, 0.1, 0.316, 1.0, 3.16 or 10 mg/ml of CHPTAC 10 µCi/ml ^{3}H-thymidine were prepared. The rationale for concentration selection was not given. Negative control contained media only and 2-acetylaminofluorene served as the positive control (at four different concentrations). Triplicate cultures containing the test substance and ^{3}H-thymidine in the medium were incubated for 18 hours. After the incubation, the cells were washed for three 30-minute intervals with 1 mM non-labelled thymidine in medium at 37 C. The cells were fixed on coverslips for microautoradiography. Fifteen cells per each of two slides were evaluated per dose level and grain counts were reported as mean +/- standard deviation.
CHPTAC elicited a significant dose-related increase in unscheduled DNA synthesis at concentrations higher than 0.1 mg/ml. However, CHPTAC caused marked dose-related toxicity at these higher concentrations, varying from slightly granular appearance at 0.1 mg/ml to complete detachment of the cells at 10 mg/ml. The concentrations below 0.1 mg/ml were comparable to negative control cells. According to the authors' interpretation, the positive response seen in this experiment is due to 2,3-epoxypropyltrimetyhlammonium chloride, which could be present via conversion from CHPTAC. The authors expected a 1 to 3 % conversion of CHPTAC to EPTAC based on the pH titration of CHPTAC and the test

system pH 7.4. Since the epoxide is likely to be consumed, e.g., via reaction with nucleophilic sites of cellular macromolecule, the equilibrium should favour formation of additional epoxide. CHPTAC increases unscheduled DNA synthesis, but causes marked toxicity at the highest concentration.

Gene mutations in Chinese hamster ovary cells

The ability of CHPTAC to cause forward mutations in the Chinese hamster ovary cell hypoxanthine phosphoribosyl transferase (CHO/HGPRT) gene location was investigated using a 51 % aqueous CHPTAC solution (Mendrala, 1984b). The study was conducted in compliance with GLP. The assay was mostly in line with the OECD guideline 476 recommendations. The solution had a 1.3 % 2,3-epoxypropyltrimethyl ammonium chloride (EPTAC) content. The pH of the study system was 7.4, which implies an up to 50 % conversion to EPTAC, based on the titration curve of the pure substance. There was no data on osmolality or of pH monitoring during treatment. Based on the cytotoxicity evaluation six dose levels were selected for the experiment, namely 0.1, 1.0, 5.0, 10.0, 25.0 and 50.0 mg/ml. With S9-activation added the concentrations were: 0.09, 0.9, 4.6, 9.1, 22.7 and 45.5 mg/ml. Cells were plated at a density of $2x10^4$ about and left to grow for 16-18 hours before the treatment. Then the cells were incubated in a serum free medium with the test substance for 4-5 hours. After treatment, cells were changed to a serum containing medium and left to grow for 16 to 24 hours and then trypsinised and diluted to the concentration of $2x10^4$ cells/cm^2 for phenotypic expression. The cells were subcultured until the 8^{th} day after which they were diluted by a factor of 5 and transferred to a selection media of the detection of HGPRT-mutants. After colony formation, the cells were fixed and mutation frequency was calculated by dividing the total mutant colony number by the total number of cells corrected with cloning efficiency. The activation assay differed from the non-activation assay only by the addition of S9-fraction of the rat liver homogenate during the treatment. Ethyl methanesulfonate was used as the positive control. In the activation assay, 3-methylcholoroanthrene was used. Negative control was identical to the non-activation assay except for the test substance. The result was considered positive if significant dose-related increase in mutagenic activity at three dose levels or if there was a significant and reproducible positive response at the highest toxicity test point were considered mutagenic. Without S9, concentrations greater than 1 mg/ml caused significant and dose-related increase in mutation frequency. With metabolic activation, concentrations of 0.9 mg/ml and higher caused a significant and dose-related increase in mutation frequency. The highest concentration was lethal to the cells.

4.1.2.7.2 Studies in vivo

Mouse micronucleus test

In a study conducted according to OECD guideline 474, the ability of 60 % (purity: 99.92 %) CHPTAC to induce mutations was investigated in 21 male and 24 female BOR:NMRI mice. The CHPTAC dose used was 147 mg/kg (Degussa, 1992). Physiological saline solution was given for the negative control group while positive group received 51 mg/kg cyclophosphamide by oral gavage. Both control groups had 18 males and 18 females. The treated groups and negative control groups were dosed with an intraperitoneal injection. Clinical symptoms were recorded during the experiment. Animals that died during the experiment were subjected to gross necropsy. At 24, 48 and 72 hours, at least six mice per sex were killed to prepare bone marrow smears. From each animal, 1000 polychromatic

erythrocytes (PCE) were scored and their ratio to normochromatic erythrocytes was calculated to determine the toxic efficacy of the test.
The clinical symptoms included clonic convulsions, decrease of muscle tone loss of righting reflex with lateral and dorsal position, sunken sides and stilted gait. Five test material group females died within 14 minutes after the administration. Neither the negative nor positive control animals showed abnormal clinical signs.
No statistically significant increase in micronucleated PCE was seen at any of the three time points in either the female or male animals. A slight, but statistically significant increase of micronucleated PCE was noted at 48 hours when the analysis was performed on both sexes combined. However, the authors did not consider this finding to be substance-related and suspected it to have been caused by an exceptionally low incidence of PCE in the negative control males when compared to historical data of the test facility. There was no reduction of PCE-NCE ratio when compared to negative control animals, with the exception of one male at 48h sampling time. The authors concluded that CHPTAC causes no chromosome mutations in mice at 24, 48 or 72 h after the animals had received a single intraperitoneal dose of 147 mg/kg of the substance.

Table 4.8 PCEs with micronuclei scored in 1000 PCEs with PCE/NCE in control animals

PCE and PCE/NCE / animal 82.5 mg/kg CHPTAC (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	3.47
4	2	2.45	2	1.67	0	1.20	2	1.57	0	2.80	1	3.13
5	2	1.89	1	1.96	0	1.75	2	1.42	0	3.41	1	1.78
Mean	1.6		1.4		0.6		1.6		0.4		0.6	

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

PCE and PCE/NCE / animal 82.5 mg/kg CHPTAC (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	0	1.41	0	1.62	2	1.92	2	1.58	1	3.93	1	2.65
2	2	3.31	1	1.82	0	1.97	3	2.88	2	3.12	2	3.42
3	3	2.53	1	1.21	2	1.89	1	1.64	2	2.39	1	2.38
4	2	1.49	1	1.19	1	0.69	4	2.88	1	1.59	0	1.86
5	1	2.07	3	0.96	3	2.10	4	1.75	2	3.12	0	3.22
Mean	1.6		1.2		1.6		2.8		1.6		0.8	

Table 4.10. The statistical evaluation of mouse micronucleus test (Poisson test)

PCE with micronuclei/Group	24h		48h		72h	
	M	F	M	F	M	F
CHPTAC	8	6	8	14	8	4
Negative control	8	7	3	8	2	3
F	0.8889	0.7500	2.0000	1.5556	2.6667	1.0000
p-value	0.598	0.7090	0.113	0.143	0.055	0.500
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

All in vitro tests mutagenicity tests conducted with CHPTAC have given a positive result. However, the interpretation of these results is somewhat complicated because the purity of the CHPTAC used was sometimes questionable. Looking at the results of the AMES tests, the typically positive strains TA1535 and TA100 are the same which were positive also with 2,3-epoxypropyltrimethylammonium chloride (EPTAC). There can be at least two explanations for this: If technical grade CHPTAC was used it contained approximately 2-3 % EPTAC as an impurity. Even when purified CHPTAC is used, it converts pH dependently to the more reactive epoxy form. At pH 9, approximately 80 % of CHPTAC are converted to EPTAC and at the typical *in vitro* test system pH, 7.5, up to 50 % conversion could occur ((Mendrala, 1984a), (Raisio Chemicals, 2004a)). Moreover, (Richold et al., 1982a) showed that when the vehicle for the substance was buffered to 4.0 or 5.5. No mutagenic activity was seen in TA1535, which was typically positive. Therefore, even if CHPTAC might not be a mutagen itself a partial conversion to the mutagenic EPTAC could occur in the body. However, it is unclear, how CHPTAC behaves on entering the body. There is no information about the possible toxicokinetic fate of this substance. In the mouse micronucleus test *in vivo*, the result was negative when almost pure (99.7 %) CHPTAC was administered to rats in a 69 % water solution with at pH 3-6. Since the test substance was administered by an intraperitoneal injection, at least a couple options of its fate can be envisaged. When given via the intraperitoneal route, a substance may enter the general circulation directly from the intraperitoneal space or it may also enter the liver via the portal vein and be biotransformed there before reaching rest of organs. Thus, CHPTAC may either enter the general circulation unchanged or it was biotransformed and extracted to the bile without ever entering the systemic circulation or the bone marrow. Because there is no toxicokinetic knowledge of CHPTAC it is difficult to draw any definitive conclusions of its mutagenicity in vivo. An additional in vivo mutagenicity test (e.g. UDS) in another tissue would help to solve this issue.

Table 4.11: Mutagenicity of CHPTAC in mammalian cells

Test system	Concentrations	Result	Reference
Clastogenic effects in lymphocyte chromosomes (*in vitro*)	from 0.016, 0.049, 0.148, 0.444, 1.333, 4.000 12.000 mg/ml	Positive	(Wilmer, 1984)
Rat liver UDS (*in vitro*)	0.001, 0.00316, 0.01, 0.0316, 0.1, 0.316, 1.0, 3.16 and 10 mg/ml	Positive	(Mendrala, 1984c)
Chinese hamster ovary cell mutation (*in vitro*)	0.1, 1.0, 5.0, 10.0, 25.0 and 50.0 mg/ml, 0.09, 0.9, 4.6, 9.1, 22.7 and 45.5 mg/ml with S	Positive	(Mendrala, 1984b)
Mouse micronucleus test (*in vivo*)	147 mg/kg	Negative	(Degussa, 1992)

Conclusion

CHPTAC is an *in vitro* mutagen. Mutagenicity in vivo was negative in the mouse micronucleus test. Because only one study is available, there is uncertainty whether CHPTAC is an *in vivo* mutagen. No definitive conclusion can be drawn for this end-point at the moment. However, for the purposes of this risk assessment it is not seen necessary to produce further in vivo data on this end-point, because it is likely that this information would not help to refine the risk reduction measures.

4.1.2.8 Carcinogenicity

4.1.2.8.1 Studies in animals

In vivo studies

Dermal

Groups of 50 NMRI mice of each sex per dose were treated twice a week with dermal doses of 0, 0.018 and 0.18 ml of 65.79% CHPTAC (QUAB 188) corresponding to nominal doses of 0, 13.8, and 138 mg per animal (Degussa, 1997). The substance was reported to contain 32.36 % water but the content of the remaining 1.85 % was not accounted for. The pH was 4. The product specifications from the sponsor company current web page list the impurities for 65 % QUAB at pH 4-6 the following: epoxide content ≤500 ppm glycol content ≤0.8 %, epichlorohydrin ≤10 ppm and ≤20 ppm 1,3-dichloropropanol (Degussa, 2003). Taking the average mouse body weight of 48 g during the study doses of 2875 mg/kg for the high dose and 288 mg/kg for the low dose per application are obtained, which amounts to 575 mg/kg or 5750 mg/kg per week. Male mice were treated for 105 weeks and females for 89 weeks. The substance (65.79 % and 32.36 % water) was dissolved in 10 % ethanol, which was applied to 2 cm^2 clipped dorsal skin area in constant volume of 0.2 ml. The applied concentrations corresponded to 5.9% and 59.2 % of CHPTAC respectively. It should be noted that the study was of longer duration than the average of the historical control data which will lead to a tendency to have a higher background incidence. The test animals were clinically examined for mortality, symptoms, palpated for tissue enlargements or alterations, reflexes, eyes, hearing and teeth. Food consumption and body weight were monitored. Blood samples were taken at 52 weeks (females) and at 79 weeks (males) for a determination of differential leukocyte count, and at termination including the examination of differential leukocyte and basic red cell parameters. Sacrificed animals were subjected to full gross necropsy including examination of cranial, thoracic and abdominal cavities. Samples from 50 different tissues were preserved including all tissues with lesions. Adrenals, kidneys, liver, ovaries and testes were weighed. Histopathological samples were prepared from the preserved tissues. The statistical significance of the tumour incidence differences between the treated and control groups were evaluated using Dunnett-test. The study conducted in accordance with Good Laboratory Practice and OECD guideline 451 (1).
No treatment related clinical signs were observed during the study. There were no significant treatment related differences between the test substance and control group animals. The 25 % survival limit in females was reached after 89 weeks of treatment in females and after 105 weeks of treatment in males. No treatment related changes in food consumption were noted, but there were occasional statistically significant changes in the high dose males, which consumed more food in weeks 3/4, 10/11, 25/26, and 97/98. During week 49/50, these animals had slightly lower food consumption. The low dose group had slightly lower food consumption in week 65/66. The high dose females had marginally higher food consumption in weeks 3/4, 11/12, 13/14, 65/66 to 73/74. Low dose females had slightly increased food consumption in weeks 3/4, 11/12 and 81/82. The overall food consumption was 3.3% higher in low dose females and 6.6 in high dose females. These changes were considered to reflect biological variation since they were marginal, less than 10 % overall. No treatment related body weight changes were observed during the study. The body weight of low dose males was slightly higher during weeks 11 to 21 (max. 6.5 %) 57, to 61 (5.0 %) and in the week 73 (6.1 %). The body weight of low and high dose females was slightly higher in week 65 (7.4 %

in low and 7.7% in high dose). In the pathological examination, a small but statistically significant decrease of left testis absolute (0.223 g control, 0.214 g low dose (-4%) and 0.192 g high dose (-14%)) and organ weight relative to body weight (0.488 control, 0.477 (-2%) low dose and 0.414 high dose (-15%)) was seen in the high dose male mice. The female mice of the same dose group had an increased absolute and relative weight of the liver, and adrenals. The absolute weight of the right kidney was increased in the high dose females. In histopathology, the microscopical examination revealed a slight dose-related increase in the incidence of minimal to mild focal acanthosis and hyperkeratosis at the application site. The occasional tumours or hyperplastic findings found in or near the application site were not considered treatment-related. A dose-related increase in the occurrence of bronchio-alveolar adenomas and/or carcinomas (combined incidence) was observed in both sexes. The tumour incidences and their types are summarised in the table below.

Table 4.12: Neoplastic Findings in Lungs (absolute incidence in the study)

Finding	0 mg/kg/week		575 mg/kg/week		5750 mg/kg/week	
	M	F	M	F	M	F
Hyperplasia	4	0	5	2	4	3
Benign Tumour	7	3	8	8	12	7
Malignant Tumour	10	6	14	5	16	10
Benign or Malignant tumour	17	9	22	13	28*	17

All groups had 50 animals. * = $p < 0.05$, incidental analysis (Fisher exact test)

None of the individual incidences of the lung carcinomas and adenomas or hyperplasia findings were statistically significantly increased. Additional statistical analyses showed evidence of a positive trend relating to the increased incidence at the **5750 mg/kg/week** dose group. The incidence of these findings was somewhat higher in the low dose group, which contributed to the positive result in the trend test. However, none of the group comparisons was statistically significant in any of the statistical analyses.
The glandular mucosa of the stomach had higher incidence of focal hyperplasia in the high dose group of both sexes resulting in a statistically significant positive trend ($p < 0.05$). Only high dose females or both sexes combined showed significant differences in group comparison. The higher incidence of hyperplasia, rather than an increase of high-grade lesions, primarily contributed to this finding. In testis, when the combined incidences of hyperplasia and tumours were statistically analysed, a significantly reduced incidence of testicular neoplasia was seen in the low dose group (**575 mg/kg/week**). However, since there was no dose-relation, this was considered a non-treatment-related finding. Although slightly more neoplasias were found in the Harderian gland of the treated animals, no significant relation to the treatment could be found in the statistical analysis. However, a slightly significant positive trend in the tumour incidence was seen when the results of both sexes were combined. The significance was lost when the combined incidence of tumours and hyperplasia was analysed. When overall tumour incidence was examined, the **5750 mg/kg/week** dose group had the greatest incidence of malignant tumours of multiple sites. The trend was significant only for combined sexes of that dose group. The authors considered this an incidental finding due to the high frequency of pulmonary tumours and incidental tumours in that dose group. In addition, in the analysis of overall tumours, there was a high frequency of tumours with very low incidence, which did not represent well any target tissue. This finding had a high significance ($p < 0.01$) but it was considered an artefact from pooling several unrelated tumours together. No non-neoplastic toxic changes relating to the treatment were found.

Discussion

CHPTAC did not produce skin tumours in mice in a 2-year skin painting study. The only end-point of the carcinogenicity study that appears to have treatment relation is the increase in incidence of the bronchiolo-alveolar tumours and hyperplasia. There are facts to support a positive relationship between the tumours and treatment.
Although the low-dose group tumour incidence did not show a significant difference to control group there seemed to be a positive trend. Moreover, the high dose group incidence was not only significant but also exceeded the spontaneous tumour incidence observed in this species historically (another company using the same species and breeder).
The pulmonary tumours could also be of no relation to the treatment and a chance finding. This is supported by the fact that the duration of this study was considerably longer than the typical duration of the studies referred to in the historical data, which would skew the tumour incidence figures upwards. Furthermore, as the level of significance obtained in the statistical analysis is not very high ($p<0.05$), further supporting the possibility of a false positive response in the lung tumours. The slight increase of lung tumours might also represent promoter activity rather than tumour inducing property. Although the evidence is rather weak, the possibility that it presents a real effect cannot be completely excluded.
The glandular mucosa of the stomach of both sexes at high dose had a higher incidence of focal glandular hyperplasia, which resulted in a statistically significant dose related trend. In group-comparison, significant differences were noted only for high dose females and for the sexes combined. The hyperplastic changes were mostly minimal or slight. This might indicate oral exposure through licking of the treated site or it could well be incidental since this is a common lesion in old mice.
CHPTAC has been positive in most of the *in vitro* tests performed. As was shown by (Richold et al., 1982a) pH seems to play a role in *in vitro* mutagenicity. When the low pH was used in the Ames assay, no mutagenic response was noted. Formation of the closely related epoxide, 2,3-epoxypropyltrimethylammonium chloride (EPTAC), to which about 1-3 % CHPTAC is expected to spontaneously convert at physiological pH might be causing the mutagenic response seen in many of the *in vitro* assays (Mendrala, 1984a). However, in contrast to that, the only *in vivo* micronucleus test in mouse bone marrow available was negative.

Calculation of systemic dose for CHPTAC

Assuming that the oral exposure did not significantly contribute to the systemic dose, the skin absorption study results are taken to calculate the systemic dose of the skin painting study. As the amount absorbed varies with the concentration of the applied solution two different absorption percentages are used.

<u>High dose group</u>
External dose: 5750 mg/kg/week.
Concentration applied: 59%, amount applied: 138 mg per animal twice per week, average bw. 48 g. Total percent absorption for the 65 % solution (result from the in vitro skin absorption study): 13 %. Calculated dose with 13% absorption: Application of 5750 mg/kg bw per week with: 13 % absorption would correspond to 748 mg/kg per week or 107 mg/kg per day (calculated for 7 days).

<u>Low dose group</u>
External dose 575 mg/kg bw per week.

Concentration applied: 5.9 % or 13.8 mg/animal twice per week, average bw 48 g
Total percent absorption (from the in vitro skin absorption study, 1% solution): 29.2 %.
Calculated dose with 29.2% percent absorption of 575 mg would correspond to 168 mg/kg bw/week or 24 mg/kg/day (7 days).

Considering that the mode of action had a threshold, determination of the lowest adverse effect level or a benchmark dose can be performed. A benchmark dose calculation has been conducted by Degussa (see Annex 1) using the benchmark dose (BMD) approach (US EPA) to estimate the carcinogenic potential of CHPTAC. By applying the available tumour data to a multistage model, an estimate of a BMD (ED_{10}) and benchmark dose level (LED_{10},) for a 10 % extra risk for both substances can be obtained. ED_{10} refers to the dose giving an excess level of response of 10 %. LED_{10} corresponds to the lower limit of a one-sided 95% confidence interval on the BMD. The benchmark dose can then serve as the starting point for linear extrapolation or non-linear quantitative approach, depending on the mode of action of the carcinogen. From the calculation, a $BMD_{0.1}$ of 465 mg/kg for a 5 d/week exposure for malignant and benign tumours combined was obtained. See summary of the calculation in Annex 1.

4.1.2.8.2 Summary of carcinogenicity

Under the conditions of exposure, CHPTAC is not a local carcinogen in mice when administered via skin but there is a possibility that it is a systemic carcinogen based on the increased incidence of bronchiolo-alveolar tumours. However, the evidence on the systemic tumours is relatively weak and partly confounded by the duration of the study, which was longer than usually. Because there is not enough information on the mutagenicity in vivo, a directly genotoxic non-threshold mode of action of these tumours cannot be ruled out. Classification and labelling working group agreed to classify CHPTAC as Xn; Carc. Cat. 3; R40.

4.1.2.9 Toxicity for reproduction

4.1.2.9.1 Effects on fertility

Studies in animals

There are no reproductive studies available. The 28-day study in rat showed no effects to gonads at 1085 mg/kg. In a two-year skin painting study where mice were administered up to 138 mg CHPTAC twice weekly, in the high dose animals, a slight but significant (max 14%) reduction of the left testis was seen in the high dose group (Degussa, 1997). The high dose animals showed a 14 % weight reduction in the absolute left testis weight and 15 % reduction of the left testis weight relative to bodyweight when compared to control. The low dose animals did not have a statistically significant reduction in absolute testis weight but the weight was about 4 % lower than in the controls. The absolute weights of the right testis were 5 % lower in the low dose group and 9 % lower in the high dose group, but neither was statistically significant. A similar but not statistically significant decrease was noted in the relative right testis weight. The significance to the weight change to reproduction is unknown.

Derived from the 28-day oral exposure study LOAEL (a NOAEL for gonad effects) of 1085 mg/kg, a calculated systemic dose of 543 mg/kg bw/day is derived using a 50% G-I absorption assumption. For the dermal study using the percentage of total absorption at the high dose: LOEL: 107 mg/kg per day, NOAEL: 24 mg/kg/day (as per the above supplied calculations).

4.1.2.9.2 Developmental toxicity

There are no studies available which would enable the evaluation of developmental toxicity.

4.1.2.9.3 Summary of toxicity for reproduction

No definite conclusion can be drawn for reproductive toxicity at this state.

4.1.3 Risk characterisation [5]

4.1.3.1 General aspects

Toxicity

There is no toxicokinetic data available for (3-chloro-2-hydroxypropyl)trimethylammonium chloride. Inhalation absorption of 75% for a polar substance and oral absorption of 50% is assumed. Based on the in vitro skin penetration study with CHPTAC, 6 % skin absorption in humans is assumed. This figure is used also when estimating the dermal exposure to 2,3-epoxypropyltrimethylammonium chloride (EPTAC) in the use scenarios during cationising. Acute oral toxicity is about 2170 mg/kg orally and based on a limit test dermal LD50 value is more than 2000 mg/kg. Based on relatively limited data, acute toxicity via inhalation is likely over 12.05 mg/l. CHPTAC does not irritate the eyes or the skin. CHPTAC does not cause a contact hypersensitisation in guinea pigs. In repeated dose toxicity, only one single dose, 28-day oral gavage study is available. This study reported a decrease of absolute and relative heart weight in males and a 20 % increase of relative kidney weight in males. Females had no statistically significant changes in their organ weights. In the macroscopical examination of the necropsy, focal alopecia of the forepaws and neck in two animals and reddening of the proximal parts of the small intestine or the glandular stomach was seen. The reddening of intestine was only observed in the animals that died on day two for substance unrelated reasons. Microscopically, vacuolisation of proximal tubule cells of the inner cortical and outer medullar regions of the kidney was seen. The rats with alopecia were diagnosed to have moderate atrophy of hair glands and sebaceous glands in the affected skin areas. Thus, based on the effects seen especially in the kidney, a LOAEL of 1085 mg/kg is set. For the purposes of risk assessment and inhalation exposure route, an internal LOAEL of 543 mg/kg will be used, which is based on the assumption that 50 % of the oral dose is absorbed. Using a

[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.

LOAEL in the risk characterisation leaves some uncertainty over the safety margins. On the other hand, in a 2-year skin painting study, in which mice were applied dermally up to 138 mg CHPTAC twice weekly (5750 mg/kg/week, resulting to an internal dose of 748 mg/kg/week), no significant non-neoplastic treatment related organ changes were observed. This value will not be used for the risk characterisation due to the twice-week dosing regime. CHPTAC has caused a positive response in several *in vitro* tests. However, this could be caused by the presence of 2,3-epoxypropyltrimethylammonium chloride (EPTAC) either as an impurity or through conversion due to the pH dependent chlorohydrin-epoxide equilibrium. Because of the equilibrium, conversion of CHPTAC to EPTAC is likely in an environment where pH is near 7.4 (Raisio, 2004). The conversion rate to EPTAC could be up 50 % near physiological pH. Salmonella typhimurium strain 1535 and 100 have been reported positive; these strains were positive also when pure EPTAC was tested. In mammalian cells, a positive result was seen in the chromosome analysis, liver unscheduled DNA synthesis and Chinese hamster ovary cell hypoxanthine phosphoribosyl transferase (CHO/HGPRT) gene location test. Mouse bone marrow micronucleus test *in vivo* (single i.p.), however, was negative. EPTAC was positive in mouse bone marrow micronucleus test (single i.p.). CHPTAC did not produce tumours locally in a two-year dermal carcinogenicity study with mice. However, there was an increase of bronchiolo-alveolar tumours at 5750 mg/kg/week, albeit significant only when both benign and malign tumours were combined. The data does not allow a definitive conclusion on CHPTAC's mutagenicity. However, no further testing is considered necessary for the purposes of this risk assessment, because it is not likely to bring added value which would help to refine the risk reduction measures. CHPTAC is classified Carc. Cat 3; R40. There are no studies on reproductive toxicity. For consumer exposure and indirect exposure via the environment, an internal NOAEL of 5000 ug/kg for gonad toxicity from the EPTAC 28-day repeated dose toxicity study was used for these scenarios. Any additional reproductive studies are not expected to significantly enhance the risk characterisation of CHPTAC when balanced against animal welfare concerns.

Exposure

Worker

There are two main scenarios of worker exposure. Exposure can occur in the different tasks during the production, the use of CHPTAC, e.g. in the cationisation of starch, which is main use for CHPTAC. Although CHPTAC is quantitatively converted to 2,3-epoxypropyltrimethylammonium chloride (EPTAC) during the cationisation process residual amounts of CHPTAC can still be present in the end-product. The biggest use of cationised starch is in the paper industry as an additive in papermaking. Minute amounts of CHPTAC can still be present at this stage. The exposure from cationised starch occurs via either the skin or the respiration. Inhalation exposure occurs typically only in the loading/unloading to residual CHPTAC in the dry cationising process. 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.

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. Detailed instructions how to properly avoid dermal exposure are given and management systems applied.

Since most of the CHPTAC is converted to EPTAC during cationisation process, the formation of genotoxic carcinogen EPTAC is the main risk component in the use scenarios.

Therefore, to perceive the true risk from CHPTAC use, also the risk from EPTAC is assessed in the risk characterisation for worker for the following end-points which are considered to be the most problematic: sensitisation, mutagenicity and carcinogenicity.

For the risk characterisation, and its implications for risk reduction it is important to consider the fact that in the production scenarios the risk reduction measures are driven by the handling of epichlorohydrin that is currently classified as category 2 carcinogen and that in the use scenarios the risk reduction will be driven by EPTAC (see RAR of EPTAC).

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.

Consumer

CHPTAC is not intentionally used in consumer products. However, in the cationising process residues of CHPTAC are left in the cationised starch, which is used as an additive in papermaking. Part of the CHPTAC in paper or cardboard is as EPTAC (2,3-epoxypropyltrimethylammonium chloride). When estimating the potential consumer exposure, information on measurements of CHPTAC in residues, the amount of cationised starch used in cellulose, and adsorption rate of CHPTAC to paper were used. Three potential scenarios were assessed where exposure to CHPTAC could occur: Migration from paper, e.g., copy paper or newsprint to skin, migration from food packaging material to food, which might be ingested, and migration from mouthing of board in children's books by small children of age 6 to 12 months.

The migration of CHPTAC from copy and newspaper 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 0.000018 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 laminated paper in the outer layer of children book covers. 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, CHPTAC exposure from children's books was estimated 0.6-1.2 µg. Calculating for a 6-12 months-old person weighing person 7.5-9.9 kg and assuming all is ingested, a daily dose of 0.06-0.16 µg/kg of b.w. is obtained.

The migration from packages to food is expected to occur only when the food is partly (10 %) moistened. In worst case, up to 0.31-1.22 µg CHPTAC is expected become ingested in food via migration from packaging. In a 70-kg person, this would correspond to a dose of 0.017 µg/kg bodyweight or with assumed 50% absorption a systemic dose of 0.0085 µg/kg bw. This exposure source is considered to be occasional in nature, i.e., clearly less than once a day in frequency. The average long-term exposure is estimated likely about 2-3 magnitudes lower.

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 CHPTAC is below 0.74 ppm. Using the application amount assumptions given in the revised TGD together with the maximum CHPTAC content of 0.74 ppm, the daily dose of CHPTAC 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, 0.0042-0.2 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.

Table 4.14 Summary of effects

Substance name	Inhalation LC50/ NOAEL	Dermal LD50/ NOAEL	Oral LD50 / LOAEL
Acute toxicity	>12500 mg/m^3	>2000 mg/kg	>2000 mg/kg
Irritation / corrositivity	No data.	Negative	No data.
Sensitization	No data.	Negative	No data.
Repeated dose toxicity (systemic)	No data.	5750 mg/kg/week	1085 mg/kg
Mutagenicity	Mostly positive *in vitro*, negative in vivo (one mouse micronucleus test)		
Carcinogenicity	No data.	Bronchiolo-alveolar tumours at 5750 mg/kg/week	No data.
Fertility impairment	No data.	No data.	No data.
Developmental toxicity	No data.	No data.	No data.

4.1.3.2 Workers

In the work environment, there are two main scenarios, which have been considered: manufacture and use of CHPTAC. Table 4.1.3.2A contains only the highest exposure figures of the use scenarios. EPTAC exposures and doses are added in brackets.

Table 4.15 Estimated reasonable worst-case and typical daily systemic CHPTAC and 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	
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	0.02 *[0.0006]*	$2.5x10^{-4}$ [$6x10^{-5}$]	-	-	$1.7x10^{-5}$ *[$5.1x10^{-7}$]*	$2.1x10^{-7}$ *[$5.1x10^{-8}$]*	-	-
Use (Dry cationising or wet cationising with drying)								
Bagging (full shift)	0.4 *[0.01]*	0.005 *[0.001]*	0.002* *[$8x10^{-5}$]*	$3x10^{-5}$* *[$6x10^{-5}$]*	$3.4x10^{-4}$ *[$8.6x10^{-6}$]*	$4.3x10^{-6}$ *[$2.1x10^{-7}$]*	$2.1x10^{-4}$ *[$8.6x10^{-6}$]*	$3.2x10^{-7}$ *[$6.4x10^{-6}$]*
Clean-up (weekly)	0.4 *[0.01]*	0.001 *[0.00025]*	0.02 *[0.0008]*	$6x10^{-5}$ *[$2x10^{-5}$]*	$3.4x10^{-4}$ *[$8.6x10^{-6}$]*	$8.6x10^{-7}$ *[$2.1x10^{-7}$]*	$2.1x10^{-3}$ *[$8.6x10^{-5}$]*	$6.4x10^{-7}$ *[$2.1x10^{-6}$]*
Laboratory work	0.2 *[0.006]*	0.0005 *[0.0001]*	-	-	$1.7x10^{-4}$ *[$5.1x10^{-6}$]*	$4.3x10^{-7}$ *[$8.6x10^{-8}$]*	-	-
Sampling	0.1 *[0.003]*	0.00025 *[$6x10^{-5}$]*	-	-	$8.6x10^{-5}$ *[$2.6x10^{-6}$]*	$2.1x10^{-7}$ *[$5.1x10^{-9}$]*	-	-
Maintenance (≤ 4 times per year)	0.4 *[0.01]*	0.0001 *[$2.5x10^{-5}$]*	0.02 *[0.0008]*	$6x10^{-5}$ *[$2x10^{-5}$]*	$3.4x10^{-4}$ *[$8.6x10^{-6}$]*	$8.6x10^{-8}$ [$2.1x10^{-8}$]	$2.1x10^{-3}$ *[$8.6x10^{-5}$]*	$6.4x10^{-7}$ *[$2.1x10^{-6}$]*

75 % absorption was assumed via the inhalation and 6 % via skin, * = based on measurements, 70 kg body weight person, 8 h respiratory volume assumed 10 m^3, EPTAC exposure is given in italic square brackets.

4.1.3.2.1 Acute toxicity

Only dermal and inhalation routes are relevant. With a dermal LD50 limit test value of >2348 mg/kg the MOSs for acute dermal toxicity are relatively high, >5460 for the scenarios with highest daily exposures, namely laboratory work. As even the highest daily inhalation exposure is very small (0.04 mg/m3), acute toxicity via this route is not likely to be a problem. Assuming an inhalation LD50 value of 125000 mg/m3, a MOS of 312500 would be obtained.

Table 4.16 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	-	>12500	-	ii	0.13	>2000	>15384	ii
Laboratory work	-	>12500	-	ii	0.26	>2000	>7692	ii
Maintenance	-	>12500	-	ii	0.05	>2000	>40000	ii
Loading/ Unloading and sampling after loading	0.04	>12500	$>3.1x10^5$	ii	0.02	>2000	$1.0x10^5$	ii
Use Wet cationising								
Sampling	-	>12500	-	ii	-	>2000	-	ii
Laboratory work	-	>12500	-	ii	-	>2000	-	ii
Maintenance	-	>12500	-	ii	-	>2000	-	ii
Filling	-	>12500	-	ii	$1.7x10^{-5}$	>2000	$1.2x10^8$	ii
Use Dry cationising or wet cationising with drying								
Bagging	0.002	>12500	$>6.3x10^6$	ii	$3.4x10^{-4}$	>2000	$5.8x10^6$	ii
Clean-up work	0.02	>12500	$>6.3x10^5$	ii	$3.4x10^{-4}$	>2000	$5.8x10^6$	ii
Laboratory work	-	>12500	-	ii	$1.7x10^{-4}$	>2000	$1.2x10^7$	ii
Sampling	-	>12500	-	ii	$8.6x10^{-5}$	>2000	$2.3x10^7$	ii
Maintenance work	0.02	>12500	$>6.3x10^5$	ii	$3.4x10^{-4}$	>2000	$5.8x10^6$	ii

4.1.3.2.2 Sensitisation

Skin

The CHPTAC is not sensitising. This end-point is not relevant in production scenarios where only CHPTAC is present. However, during use (cationising) virtually all CHPTAC is converted to EPTAC, which is a potent human sensitiser. 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. Residual EPTAC in cationised starch did not produce a reaction. According to exposure assessment, tasks in CHPTAC use in 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 containing material 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 containing material, there is no certainty that this is the situation of all plants in the EU.

Although CHPTAC itself is not a sensitiser, it is considered a potential source of sensitisation in the use scenarios where it is converted to EPTAC. Conclusion ii is reached for all production scenarios and conclusion iii for all use scenarios.

4.1.3.2.3 Repeated dose toxicity

An oral LOAEL of 1085 mg/kg/d from a 28-day OECD guideline study is used for calculation of the margins of safety in inhalation exposure. Because it is assumed that 50 % of the ingested dose is absorbed, an internal LOAEL of 543 mg/kg shall be used. The LOAEL is based on the degenerative effects in the kidney proximal tubules of the rat. 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.

Because in use scenarios CHPTAC is converted to EPTAC, for which the 28-day MOS is significantly lower, a separate MOS is calculated for EPTAC. For the estimation of EPTAC MOSs, a 28-day LOAEL of 3.16 mg/kg is used. Accounting for the assumption of 50 % absorption, an internal LOAEL of 1.58 mg/kg is obtained. A minimal MOS is derived 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.

Table 4.17 Occupational risk assessment for repeated dose toxicity

	Inhalation				Dermal			
	Exposure mg/kg	Internal LOAEL mg/kg	MOS	Conclusion	Exposure mg/kg/d	Internal LOAEL mg/kg	MOS	Conclusion
Production								
Sampling	-	543	-	ii	0.13	543	4177	ii
Laboratory work	-	543	-	ii	0.26	543	2088	ii
Maintenance	-	543	-	ii	0.05	543	10860	ii
Loading/ Unloading and sampling after loading	0.004	543	$7.4x10^{-6}$	ii	0.02	543	27150	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	-	543/ *[1.58]*	-	ii	$1.7x10^{-5}$ *[$5.1x10^{-7}$]*	543 *[1.58]*	$3.2x10^{7}$ *[$3.1x10^{6}$]*	ii
Use Dry cationising or wet cationising with drying								
Bagging	$2.1x10^{-4}$	543/ *[1.58]*	$2.6x10^{6}$ *[7524]*	ii	$3.4x10^{-4}$ *[$8.6x10^{-6}$]*	543 *[1.58]*	$1.6x10^{6}$ *[$1.8x10^{5}$]*	ii
Clean-up work	$2.1x10^{-3}$	543/ *[1.58]*	$2.6x10^{5}$ *[752]*	ii	$3.4x10^{-4}$ *[$8.6x10^{-6}$]*	543 *[1.58]*	$1.6x10^{6}$ *[$1.8x10^{5}$]*	ii
Laboratory work	-	543/ *[1.58]*	-	ii	$1.7x10^{-4}$ *[$5.1x10^{-6}$]*	543 *[1.58]*	$3.2x10^{6}$ *[$3.1x10^{5}$]*	ii
Sampling	-	543/ *[1.58]*	-	ii	$8.6x10^{-5}$ *[$2.6x10^{-6}$]*	543 *[1.58]*	$6.3x10^{6}$ *[$6.1x10^{5}$]*	ii
Maintenance work	$2.1x10^{-3}$	543/ *[1.58]*	$2.6x10^{5}$ *[752]*	ii	$3.4x10^{-4}$ *[$8.6x10^{-6}$]*	543 *[1.58]*	$1.6x10^{6}$ *[$1.8x10^{5}$]*	ii

75 % absorption was assumed via the inhalation and 6 % via skin, * = based on measurements, 70 kg body weight person, 8 h respiratory volume assumed 10 m^3, EPTAC exposure is given in italic square brackets. EPTAC MOSs are shown in brackets and in italics.

4.1.3.2.4 Mutagenicity

Production

CHPTAC showed positive results in *in vitro* tests, but a mouse micronucleus assay gave a negative result. Because no additional mutagenicity tests in vivo were available, no definite conclusion can be drawn about mutagenicity without further data. It should be noted, however, that risk reduction measures are being taken already because of the raw materials used in manufacture, i.e. epichlorohydrin which is classified as a category 2 carcinogen.

Use

Although there is exposure to CHPTAC in the use scenarios, CHPTAC is to a large extent converted to EPTAC during use (cationising). Therefore, potential CHPTAC exposure is also exposure to mutagenic EPTAC during use, which will be taken in to account when drawing conclusions.

4.1.3.2.5 Carcinogenicity

Production

Although CHPTAC did not show similar carcinogenic potential as EPTAC, it is likely that on entering the body CHPTAC is converted to carcinogenic EPTAC. This leaves some uncertainty in the production scenario, where exposure is to CHPTAC only. The systemic benchmark dose of 55 mg/kg bw/day (BMD0.1 (5d) combined malignant and benign tumours See appendix 1) for workers can be used as a starting point to calculate an MOE (Margin of Exposure) for workers in the production scenario. See summary table 4.18 for MOE values. It should be noted that in CHPTAC production phase, epichlorohydrin used in the synthesis is the most abundant and possibly the most potent carcinogen. In the end product, formation of EPTAC is controlled by pH. Therefore, risk reduction measures are already taken because of the raw materials used in manufacture, i.e., epichlorohydrin, which is classified category 2 carcinogen. However, an exposure or risk assessment of epichlorohydrin is not considered to be in the scope of this assessment.
Conclusion ii is reached for CHPTAC production scenarios.

Use

In cationising use, CHPTAC is converted to EPTAC during use (cationising). EPTAC has been shown to be a skin carcinogen in mice. Thus, the potential CHPTAC exposure is also exposure to carcinogenic EPTAC during use will be considered in the conclusion.

4.1.3.2.6 Toxicity for reproduction

There are no studies on reproductive toxicity. According to the revised Technical Guidance document, there would be motivation to investigate further the reproductive toxicity in a 2-generation fertility test and a developmental toxicity test. No adverse effects were noted in a 28-day oral exposure study with rat. Derived from this study LOAEL for general toxicity of 1085 mg/kg (a NOAEL for gonad effects), a calculated systemic dose of 543 mg/kg bw/day can be derived using a 50% G-I absorption assumption.

In the production scenarios, exposure to CHPTAC occurs dermally. No inhalation exposure is expected. The highest dermal dose for worker is 0.26 mg/kg/d or 1.8 mg/kg/week. No severe treatment-related effects are seen in gonads after a two-year dermal administration of up to 138 mg/animal CHPTAC twice weekly or 5750 mg/kg/week. Only a slight but significant reduction of the left testis was seen in the high dose group (Degussa, 1997). For the testis decrease noted in the dermal study a LOEL of 107 mg/kg per day, and NOAEL of 24 mg/kg/day (as per the above supplied calculations) could be derived.

Although the formal data requirements for reproduction toxicity are not met, the situation at the time does not indicate an urgent need for additional testing. In the CHPTAC production scenario, risk reductions measures are being taken because of the raw materials used in manufacture, i.e., epichlorohydrin, which is classified as a category 2 carcinogen.

In the CHPTAC use scenarios, the principal concern is in the formation of EPTAC, a genotoxic carcinogen, to which the worker is exposed. In the 28-day repeated dose toxicity study, an NOAEL of 10 mg/kg was obtained based on effects to especially female gonads at 31.6 mg/kg. No calculation of MOS for reproductive toxicity is performed. Because the internal NOAEL of 5 mg/kg is greater than the one obtained in the repeated dose toxicity, the MOSs for reproductive toxicity would be higher in any case. For scenarios where EPTAC is formed, strictest worker protection would be expected already. Furthermore, on animal welfare grounds, generation of more reproductive toxicity data is not considered justified.

4.1.3.2.7 Summary of risk characterisation for workers

Table 4.18 Overview of the conclusions with respect to occupational risk characterisation

		Acute toxicity		Sensitisation	Repeated dose toxicity Systemic		Mutagenicity	Carcinogenicity§	Reproductive toxicity
		Dermal	Inhalation		Dermal	Inhalation			
Production									
Sampling	MOS	>15384	-	-	4177	-	-	*523*	-
	Concl.	ii	ii	ii	ii	ii	i on hold	ii	i on hold
Laboratory work	MOS	>7692	-	-	2088	-	-	*211*	-
	Concl.	ii	ii	ii	ii	ii	i on hold	ii	i on hold
Maintenance	MOS	>2.2x10^5	-	-	10860	-	-	*1100*	-
	Concl.	ii	ii	ii	ii	ii	i on hold	ii	i on hold
Loading/ Unloading and sampling after loading	MOS	5.0x10^5	>3.1x10^5	-	27150		-	*2750*	-
	Concl.	ii	ii	ii	ii	ii	i on hold	ii	i on hold
Use Wet cationising									
Sampling	MOS	-	-	[0]	*-/ [395]*	-	-	[0]	*[-]*
	Concl.	ii	ii	[iii]	ii	ii	i on hold	iii	i on hold
Laboratory work	MOS	-	-	[0]	*-/ [176]*	-	-	[0]	*[-]*
	Concl.	ii	ii	[iii]	ii	ii	i on hold	iii	i on hold

Maintenance	MOS	-	-	[0]	*-/ [527]*	-	-	[0]	*[-]*
	Concl.	ii	ii	[iii]	ii	ii	i on hold	iii	i on hold
Filling	MOS	$6.6x10^8$	-	[0]	$3.2x10^7$ *[$3.1x10^6$]*	-	-	[0]	*[-]*
	Concl.	ii	ii	[iii]	ii	ii	i on hold	iii	i on hold
Use Dry cationising or wet cationising with drying									
Bagging	MOS	$3.3x10^7$	$>6.3x10^6$	[0]	$1.6x10^6$ *[$1.8x10^5$]*	$2.6x10^6$ *[7524]*	-	[0]	*[-]*
	Concl.	ii	ii	[iii]	ii	ii	i on hold	iii	i on hold
Clean-up work	MOS	$3.3x10^8$	$>6.3x10^5$	[0]	$1.6x10^6$ *[$1.8x10^5$]*	$2.6x10^5$ *[752]*	-	[0]	*[-]*
	Concl.	ii	ii	[iii]	ii	ii	i on hold	iii	i on hold
Laboratory work	MOS	$6.6x10^7$	-	[0]	$3.2x10^6$ *[$3.1x10^5$]*	-	-	[0]	*[-]*
	Concl.	ii	ii	[iii]	ii	ii	i on hold	iii	i on hold
Sampling	MOS	$2.0x10^9$	-	[0]	$6.3x10^6$ *[$6.1x10^5$]*	-	-	[0]	*[-]*
	Concl.	ii	ii	[iii]	ii	ii	i on hold	iii	i on hold
Maintenance work	MOS	$3.3x10^8$	$>6.3x10^5$	[0]	$1.6x10^6$ *[$1.8x10^5$]*	$2.6x10^5$ *[752]*	-	[0]	*[-]*
	Concl.	ii	ii	[iii]	ii	ii	i on hold	iii	i on hold

§Production scenario MOEs are based on a theoretical systemic benchmark dose obtained by extrapolation from one dermal carcinogenicity study in mice with CHPTAC. MOSs for use scenarios are based on data from EPTAC are shown in brackets.

Consumers

In consumer exposure, exposure is only to negligible amount of residual CHPTAC or converted EPTAC.

4.1.3.2.8 Acute toxicity

Only dermal and oral route is relevant. An oral LD50 value of greater than 2170 and a dermal LD50 value greater than 2348 mg/kg have been obtained. The maximum daily oral exposure in consumer use is about 0.02 µg/kg/day. The level of exposure is negligible when compared to the LD50 values. Conclusion ii is drawn.

4.1.3.2.9 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 from cosmetics, which are left on the skin. With a daily dose 0.02 µg/kg/d and an internal LOAEL of 1580 µg/kg a MOS of 79000 is obtained. Conclusion ii is drawn.

4.1.3.2.10 Mutagenicity

Exposure caused to consumer is very low. Consumer is occasionally exposed to a few nanograms of CHPTAC per kg of body weight. Although the risk of mutagenicity from residual CHPTAC might is negligible, theoretically this could be converted to EPTAC which is a more potent mutagen than CHPTAC. In any case, the overall risk from either substance is considered negligible. Conclusion ii is drawn.

4.1.3.2.11 Carcinogenicity

Residual CHPTAC and EPTAC are likely to pose only a negligible carcinogenicity risk, of little relevance to the consumer. Conclusion ii is drawn.

4.1.3.2.12 Toxicity for reproduction

There are no studies on reproductive toxicity. According to the revised Technical Guidance document, there would be motivation to investigate further the reproductive toxicity in a 2-generation fertility test and a developmental toxicity test. However, no adverse gonad effects were noted in a 28-day oral exposure study with rat. Derived from this study LOAEL for general toxicity of 1085 mg/kg (a NOAEL for gonad effects), a calculated systemic dose of 543 mg/kg bw/day can be derived using a 50% G-I absorption assumption. In addition, no severe treatment-related effects are seen in gonads after a two-year dermal administration of up to 138 mg/animal CHPTAC twice weekly or 5750 mg/kg/week. Only a slight but significant reduction of the left testis was seen in the high dose group (Degussa, 1997). For the testis decrease noted in the dermal study a LOEL of 107 mg/kg per day, and NOAEL of 24 mg/kg/day (as per the above supplied calculations) could be derived. Comparing this to the maximum daily consumer exposure of 0.02 µg/kg/d, a MOS of 1200000 can be derived.

Although a 28-day study cannot be used to draw direct conclusions about reproductive toxicity itself, it is considered likely that the level of exposure is negligible to warrant concern.

Conclusion ii is drawn.

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. However, for formal reasons, because no valid study is available, conclusion i (on hold) is drawn.

4.1.3.2.13 Summary of risk characterisation for consumers

Table 4.19 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 relevant in consumer exposure scenarios due to very low exposure. Conclusion ii in all scenarios.		-	Lowest MOS found in cosmetics scenario: MOS of 79000. Conclusion ii in all scenarios.		-	-	Lowest MOS found in cosmetics scenario: MOS of 120000. Conclusion i on hold.
	Concl.			ii			i on hold	ii	
Children's books	MOS			-			-	-	
	Concl.			ii			i on hold	ii	
Copy paper & newspapers	MOS			-			-	-	
	Concl.			ii			i on hold	ii	
Cosmetics	MOS			-			-	-	
	Concl.			ii			i on hold	ii	

4.1.3.3 Humans exposed via the environment

Because no actual emission CHPTAC calculations were available, EUSES modelling was conducted to estimate indirect exposure resulting from cationising process. No degradation has been assumed in the model.

The same end points are considered relevant as for the consumer scenario. The MOSs are presented only in form of a summary table (4.28).

4.1.3.3.1 Exposure via air

Daily external exposure via air is estimated about 3.1×10^{-6} mg/kg, which about one thousandth of the total indirect exposure. Contribution from this scenario to the total indirect exposure is considered negligible.

4.1.3.3.2 Exposure via food and water

According to EUSES model the total indirect exposure to CHPTAC from food and water is about 2 ug/kg b.w (table 4.2c).

Using an oral absorption rate of 50% a total internal exposure of 1 ug/kg b.w is obtained, which is used to calculate the MOSs for indirect exposure against an internal LOAEL of 543000 ug/kg. For the carcinogenicity MOS, benchmark dose of 55000 ug/kg bw/day (BMD0.1 (5d) was used. The reliability of the calculated MOSs is not very high due to the probable gross overestimation of the indirect exposure scenarios.

There are no studies on reproductive toxicity conducted with CHPTAC. According to the revised Technical Guidance document, this could be seen as motivation to investigate further the reproductive toxicity in a 2-generation fertility test and a developmental toxicity test. However, no adverse gonad effects were noted in a 28-day oral exposure study with rat. Derived from this study LOAEL for general toxicity of 1085 mg/kg (a NOAEL for gonad effects), a calculated systemic dose of 543 mg/kg bw/day can be derived using a 50% G-I absorption assumption. In addition, no severe treatment-related effects are seen in gonads after a two-year dermal administration of up to 138 mg/animal CHPTAC twice weekly or 5750 mg/kg/week. Only a slight but significant reduction of the left testis was seen in the high dose group (Degussa, 1997). For the testis decrease noted in the dermal study a LOEL of 107 mg/kg per day, and NOAEL of 24 mg/kg/day (as per the above supplied calculations) could be derived. Comparing this to the maximum daily consumer exposure of 1 µg/kg/d, a MOS of 24000 can be derived. Although a 28-day study cannot be used to draw direct conclusions about reproductive toxicity itself, it is considered likely that the level of exposure is negligible to warrant concern.

The results of the risk characterisation for indirect exposures are summarised in table 4.27.

4.1.3.3.3 Summary of risk characterisation for exposure via the environment

According to EUSES calculations, the combined daily internal dose is 1 ug/kg with the greatest exposures coming from leaf crops and drinking water. However, the assessed total exposure could be an overestimation.

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 543000 Conclusion ii in all scenarios.		-	*[55000]*	24000*
	Concl.			ii			ii	ii	Conclusion i on hold.

* The MOS was derived using a controversial modelled exposure figure. Therefore this MOS is likely not likely to have relevance to the general population.

4.1.3.4 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.

4.2.1.1 Humans exposed via the environment

[click here to insert text]

4.2.2 Effects assessment: Hazard identification

4.2.2.1 Explosivity

CHPTAC is not explosive.

4.2.2.2 Flammability

CHPTAC is not flammable.

4.2.2.3 Oxidizing potential

CHPTAC is not oxidising.

4.2.3 Risk characterisation

Not relevant.

5 RESULTS [6]

[Note: In the final report, chapters 0 and 5 should be as close as possible to the OJ]

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 for four sites with wet process (Industrial use 1) at the local scale (i.e. sites B9, B10, B23 and B25).

From these four starch cationisation sites, which have risk ratio higher than one, only one site (B25) has monitoring data on CHPTAC releases to waste water. However, the detection limit of CHPTAC from waste water effluent (2 mg/l) has been rather high compared to PNEC (0.051 mg/l l). Use of lower detection limit might decrease risks from this site. For those three sites where no monitoring data is available (B9, B10 and B23), releases have been calculated with an emission factor from a starch cationisation site with highest release factor (2.2 %). 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, cationisation of starch for seven sites with dry process (B6, B11, B12, B13, B15, B22 and B28) and for eight sites with wet process (B3, B4, B5, B14, B16, B17, B18, B21) (Industrial use 1), 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:

[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.

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 production and all use scenarios.

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 to all use scenarios because of concerns for mutagenicity, carcinogenicity and sensitisation.

Conclusion ii is drawn in the CHPTAC production scenario. In CHPTAC production phase, a category 2 carcinogen, namely epichlorohydrin, is used in the synthesis. Due to the presence of epichlorohydrin, sufficient risk reduction measures need to be in place already during synthesis. These are considered sufficient also for limiting the theoretical risk from CHPTAC exposure during manufacturing phase. In the end product, formation of EPTAC is controlled by pH. Therefore, due to current risk reduction measures in the production phase the risk is foreseen as minor and thus, conclusion ii is drawn.

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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.

5.2.1.3 Humans exposed via the 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 (ii) applies to all scenarios.

5.2.1.4 Combined exposure

This section was not separately assessed due to negligible additive significance from consumer exposure.

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.

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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

Carcinogenicity benchmark dose (BMD) calculation for CHPTAC

Introduction

A benchmark dose calculation has been performed by (Degussa, 2002a) using the benchmark dose (BMD) approach (US EPA) to estimate the carcinogenic potential of CHPTAC. BMD can be used as an alternative for estimating NOAEL/LOAEL. By applying the available data to a multistage model, an estimate of a BMD (ED_{10}) and benchmark dose level (LED_{10},) for a 10 % extra risk for both substances can be obtained. ED_{10} refers to the dose giving an excess level of response of 10 %. LED_{10} corresponds to the lower limit of a one-sided 95% confidence interval on the BMD. The benchmark dose can then serve as the starting point for linear extrapolation or non-linear quantitative approach, depending on the mode of action of the carcinogen.
For this calculation, the data was taken from the 2-year skin painting study. Although other models were available (quantal quadratic and quantal linear, probit, Weibull, Gamma, log-logistic) BMD's were calculated using the multistage model. As discussed above, the multistage model was used because it is the default model used by EPA for cancer bioassay data; although, in the future there will be a specific algorithm for modelling such cancer data. A multistage (polynomial) model with some constraints is used.
The model offers several algorithms for dichotomous data.
Risk type: extra risk.
As 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.

Model
US-EPA Benchmark dose model Version 1.3.2 2003
(http://www.epa.gov/nceawww1/software.htm)
For description of the algorithms see Help manual

The model offers several algorithms for dichotomous data.
Risk type: extra risk.
As 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. A calculation at the BMD05 level could not be done as it did not result in a difference between expected and observed tumour incidences again indicating the borderline nature of the results.

Calculation of systemic dose
The internal dose levels as mg/kg per week were calculated using the specific percent total absorption values of the in vitro skin permeation study in mice at the concentration levels applied to the animal. As the study was performed using twice weekly exposure the weekly dose is two times the single applied dose:

Assuming that the oral exposure did not significantly contribute to the systemic dose, the skin absorption study results are taken to calculate the systemic dose of the skin painting study. As the amount absorbed varies with the concentration of the applied solution two different absorption percentages are used.

High dose group:
External dose: 5750 mg/kg/week.
Concentration applied: 59%, amount applied: 138 mg per animal twice per week, average bw. 48 g.
Total percent absorption for the 65 % solution (result from the in vitro skin absorption study): 13 %.
Calculated dose with 13% absorption: Application of 5750 mg/kg bw per week with 13 % absorption would correspond to 748 mg/kg per week or 107 mg/kg per day (calculated for 7 days).

Low dose group:
External dose 575 mg/kg bw per week.
Concentration applied: 5.9 % or 13.8 mg/animal twice per week, average bw 48 g
Total percent absorption (from the in vitro skin absorption study, 1% solution): 29.2 %

BMDs were calculated for the total tumour incidences combined for males and females only, as they seemed to show the most important dose response.
The BMD0.1 and the 95% lower confidence limits are summarised in table 2.
BMD 0.1 is the EPA default value.
According to the EPA guidance document the appropriate model should be selected using the following criteria:

- Chi-square values should be > 0.1.
- Results of fitting the models, sorted in order of increasing 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].

- The standardised residuals [*i.e.*, (observed value - expected value)/standard error] should be small.

For each calculation the goodness of fit criteria are tabulated separately.

BMDs were calculated for the total tumour incidences combined for males and females only, as they seemed to show the most important dose response.
The BMD0.1 and the 95% lower confidence limits are summarised in table 2.
BMD 0.1 is the EPA default value.
According to the EPA guidance document the appropriate model should be selected using the following criteria:

- Chi-square values should be > 0.1.
- Results of fitting the models, sorted in order of increasing 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].
- The standardised residuals [*i.e.*, (observed value - expected value)/standard error] should be small.

For each calculation the goodness of fit criteria are tabulated separately.

Table 1, model input data

Dose mg/kg bw/week	Number of animals	Animals with benign tumours m+f	Animals with malignant tumours m+f	Animals with benign or malignant tumours, m+f
0	100	10	16	26
168	100	16	19	35
748	100	19	26	45

Results:

The results of the calculations for malignant tumour incidence, benign tumour incidence and combined tumour incidence are summarised in the tables below and the graphic outputs of the curve fits are included. The detailed model outputs can be found in the appendices.

Table 2.1 BMDs
Malignant tumour incidence

Model	Quantal quadratic	Probit	Weibull	Gamma	log-logistic	multistage	quantal linear
BMD0.1	720.6	656.2	599	600.6	660.1	574	629.4
BMDL95	499.7	383.4	Not possible to calculate, lower limit included 0	Not possible to calculate, lower limit included 0	394.8	112.6	312.3

Table 2.1.1
Goodness of fit:

Model	**Chi²**	**P-value**	**AIC[1]**	**Residuals[2]**
Quantal quadratic	0.22	0.64	304.0	-0.32 to 0.34
Probit	0.04	0.84	303.8	-0.12 to 0.15
Weibull	0.00	NA	305.8	$-5.5x10^{-5}$to $6x10^{-5}$
Gamma	0.00	N.A.	305.8	$-1.7x10^{-5}$ to 0.0003
Log-logistic	0.04	0.83	303.8	-0.13 to 0.16
Multistage	0	Undefined	305.8	0
Quantal linear	**0.02**	**0.89**	**303.8**	**-0.07 to 0.1**

[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]
[3] chi² residuals

The only model that was able to calculate the incidence satisfying the criterion of chi2 > 0.1 was the quantal quadratic model. With that model a BMD01 of 720 mg/kg bw per week and a BMDL95 of 499.7 mg/kg bw per week was obtained. For 5 days of exposure this would result in a BMD01 value of 144 mg/kg bw/day and a BMDL95 of 100 mg/kg bw per day and for 7 days of exposure a BMD01 of 103 mg/kg per day and a BMDL95 of 71.4 mg/kg bw per day.

Table 2.2 BMDS
Benign tumour incidence males and females

Model	Quantal quadratic	Probit	Weibull	Gamma	log-logistic	Multistage1	quantal linear
BMD0.1	872.8	842.1	748	747	845.1	302.8	812.3
BMDL95	572	471.5	Not possible to calculate, lower limit included 0	Not possible to calculate, lower limit included 0	485.8	98.2	380.9

[1] fitted curve not monotone with regard to dose response. BMDL out of three times range

Table 2.2.1
Goodness of fit:

Model	Chi2	P-value	AIC1	Residuals2
Quantal quadratic	1.43	0.23	255.6	-0.82 to 0.87
Probit	0.94	0.33	255.1	-0.58 to 0.75
Weibull	0	NA	256.2	0.18
Gamma	0	NA	256.2	-6.9x10-5 to 0.00016
Log-logistic	0.96	0.33	255.1	-0.61 to 0.75
Multistage	0	0	256.2	0
Quantal linear	0.82	0.37	255.0	-0.51 to 0.71

[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]
[3] chi² residuals

The Gamma-, Weibull- and Multistage models could not calculate a BMDL and are therefore omitted. All other models have acceptable Chi-squares and the AICs are also comparable. The residuals are lowest with the quantal linear model which is therefore taken forward as preferred. For comparability with the malignant tumours also the quantal quadratic model could be used. Again the highest dose is still within the background data and the calculated BMD is above the highest dose applied.

The $BMD_{0.1}$ for benign lung tumours would be 812.3 mg/kg bw per week with the quantal linear and 872.8 mg/kg per week using the quantal quadratic model the $BMDL_{95}$ would be

380.9 and 572 mg/kg week respectively. For a 5-day per week exposure the corresponding daily doses for the BMD_{01} would be 162.5 (174.6) mg/kg/d and for the $BMDL_{95}$ 76.2 (114.4) mg/kg/day respectively and for a 7 day per week exposure the BMD_{01} would be 116 (124.7) mg/kg/day and the $BMDL_{95}$ 54.4 (81.7) mg/kg/day.

Table 2.3 BMDS
Combined tumour incidence males and females, benign and malignant tumours

Model	Quantal quadratic	Probit	Weibull	Gamma	log-logistic	multistage	quantal linear
BMD0.1	487.2	323.38	No, all expected tumor rates = observed rates	273.7	242.9	273.7	273.7
BMDL95	369.5	219.5	no	164.1	132.2	164.1	164.1

Table 2.3.1
Goodness of fit:

Model	Chi2	P-value	AIC1	Residuals2
Quantal quadratic	1.57	0.21	387.3	-0.85 to 0.92
Probit	0.71	0.4	386.4	-0.52 to 0.65
Weibull	-	-	-	-
Gamma	0.52	0.47	386.2	-0.4 to 0.57
Log-logistic	0.40	0.53	386.1	-0.32 to 0.51
Multistage	0.52	0.47	386.2	-0.09 to 1.233
Quantal linear	0.52	0.47	386.2	-0.4 to 0.57

[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]
[3] chi^2 residuals

5 models give approximately the same AIC and 3 of them give the same BMD and BMDL. The multistage model has the least residuals and is therefore chosen. The log logistic model gives slightly lower values for the BMD and also has a lower span of residuals then some of the other models except the multistage model. It could therefore also be considered for precautionary reasons. The Weibull model was not able to calculate a BMD as the observed tumour incidences matched the expected at all dose levels.

Using the multistage model the $BMD_{0.1}$ would be 273.7 mg/kg per week and the BMDL 164.1 mg/kg per week. For a 5-day exposure per week this would result in a daily dose of 54.7 mg/kg/d and 32.8 mg/kg/d respectively and for 7 days per week of exposure in a daily dose of 39.1 mg/kg/d or 23.4 mg/kg/d.

Using the log-logistic model the $BMD_{0.1}$ is 242.9 and the BMDL 132.2 mg/kg per week. For a 5-day exposure per week this would result in a daily dose of 48.6 and 26.4 mg/kg/day respectively and for a 7 days per week exposure in a daily dose of 34.7 and 19 mg/kg/day.

Summary

The daily benchmark internal doses for 10% increase of tumour incidence and their lower bound 95% confidence limits that can be derived for malignant, benign and malignant and benign tumours are summarised in table 3 for 5 and 7 days of exposure.

Table 3

	Malignant lung tumours	Benign lung tumours	Malignant and benign

			lung tumours
BMD0.1 (5d) mg/kg bw	144	163 (175)	55
BMDL (5d) mg/kg bw	100	76 (114)	33
BMD0.1 (7d) mg/kg bw	103	116 (125)	49
BMDL (7d) mg/kg bw	71.4	54 (82)	23

The calculations show that in the high dose group the incidence of benign tumours is lower than the calculated benchmark dose and that of malignant tumours is close to the BMD estimate. The combined tumour incidence gives the most reliable dose response and the lowest benchmark dose estimates.

The BMD obtained for the combined tumour incidence, 55 mg/kg per day for workers and 49 mg/kg per day for consumers should be used as the dose for the MOS estimation for carcinogenicity.

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The report provides the comprehensive risk assessment of the substance (3-Chloro-2-hydroxypropyl)trimethylammonium chloride (CHPTAC) 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 four 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 for all use scenarios as a consequence of exposure to EPTAC due to the intentional conversion of CHPTAC to EPTAC during use. For consumers, for humans exposed via the environment 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.