TRIS (2-CHLOROETHYL) PHOSPHATE, TCEP

CAS No: 115-96-8

EINECS No: 204-118-5

SUMMARY RISK ASSESSMENT REPORT

Final report 26.05 2008

Germany

FINAL APPROVED VERSION

Rapporteur for the risk assessment of TCEP is Germany.

Contact point:

Bundesanstalt für Arbeitsschutz und Arbeitsmedizin (BAuA)
Chemikalien, Anmeldung und Zulassung
Federal Institute for Occupational Safety and Health
Division Chemicals, Notification and Authorisation
Friedrich-Henkel-Weg 1-25
44149 Dortmund

fax: +49-(0)231-9071-2679
e-mail: chemg@baua.bund.de

Date of Last Literature Search:	**[insert year]**
Review of report by MS Technical Experts finalised:	**[insert month and year]**
Final report:	**[insert year]**

PREFACE

This report provides a summary, with conclusions, of the risk assessment report of the substance TCEP that has been prepared by Germany in the context of Council Regulation (EEC) No. 793/93 on the evaluation and control of existing substances.

For detailed information on the risk assessment principles and procedures followed, the underlying data and the literature references the reader is referred to the comprehensive Final Risk Assessment Report (Final RAR) that can be obtained from the European Chemicals Bureau[1]. The Final RAR should be used for citation purposes rather than this present Summary Report.

[1] European Chemicals Bureau – Existing Chemicals – http://ecb.jrc.it

CONTENTS

1 GENERAL SUBSTANCE INFORMATION 3

1.1 IDENTIFICATION OF THE SUBSTANCE 3

1.2 PURITY/IMPURITIES, ADDITIVES 4

1.3 PHYSICO-CHEMICAL PROPERTIES 4

1.4 CLASSIFICATION 5

2 GENERAL INFORMATION ON EXPOSURE 6

3 ENVIRONMENT 8

3.1 ENVIRONMENTAL EXPOSURE 8

3.2 EFFECTS ASSESSMENT 9

3.3 RISK CHARACTERISATION 10

4 HUMAN HEALTH 12

4.1 HUMAN HEALTH (TOXICITY0 12
4.1.1 Exposure assessment 12
4.1.2 Effects assessment 15
4.1.3 Risk characterisation 18

5 RESULTS 32

5.1 ENVIRONMENT 32

5.2 HUMAN HEALTH 32
5.2.1 Human health (toxicity) 32

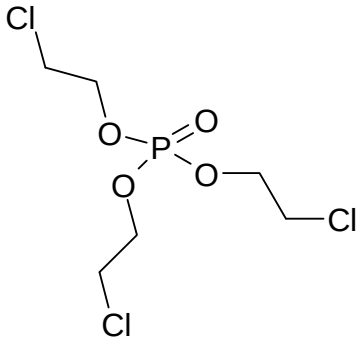
TABLES

Table 1.1 Summary of physico-chemical properties 4
Table 2.1 Main, industrial and use category of TCEP 6
Table 3.1Summary of PECS for TCEP 9
Table 3.2Risk characterisation for aquatic compartment 10
* for information only, since no production of TCEP in EU anymore 10

1 GENERAL SUBSTANCE INFORMATION

1.1 IDENTIFICATION OF THE SUBSTANCE

CAS Number: 115-96-8
EINECS Number: 204-118-5
IUPAC Name: Tris(2-chloroethyl) phosphate



Synonyms: Tris(2-chlorethyl)phosphat
Ethanol, 2-chloro-, phosphate (3:1)
Tris(β-chloroethyl) phosphate
Tris(chloroethyl) phosphate
Tris(2-chloroethyl) orthophosphate
Tri(2-chloroethyl) phosphate
Tri(β-chloroethyl) phosphate
Tris(.beta.-2-chloroethyl) phosphate

Molecular weight: 285.49 g/mol
Molecular formula: $C_6H_{12}Cl_3O_4P$
Structural formula:

1.2 PURITY/IMPURITIES, ADDITIVES

Purity: 99.5 %
Impurities: water

1.3 PHYSICO-CHEMICAL PROPERTIES

Table 1.1 Summary of physico-chemical properties

Property	Value
Physical state	liquid at 20 °C
Melting point	< -70 °C
Boiling point	decomposition at 320 °C at 1013 hPa
Relative density	1.4193 g/cm^{3}at 25 °C
Vapour pressure	43 Pa at 136.9 °C 0.00114 Pa at 20 °C (extrapolated)
Water solubility	7820 mg/l at 20 °C
Partition coefficient n-octanol/water (log value)	1.78
Granulometry	
Conversion factors	
Flash point	200 °C at 1013 hPa
Autoflammability	480 °C
Flammability	not extremely flammable not highly flammable not flammable
Explosive properties	not explosive (structural reasons)
Oxidizing properties	not oxidizing (structural reasons)
Viscosity	
Henry's constant	4.155 x 10^{-5} Pa m^{-3} mol^{-1}
Surface tension	

1.4 CLASSIFICATION

Classification
According to Commission Directive 98/98/EC ([1]) of 15 December 1998, adapting to technical progress for the 25th time Council Directive 67/548/EEC, TCEP is currently classified as:

Carcinogenic, Cat. 3	R 40	Limited evidence of a carcinogenic effect.
Harmful	R 22	Harmful if swallowed.
Dangerous for the Environment	R 51/53	Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

LABELLING: XN N R 22-40-51/53

At the meeting November 2005 the EU Classification and Labelling Working Group (Human Health) agreed finally upon the following classification for TCEP:

Reprotoxic, Cat. 2	R 60	May impair fertility.
Carcinogenic, Cat. 3	R 40	Limited evidence of a carcinogenic effect.
Harmful	R 22	Harmful if swallowed. Dangerous for the
Environment	R 51/53	Toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment.

Labelling: T N R 60-22-40-51/53

2 GENERAL INFORMATION ON EXPOSURE

The risk assessment is performed using import data from 2002. All life cycles are calculated using generic scenarios since no formulator and processor is known to the rapporteur.

Production

There is no production in Europe at present (2001/2002).

There are 3 companies importing a total of 1150 t TCEP in the EU (partly from Russia and Poland[2]). All of these importers are exclusively traders of TCEP. No specific information on formulation or processing could be obtained. However, the importing companies provided information on fields of application of their sales. These data are used in the calculation of the environmental exposure.

A tonnage of 143 t was exported outside the EU in 2002. The total EU tonnage present can be estimated to be **1007 t/a**.

TCEP is also formed as a reaction by-product in the manufacture of other commercial flame retardants in which TCEP has been declared an impurity. These flame retardants are currently undergoing ESR risk assessment (4^{th} priority list, Rapporteur: UK/IRL). This additional amount of TCEP is considered only in the calculation of the regional background concentration.

Uses

TCEP is used primarily as an additive plasticiser and viscosity regulator with flame-retarding properties for the production of unsaturated polyester resins (~ 80 %). Other fields of application are acrylic resins, adhesives and coatings.

The main industrial branches to use TCEP as a flame-retardant plasticiser are the furniture, the textile and the building industry (roof insulation); it is also used in the manufacture of cars, railways and aircrafts.

Other utilisation of TCEP is flame resistant paints and varnishes, e.g. for polyvinyl acetate or acetyl cellulose and the use as a secondary plasticiser for polyvinyl chloride to suppress the flammability resulting from plasticisers such as phthalates. It can be assumed that no TCEP is formulated into consumer paints.

Table 2.1 Main, industrial and use category of TCEP

Main category (MC)	Industrial category (IC)	Use category (UC)	Mass balance [in % of use]
Use resulting in inclusion into or onto a matrix (II)	Polymers industry (11)	Flame retardants and fire preventing agents (22)	94
Use resulting in inclusion into or onto a matrix (II)	Paints and varnishes industry (14)	Flame retardants and fire preventing agents (22)	1

[2] In the context of this Risk Assessment, Russia and Poland are considered as being outside the EU.

Main category (MC)	Industrial category (IC)	Use category (UC)	Mass balance [in % of use]
Non dispersive use (I)	Chemical industry (3)	Intermediate (33)	5

3 ENVIRONMENT

3.1 ENVIRONMENTAL EXPOSURE

Environmental releases

On the local scale releases of TCEP are expected during the industrial use of the polymer components as well as the formulation and industrial use (processing) of paints and varnishes. The less relevant use of TCEP as an intermediate should be considered additionally. Although there is no production in Europe a generic scenario for production is performed. The flame retardant TCEP is physically combined with the polymer matrix. Therefore, TCEP could migrate to the surface. Releases might be expected during service life and disposal of products containing TCEP.

Environmental fate

TCEP is considered as non biodegradable. TCEP is not expected to hydrolyse under environmental conditions. Direct photolysis in water does not play an important role either. An estimation of the half life for the atmospheric reaction of TCEP with hydroxyl radicals with the programme AOP 1.65 results in a half-life of 17.5 h (24-h day, $5x10^5$ OH/cm^3).

With a Henry's law constant of 4.155 x 10^{-5} Pa·m^3·mol^{-1}, TCEP has a low volatility.

There are no experimental results on the adsorption of TECP to soil available. A K_{OC} of 110.2 l/kg was calculated using a log K_{ow} of 1.78. The adsorption of TCEP is classified as being 'low'. TCEP does not meet the PBT criteria.

According to Mackay model (level 1) the hydrosphere is the target compartment of TCEP (94.8 %), followed by terrestrial compartment (5.06 %).

The log K_{OW} of 1.78 indicates a low bioaccumulation potential. The highest measured BCF in fish are <1.2-5.1.

Based on the physical chemical properties as well as the biodegradation rate of 0 h^{-1} in the WWTP, it can be estimated that 98.6 % of TCEP remain in the water and 1.4 % is adsorbed to sludge.

Environmental concentrations

Local and regional concentrations are estimated according to the methods of the TGD, and these are summarised in Table 3.1. The formulation of paints and varnishes is considered to represent a realistic worst case for the terrestrial assessment.

The regional concentrations are calculated by using estimated releases originating from processing/industrial use of TCEP as well as service life of polymers containing TCEP, disposal of the products and V6 production and use.

Table 3.1 Summary of PECS for TCEP

Area of use	PECwater (µg/l)	PECair (ng/m³)	PECsoil (µg/kg$_{wwt}$)
Production and processing*	28.9	0.0	
Processing only	4.20	0.0	
Processing of polymers	6.25	35.0	
Formulation of paints and varnishes	16.52	5.0	39.05
Processing of paints and varnishes (industrial use)	37.1	0.0	
Regional	0.087	2.27x10^{-4}	0.049

* for information only, since no production of TCEP in EU anymore

3.2 EFFECTS ASSESSMENT

Aquatic compartment (incl. sediment)

Results from acute toxicity tests with species from 3 trophic levels are available. The most sensitive organisms are algae (*Scenedesmus subspicatus*). However, there is a wide variation in the effect values from growth inhibition tests with algae (more than two orders of magnitude difference). As the available studies are all regarded as valid and no reason for the conflicting results can be given, the lowest effect value from these growth rate tests with algae is used for derivation of PNECaqua (48h-ErC$_{10}$ of 0.65 mg/l).

There are long-term tests with species from two trophic levels available (algae and invertebrates). Based on the acute toxicity tests it can be expected that algae are the most sensitive species and a long-term test on fish would not result in effect values below that of algae. Therefore, a PNECaqua = 65 µg/l is derived applying an assessment factor of 10.

A PNECwwtp of 32 mg/l is calculated by applying an assessment factor of 100 on the EC$_{50}$ from the OECD 209 respiration inhibition test (3.2 g/l) for the effects assessment of microorganisms in sewage treatment plants.

As there is a lack of tests on sediment-dwelling organisms the equilibrium partitioning method is used to calculate the PNECsediment of 0.2 mg/kg$_{ww}$.

Terrestrial compartment

There are reports on effects of TCEP on various species inhabiting the terrestrial compartment available (higher plants, invertebrates, microorganisms, birds). However, the information is partly of indicative value only.

Long-term tests are available for springtails and microorganisms showing similar sensitivity for 28d exposure. Since the information on springtail (*Folsomia*) covers a broader spectrum of effects, the reported lowest effect value for this species is used for derivation of PNECsoil (28d-LC_{10}=19.3 mg/kg_{dw}). Applying an assessment factor of 50, a PNECsoil of 0.341 mg/kg_{ww} can be derived.

Atmosphere

No ecotoxicological data are available for this environmental compartment.

Secondary poisoning

Since TCEP does not possess a bioaccumulation potential, the derivation of PNECoral is not necessary.

3.3 RISK CHARACTERISATION

Aquatic compartment (incl. sediment)

The aqueous PEC/PNEC ratios for all areas of production, formulation and processing are summarised in the following table.

Table 3.2 Risk characterisation for aquatic compartment

Area of use	PECwater/PNECwater
Production and processing*	0.44
Processing only	0.06
Processing of polymers	0.10
Formulation of paints and varnishes	0.25
Processing of paints and varnishes (industrial use)	0.57

* for information only, since no production of TCEP in EU anymore

The PEC/PNEC ratios for surface water are below 1 for all production and/or processing sites. **Conclusion (ii)**

The highest PEC/PNEC ratio for sediment is the same as for water as both the PEC and the PNEC are calculated from the respective water values. Hence no risk for sediment dwelling organisms can be detected. **Conclusion (ii)**

Applying the PNECmicroorganisms of 32 mg/l, the highest ratio of $Clocal_{effl}$/PNECmicroorganisms is 0.01 (industrial use of paints and varnishes). **Conclusion (ii)**

Terrestrial compartment

The comparison of the highest PECsoil of 0.039 mg/kg_{ww} with the $PNEC_{soil}$ of 0.341 mg/kg_{ww} indicates no risk for the terrestrial compartment. **Conclusion (ii)**

Atmosphere

Due to the atmospheric half-life ($t_{1/2}$ = 17.5 h), abiotic effects on the atmosphere, such as global warming and ozone depletion, are not to be expected in connection with TCEP. The highest calculated air concentration is around 0.035 $\mu g/m^3$ for processing of polymers. Since no data are available on the ecotoxicological effect of the substance in connection with this environmental compartment, it is not possible to perform a quantitative assessment of this environmental compartment. On the basis of the available information on the substance, further testing seems not necessary. **Conclusion (ii)**

Secondary poisoning

Since there is no indication of bioaccumulation of TCEP, a risk characterisation for exposure via the food chain is not necessary.

PBT assessment

TCEP has to be considered as non biodegradable (DT_{50}: ∞ days). An investigation on primary degradation of TCEP in soil showed a half life of 167 days.

The highest measured BCF in fish are <1.2 – 5.1.

The lowest long-term effect value of 0.65 mg/l was found for *Scenedesmus subspicatus*.

TCEP has been proposed to be classified as Carcinogenic (Cat. 2). There is evidence of chronic toxicity (T, R45).

It can be concluded that TCEP meets the **P/vP**- and the **T**-criteria. The **B**-criteria is not fulfilled. Overall TCEP does not meet the PBT criteria.

4 HUMAN HEALTH

4.1 HUMAN HEALTH (TOXICITY0

4.1.1 Exposure assessment

Occupational exposure

In the EU, the production and import of TCEP has declined in the past years. In the year 2001, there is no production within the EU, but marketing of TCEP-containing products is still relevant (app.1000 t of TCEP in 2002). The substance is currently produced in Poland.

TCEP is used as a plasticizer with flame-retarding properties in polyurethane, polyester, polyvinyl chloride and other polymers as well as in formulations like paints, lacquers, glues, adhesives and flame-retardant coatings for textiles. The main use of TCEP is the production of unsaturated polyester resins. According to information from the producers the use of TCEP in polyurethane foams has declined to a large extent and is currently limited to special products. Industry informed that less than 10 t/year TCEP are applied in paints.

Due to information from two producers the concentration of TCEP in products amounts to 5 - 12 % (w/w). In addition in one product (cellulose acetate) a concentration of up to 70 % TCEP is possible. The concentration of TCEP in end products is assumed to be ≤ 25 %.

Detailed information on the production volumes and the use is given in chapter 2.

Occupational Exposure Limits are not established in the EU (2008).

Relevant occupational exposure scenarios are to be expected in the following areas:

- Production of TCEP (scenario 1)
- Use of TCEP for the production of polymers and formulations (scenario 2)
- Use of formulations and products containing TCEP (scenario 3)

The flame retardant TCEP is physically bound within the polymer matrix and, therefore, TCEP could migrate to the surface especially during processing steps performed at high temperatures. Therefore release of TCEP from plastic products may be a potential way of exposure. In this, it should be considered, that not only plastic products produced in Europe but also products imported are concerned. The very low vapour pressure at room temperature and the high molecular weight lead to negligible migration. In conclusion, exposure to TCEP during subsequent use of flame retarded equipment is likely to be negligible.

Since no information on exposure levels are available, the assessment of inhalation and dermal exposure is based on EASE model estimates (Estimation and Assessment of Substance Exposure).

Industrial activities using TCEP present opportunities for exposure. Due to the low vapour pressure of the substance (< 1 Pa at 20°C) relevant inhalation exposure is likely to occur only if the plastics are handled at elevated temperatures or if dusts containing TCEP are formed.

Industry described, that the substance is neither handled at elevated temperatures nor is used in a powdery state.

TCEP is a component of different formulations like paints, lacquers, glues and adhesives. For the formulation processes, exposure relevant activities are filling, charging, cleaning, sampling, repair and maintenance activities as well as possibly mixing (scenario 2).

Exposure is to be expected when using paints, lacquers, glues, adhesives and flame-retardant coatings (scenario 3). The formulations are used in different industrial and skilled-trade areas. During spray application of paints, adhesives and other formulations the formation of droplet aerosols is possible (scenario 3a). Scenario 3b represents exposure for activities without the formation of aerosols. If foams containing TCEP are mechanically or thermally treated (e.g. cutting using hot wires) exposure is assumed to be below the level predicted for spray applications.

Dermal exposure is assessed for the unprotected worker in application of the EASE model or by taking analogous data into account.

There is no information concerning the exposure during recycling of plastic waste. Generally, the recycling of halogenated flame retardants is problematic, because of the possible release of halogenated compounds into the environment. There are two possibilities in the work up of plastic waste: thermal and shredding. It is supposed that mixtures of different plastics are recycled together.

Table 4.1: Summary of exposure data

Exposure scenario	Duration and frequency of activities relevant for exposure	Inhalation exposure Shift average [mg/m^3]	Dermal exposure Shift average [mg/p/day]
1) Production of TCEP	8 hour, daily	1.2 [1)] (EASE)	420 [2)] (EASE, without gloves)
2) Production of polymers and formulations	8 hour, daily (assumed)	1.2 [1)] (EASE)	420 [2)] (EASE, without gloves)
3) Use of formulations and products containing 25 % TCEP			
a) spray application	8 hour, daily (assumed)	8.3 (analogous data)	< 2500 (analogous data)
b) without formation of aerosols		1.2 [1)] (EASE)	210 [2)] (EASE, without gloves)

[1)] In general for vapour pressures below 1 Pa the result of the EASE estimate is 0 – 0.1 ppm, independent of the use pattern "closed system", "non-dispersive use", or "wide dispersive use", and workplaces with or without Local Exhaust Ventilation – LEV.

[2)] Producers and importers submitted information about the used glove material (rubber). But there is a lack of information with regard to the suitability of the recommended materials. Dermal exposure is assessed as worst case estimation applying the EASE model. It is not possible to consider the limited protection provided by unsuitable glove material.

Consumer exposure

It is shown, that TCEP will be released from a number of sources which have been treated with flame retardant, namely timber, foam rubber, carpets, plastic materials (e.g. electronic devices, TV, car interior etc.), glues, lacquers, and upholstery. The degree of migration from the materials is not known. TCEP is a non-volatile substance, which does not appear in its gaseous form under normal conditions. Therefore, it is released primarily by abrasion and

becomes part of the dust fraction. The latter is divided into two parts, house dust and airborne dust. Dust burden therefore reflects the sum of all the sources.

Oral exposure can occur via dust intake, hand-to-mouth behaviour, contamination of articles for daily use, e.g. toys, which can be put into the mouth. This pathway of exposure may play a particular role for children. Inhalation exposure takes place by inhaling airborne particles, and dermal exposure can occur from direct contact with articles, e.g. furniture coverings, as well as with house dust and airborne dust.

Absorption rates in this approach include desorption of TCEP from dust and the subsequent absorption in the GI-tract or in the lungs and were set to 100% as a worst case approach.

TCEP concentrations in house dust measured in appr. 1000 German households ranged between zero and 121 µg/kg. Further probabilistic exposure assessment using the @RISK 4.5 professional software tool and MS-EXCEL gave a log-logistic distribution function with a 95th percentile of 11.9 mg/kg and a median of 0.6 mg/kg. The range of airborne dust concentrations of TCEP as found to lie between zero and a maximum of 6000 ng/m³, which is in agreement with other authors. Further analysis of the data revealed a log-normal distribution with a 95th percentile of 134 ng/m³ and a median of 10 ng/m³.

The Danish EPA analysed the content of TCEP in a toy for babies (recommended for 0 months and above) which was a cube of 10 x 10 x 10 cm length and 100 g weight consisting of a PUR foam core covered with coloured textile. The PUR foam had a content of 3300 and 5200 mg TCEP/kg, whereas the textile covering the cube had a content of 160 mg TCEP/kg. A migration test in an aqueous medium showed that TCEP is easily dissolved and migrates into the solution.

Oral exposure

Oral exposure to TCEP is characterised by the uptake of house dust. The amount estimated for an adult accounts for 0.0033 µg/kg bw/day, representing the 99th percentile. For children age 1-3, representing a vulnerable population due to their specific hand-mouth-behaviour, the respective value is 0.2 µg/kg bw/d.

For babies a significant source of exposure could be sucking on toys. Under worst case assumptions values can be achieved up to 240 µg/kg bw per day (calculation by Danish EPA).

Inhalation exposure

From measurements of air concentrations of TCEP a value of 0.6 µg/m³ is taken as a 98th percentile. This value represents an extreme upper range of a large number of measurements and is regarded as a reasonable worst case estimate. The major part of the substance is bound to dust and the degree of desorption is unknown. A model estimate based on 100% absorption results in an uptake by inhalation (99th percentiles) of 0.4 µg/kg bw/d for adults and 0.96 µg/kg bw/d for children.

Dermal exposure

The worst case estimation of TCEP by exposure from migration from upholstery accounts for 3.9 µg/kg bw and day. Dermal exposure from airborne dust can be neglected due to the low concentrations of TCEP in dust (max. 0.1 µg/m³). Dermal exposure from house dust accounts for a maximum of 0.02 µg/kg bw per day (in children).

Dermal exposure to TCPE from different sources can be estimated to a total of about ~ 4 µg/kg bw per day. Dermal exposure of children (10 µg/kg bw/day) as related to bodyweight can exceed that in adults.

Total body burden

For female adults, a body burden would account for ~ 4.5 µg/kg bw/day, under reasonable worst case conditions, and taking all paths into consideration. The respective value for 1 - 3 year-old children is then 11 µg/kg bw/day. However, for babies of about 3 months a body burden would account up to 240 µg/kg bw per day by sucking on toys, the other paths can be neglected.

Humans exposed via the environment

For the indirect exposure to humans via the environment on the local scale, the default scenario for the formulation of paints is used, representing the local worst case. The resulting total daily dose (local) is calculated as 5.84 µg/kg bw/d.

For the average intake due to the regional background concentration a total dose (regional) of 0.01 µg/kg bw/d is calculated.

For both the local and the regional approach, the main route of exposure is via the stem of plants, followed by drinking water.

4.1.2 Effects assessment

Toxicokinetics, metabolism and distribution

Data on human experience with tris(2-chloroethyl) phosphate (TCEP) are not available. TCEP is well absorbed (> 90% of the dose) and distributed in rats after oral administration. Higher concentrations were found in liver and kidney up to 24h after administration. An enterohepatic circulation is supposed to occur. Elimination from plasma and red blood cells occurred biphasic with a half-life of 3 and 3.4 hours in the beginning and 1.8 and 10.8 days in the second phase. Metabolism and elimination are the same after single and repeated application. Metabolites in urine were identical in rats and mice. Main metabolites were bis(2-chloroethyl) carboxymethylphosphate, bis(2-chloroethyl)hydrogen phosphate and bis(2-chloroethyl)-2-hydroxyethyl-phosphate glucuronide. Data are not available for inhalation and dermal exposure. For risk characterisation purposes, the rates of oral, dermal, and inhalation absorption are assumed to be 100%.

Acute toxicity

TCEP demonstrated moderate toxicity after oral application (LD50 for rats in the range of 430-1230 mg/kg bw). In an experiment with rabbits, the substance has demonstrated low acute dermal toxicity (LD50 > 2150 mg/kg bw)**.** In experiments with rats low acute inhalation toxicity was detected since rats survived by 8-hours exposure to saturated substance aerosols or by 1-hour exposure to a nominal concentration of 25.7 mg/L. Information on human experience with TCEP is not available. The substance is to be classified as "harmful" according to EEC classification guidelines, labeling with "R 22, Harmful if swallowed" is appropriate.

Irritation and corrosivity

Draize tests with rabbits revealed weak irritation of the skin and mild irritation of the conjunctivae. TCEP is not considered to be a skin and eye irritant. From the data presented in the preceding text it is evident that TCEP is not a corrosive substance.

Sensitisation

Human data on skin sensitisation potential of the substance are not available. An animal study (Buehler Test) showed no skin sensitising potential of TCEP. Sensitisation data of the two other chloroalkyl phosphates TCPP and TDCP which are structurally related to TCEP indicate that these substances do not possess significant skin sensitisation potential. Taking into consideration all information on the three chloroalkyl phosphates TCEP, TCPP and TDCP including alkylating properties of these substances it is concluded that TCEP should be non-sensitising to humans upon dermal contact. No information is available on the respiratory sensitisation potential of TCEP and the two other chloroalkyl phosphates.

Repeated dose toxicity

The most reliable repeated dose toxicity studies used the oral route (gavage and feeding) of exposure to TCEP. Results of these studies give the indication that brain and kidney are the main target organs of toxicity, although there is a species and sex-related variability. There is also clear evidence that mice were less sensitive to the effects of TCEP than rats. Several experimental investigations are long-term/long-life studies designed for examination of carcinogenicity.

All listed studies were of sufficient data quality. Degenerative lesions in the brain occurred in rats in a dose related pattern, and in addition, in a clear time-response relationship in frequency, intensity and severity. Male rats were less sensitive to adverse brain effects than female rats. The lowest NOAELs for systemic effects/brain effects were derived in each case from subchronic and chronic oral toxicity studies for rats at dose levels between 44 to 88/175 mg/kg bw/d. Mice were less sensitive to TCEP than rats with respect to brain effects. NOAELs for brain effects were established between 175 to 350 mg/kg bw/d in mice of both sexes.
However, the most sensitive NOAEL/LOAEL was derived for kidney lesions. Kidney effects appear to be the most sensitive endpoint for repeated exposure of TCEP and both the rat and the mouse are the most sensitive species to TCEP. Kidney effects observed in rats and mice were dose- and time-related with respect to incidence and severity. Changes in kidney morphology were noted in Sprague-Dawley CD rats and F344/N rats and in B6C3F1 and Scl:ddY mice. There were hyperplasia, and karyomegaly in the cortical tubule epithelium in the kidneys combined with signs of cellular necrosis. In both rat strains and both mouse strains kidney lesions of this same kind were observed. Only in subchronic toxicity studies a NOAEL for kidney lesions was estimated; for male and female Sprague-Dawley CD rats at 3000 ppm (m: 192 mg/kg bw/d; f: 215 mg/kg bw/d) and for B6C3F1 mice at 350 mg/kg bw/d However, a NOAEL for tissue changes in the kidney could not be derived for male and female F344/N rats after chronic exposure to ≥44 mg/kg bw/d TCEP, furthermore, for B6C3F1 mice after long-life exposure to ≥175 mg/kg bw/d and also not for Scl:ddY mice after feeding of ≥12 mg/kg bw/d in the diet for 18 months. This carcinogenicity study in Scl:ddY mice (cf. 4.1.2.8.1) differs in some respects from the published guidelines, however,

the study is accepted due to the fact that the test procedure described is comparable to the guideline study with acceptable restrictions and is performed in accordance with generally accepted scientific standard. Therefore, the lowest LOAEL of 12 mg/kg bw/d for kidney lesions in Scl:ddY mice will be chosen as the basis for risk characterisation.

No data on dermal and inhalative uptake after repeated exposure to TCEP are available.

Mutagenicity

In general, bacterial gene mutation tests were negative. In vitro genotoxicity tests with mammalian cells were negative for gene and chromosome mutations, in a mouse-lymphoma-assay and in a UDS-test. Very weak effects in in vitro SCE tests are considered to be without relevance for mutagenicity. Two in vivo mice micronucleus tests were negative for application up to maximum tolerated doses, while a positive result of questionable validity was observed in another test. Also a Drosophila test was negative. Overall, it can be concluded that there is no relevant evidence for mutagenicity of TCEP.

Carcinogenicity

TCEP is carcinogenic in both sexes of rats and mice. It causes the formation of predominantly benign tumours in the kidney, but also benign and malignant tumours at various sites in experimental animals. It induces kidney tumours in F344/N rats at doses ≥44 mg/kg bw/d, in male B6C3F1 mice at 350 mg/kg bw/d; and in male Scl:ddY mice at diet concentrations of 300 mg/kg bw/d and above. In addition, dose-related increased incidences of hyperplasia and hypertrophy of the urinary tubule epithelium together with karyomegaly were also observed in these animals. Such findings were noted in male and female F344/N rats at doses ≥44 mg/kg bw/d, in both male and female B6C3F1 mice given ≥175 mg/kg bw/d, and in male Scl:ddY mice fed at ≥12 mg/kg bw/d tris(2-chloroethyl) phosphate. The value of 12 mg/kg bw/d is considered as LOAEL for tumour formation. In addition, TCEP induces tumours in the liver of male Scl:ddY mice at 300 mg/kg bw/d and above, and in the Harderian gland of female B6C3F1 mice at ≥175 mg/kg bw/d. Since there is no evidence of a direct genotoxic mode of action, it was assumed that carcinogenicity would be mediated by non-genotoxic (epigenetic) mechanisms. Human data on carcinogenicity are not available.

Toxicity for reproduction

TCEP treatment resulted in significant impairment of reproductive capacity and fertility during continuous breeding and for two successive generations in mice of both sexes (dose levels of 175, 300, and 700 mg/kg bw/d). The reproductive system of male mice appeared to be more sensitive to tris(2-chloroethyl) phosphate treatment than that of females. An oral NOAEL/fertility of 175 mg/kg bw/d was derived from these studies. A firm conclusion on developmental toxicity is hampered by poor reporting of rather old data as only a summary report and a reporting from a screening assay are available. However, it appears on the basis of the available data, that TCEP has no embryo-/fetotoxic or specific teratogenic properties even at maternally toxic doses. An oral NOAEL/developmental toxicity of 200 mg/kg bw/d was derived from studies with rats (NOAEL/maternal toxicity = 100 mg/kg bw/d). There are no human data on reproductive toxicity.

4.1.3 Risk characterisation

Workers

Introduction to occupational risk assessment

This occupational risk assessment is based upon the toxicological data of TCEP which have been described and discussed in section 4.1.2 and the occupational exposure scenarios summarized in section 4.1.1.

Quantitative human toxicity data are not available, therefore risk considerations and estimations have to be based on animal data which have to be extrapolated accordingly. For the majority of toxicological endpoints TCEP data originate from oral studies. Since workers are exposed either by inhalation or by skin contact, route to route transformation is essential for worker risk assessment. As a default assumption a complete absorption (100%) at all routes is assumed which is to some extent consistent with the physicochemical properties of the substance (MW < 500, solubility in water and organic solvents, Log_{pow} = 1.7).

In table 4.2 the route specific exposure values are listed and the internal body burdens of workers as result of repeated combined exposure via inhalation and dermal exposure are identified.

Table 4.2: Occupational exposure levels and internal body burden of workers

Exposure scenario		Inhalation shift average (mg/m^3)	Dermal contact shift average (mg/p/d)	Internal body burden of workers after repeated exposure (mg/p/d)		
				Inhalation(1)	Dermal(2)	Combined
1	Production	1.2	420	12	420	432
2	Production of polymers and formulations	1.2	420	12	420	432
3a	Use of formulations and products with spray application (25% TCEP)	8.3	2500	83	2500	2583
3b	Use of formulations and products without aerosol formation (25% TCEP)	1.2	210	12	210	222

(1) based on the assumption of 100% inhalative absorption; breathing volume of 10 m^3 per shift
(2) based on the assumption of 100% systemic availability of TCEP after dermal contact

MOS Approach

For toxicological endpoints with quantitative data available, MOS values are calculated as quotient of experimental NOAEL (or LOAEL) from animal studies and workplace exposure assessments. For TCEP, oral doses from experimental studies are converted to air concentrations or dermal exposure levels before calculation of scenario-specific MOS values. For this procedure the physiological default values from above are used to modify the dose unit of effects data. As result a so called "starting point" for risk assessment is identified.

MOS values for inhalation and dermal route are considered separately. The combined MOS value is calculated as quotient of the internal NAEL (or LAEL) and internal body burden of workers. Because 100 % absorption at all routes is assumed for TCEP (see above) the internal NAEL is supposed to be similar to the external NOAEL.

Risk assessment based on MOS values implies the identification of a minimal MOS as decision mark between conclusion ii and iii. To obtain this, assessment factors are identified for TCEP, which vary depending on data availability and the specific toxicological endpoint to be evaluated. Scientifically based adjustment factors describe the extrapolation of animal data to the worker population. The uncertainties in the specific calculations are weighed by expert judgement and expressed as an additional "uncertainty factor". The value of the minimal MOS results from the multiplicative combination of the different assessment factors. For carcinogenic risk assessment of TCEP, a modified MOS approach is used.

If the MOS value for a certain exposure scenario is below the minimal MOS for a specific endpoint, the corresponding risk situation is considered to be of concern. A MOS value higher than the minimal MOS indicates no concern.

Critical Exposure Levels

In a parallel procedure, which gives identical but more direct results, the toxicological starting point taken forward to risk characterisation may be divided by the endpoint-specific assessment factors. As result an exposure level is identified for TCEP which by direct comparison with the occupational exposure levels may serve as trigger for decisions. In the context of this risk assessment report it will be called "critical exposure level". Concern will be expressed for scenarios above this trigger value.

Acute Toxicity

Local effects	see irritation, no further information available
systemic effects	
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

Inhalation exposure

Acute toxicity data for humans are not available. As starting point for MOS calculation the air concentration of 25700 mg/m^3 is chosen which did not lead to severe acute effects in rats. Evaluation of the MOS values has to account for the following aspects: (a) study duration was 1 hour compared to occupational exposure of 8 hours, (b) physiological differences between humans at rest and workers account for a factor of 1.5, (c) the starting point for risk characterisation is some sort of an acute LOAEC which is transferred to an acute NOAEC

with a factor of 3, (d) human intraspecies variation is accounted for by a factor of 5, (e) a further uncertainty factor of 2 is proposed because the LOAEL is based on a nominal (not measured) air concentration which gives indication that the risk situation might be more critical than estimated. Altogether the minimal MOS calculates to 360 (8/1 x 1.5 x 3 x 5 x 2). The critical exposure level is identified as 70 mg/m^3 (25700 mg/m^3 / 360). It is recognized that the quality of the acute inhalation study is rather limited. Nevertheless, this assessment of acute inhalation toxicity to some degree is consistent with the results of oral toxicity testing (see below in the chapter on acute toxicity by combined exposure).

The highest shift average value for inhalation is 8.3 mg/m^3 for spray application (scenario 3a). The according MOS value calculates to 3096 (25700 / 8.3), which, in comparison to the minimal MOS of 360, does not give reason for concern.

Dermal contact
In a limit test in rabbits with occlusive exposure for 24 hours a dose of 2150 mg/kg did not result in apparent signs of toxicity. As starting point for MOS calculation the human dose corresponding to the dermal NOAEL in rabbits is calculated to 150500 mg/person (2150 mg/kg x 70 kg).

Evaluation of the MOS value accounts for the following aspects: (a) metabolic rate scaling from rabbits to humans reveals a factor of about 2, (b) human intraspecies variation is accounted for by a factor of 5. This gives a minimal MOS of 10 (2 x 5). Based on the result of acute dermal toxicity testing the critical exposure level is identified as about 15000 mg/person (150500 mg/person / 10).

The highest dermal exposure level is reported to be up to 2500 mg/person for spray application (scenario 3a). The according MOS value calculates to 60 (150500 / 2500) which, in comparison to the minimal MOS of about 10, does not give reason for concern.

Combined exposure
Risk assessment for acute toxicity by combined exposure starts with oral toxicity studies keeping in mind, that the resulting calculation might be probably conservative. In a rat study a LD50 between 1000 and 1260 mg/kg was calculated. At 800 mg/kg clinical signs as pilo-erection and salivation are reported, but no mortality. In a developmental oral toxicity study by Kawashima et al. (1983) pregnant dams were orally exposed (by gavage) from day 7 to 15 of pregnancy. While 200 mg/kg/d led to mortality, no changes in maternal body weight gain, food consumption and general appearance resulted from oral application up to 100 mg/kg/d. For oral application, 100% absorption is assumed.

Based on this oral (internal) starting point of 100 mg/kg/d (7000 mg/p/d) the evaluation of scenario-specific MOS values accounts for: (a) metabolic rate scaling, reflected by a factor of 4, (b) human intraspecies variation, described by a factor of 5, and (c) a factor of 1/3 because the acute NOAEL is considered to be higher than the subacute NOAEL used as starting point. Altogether, the minimal MOS calculates to about 7 (4 x 5 x 1/3).

There is only one occupational scenario (spray application, scenario 3a) for which the scenario-specific MOS (of 3) is lower than the minimal MOS (of 7). Comparison of the results of acute toxicity for the various routes of application shows that acute oral toxicity is much more pronounced than acute dermal toxicity (see above). Recognizing that the internal exposure in scenario 3a is nearly totally governed by dermal contact, conclusion ii for scenario 3a for combined exposure is warranted. This decision is consistent with the decision

for scenario 3a for dermal contact alone which is based on an acute dermal toxicity study rather than on acute oral testing.

Irritation/Corrosivity

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

Skin, Eye

In studies with rabbits slight dermal erythema and weak irritation of the conjunctivae was observed for TCEP. The effects are not sufficient for classification. There is no concern from dermal or eye irritation at the workplace.

Acute respiratory irritation

No studies are available concerning the irritation potential of TCEP after inhalation. From irritation studies at skin or eyes comes no indication that the substance may cause serious effects at the site of initial contact. A risk relevant damage of the airways by acute irritation properties is therefore not anticipated. There is no reason for concern.

Sensitisation

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

Skin sensitisation

Human data on sensitizing properties of the substance are not available. In a skin sensitisation test (Buehler method) no allergic reactions were seen in Guinea pigs. Additionally the test results of two other structurally related chloroalkyl phosphate esters (guinea pig maximisation tests) gave no evidence to skin sensitising properties. Based on all information on the structurally related chloroalkyl phosphates (results of animal testing, similarity in physicochemical data and chemical structures, as well as alkylating properties of TCEP, TCPP and TDCP) it is concluded that TCEP should be non-sensitizing to humans. There is no reason for concern.

Respiratory sensitisation

No information is available on the respiratory sensitisation potential of TCEP. For the time being a valid study to investigate respiratory sensitisation in experimental animals cannot be recommended. Considering that the production of TCEP is performed in closed systems and that TCEP has a low vapour pressure one would expect that exposure of the respiratory tract is low. However, TCEP is not suspected to be a potent respiratory sensitiser in humans according to the fact that during all the years of use no notice of specific case reports has been given. There is no concern from respiratory sensitisation at the workplace.

Repeated dose toxicity

Local effects (RDT) by inhalation or dermal contact

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

In a rabbit study TCEP caused slight irritation (dermal, eye). There is no information on irritation potency following acute or repeated exposure, there are no experimental studies or reported experiences concerning respiratory tract irritation following acute or repeated exposure. Against that background, conclusion ii is reached. However, it should be mentioned, that on the available basis of acute irritation data no valid predictions can be made about the irritation potency following repeated exposure (Rennen et al. 2002).

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

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

Several studies with repeated application, mainly by the oral route, have been performed in mice and rats. Primary target organs turned out to be the kidneys, the brain and the liver. The LOAEL of 12 mg/kg bw/d for kidney lesions in mice is chosen as the basis for risk assessment. The according human dose calculates to 840 mg/person/day (12 mg/kg/d x 70 kg), the corresponding occupational air concentration for 8-hour inhalation is identified as 84 mg/m^3 (840 mg/person/day / 10 m^3/day).

Evaluation of the MOS values accounts for the following aspects: (a) a LOAEL-to-NAEL extrapolation factor of 3 is proposed, (b) for species extrapolation from mice to humans a factor of 7 used, (c) the human intraspecies variation accounts for a factor of 5, (d) experimental dosing was 7 days per week compared to occupational exposure of 5 days per week. Altogether the minimal MOS for systemic effects after repeated exposure calculates to 75 (3 x 7 x 5 x 5/7). The according critical exposure level is 10 mg/person/day (840 mg/person/day / 75) which is used for the assessment of dermal contact (external dose) and combined exposure (internal dose). The corresponding critical exposure level for inhalation is 1 mg/m^3 (84 mg/m^3 / 75).

Conclusion iii is reached for all occupational exposure scenarios for all routes of exposure. However, those occupational scenarios with inhalation exposure levels of 1.2 mg/m^3 are considered to be borderline situations. The most critical risk situation seems to be dermal exposure during spray application (scenario 3a). For dermal scenarios 1, 2, 3a and 3b, the scenario-specific MOS values for RDT are less than 1/10 of the minimal MOS.

Mutagenicity

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

In vitro and in vivo tests have been performed to investigate the genotoxic properties of TCEP. In summary there is no relevant evidence of mutagenicity of TCEP and therefore no reason for concern.

Carcinogenicity

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

Carcinogenicity studies by gavage are available in rats and mice. These studies provide clear evidence that TCEP is carcinogenic in experimental animals. In the rat, TCEP caused an increased incidence of renal tubule adenomas in males and females at 44 mg/kg/day and above. In addition, thyroid follicular cell neoplasms and mononuclear cell leukemia may have been related to TCEP administration. In a comparable study with mice, evidence for carcinogenicity was shown by a slightly increased incidence of tubule cell neoplasms obtained in supplemental evaluation of additional kidney sections. In a further experiment with mice a significant increase of kidney and liver tumours occurred at 300 mg/kg/day and above.

There is no evidence of a direct genotoxic mode of action. For carcinogenic risk assessment it is assumed that carcinogenicity is mediated by a non-genotoxic (epigenetic) mechanism. At present available data on TCEP do not allow for a scientifically-based identification of a threshold level for TCEP carcinogenicity. Basically, there is no valid information on the specific thresholded mode-of-action that results in secondary formation of tumours (see discussion in chapter 4.1.2). Recognizing the scientific difficulties of establishing a threshold level for the carcinogenicity of TCEP, for occupational risk assessment it is nevertheless considered adequate and justifiable to give risk managers some additional practical guidance on the carcinogenic potency of TCEP. It seems possible, that one of the adverse effects described in the TCEP reports on chronic toxicity might be responsible for the induction of tumour development. Thus, risk assessment for repeated dose toxicity might give some additional guidance. If any of the reported chronic effects of TCEP is responsible as starting point for TCEP tumour development, an increase of tumour incidence is not anticipated to occur up to the critical exposure levels for repeated dose toxicity. This approach implies that the LOAEL for kidney lesions in mice is used as starting point for carcinogenic risk assessment as well.

The MOS approach for repeated dose toxicity is proposed to be modified for carcinogenic risk assessment. The main reason is, that the degree of adversity of neoplasms is considered to be much more pronounced than the degree of adversity of non-neoplastic adverse effects. This consideration supports the introduction of an additional extrapolation factor for carcinogenicity in order to increase the level of protection.

On a practical basis, it is proposed to introduce an additional adjustment factor of 5. This gives a minimal MOS for carcinogenicity of 375 (75 x 5) and the critical exposure levels of 0.2 mg/m³ (inhalation) and 2 mg/p/d (dermal contact). This value might be justified, comparing this approach with the T25 concept from Dybing et al., (1977, see also the comprehensive RAR).

For carcinogenicity conclusion iii is reached for all occupational exposure scenarios for all routes of exposure. The MOS approach used for carcinogenic risk assessment for TCEP indicates that occupational exposure levels in all three scenarios have to be reduced substantially. The most critical risk situation seems to be dermal exposure during spray application (scenario 3a). Assuming limited protection from wearing suitable gloves (e.g. 90% protection), it needs to be carefully considered whether gloves could be able to sufficiently reduce the dermal risks from TCEP.

Reproductive toxicity, developmental effects
Fertility impairment

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

In an oral study with a continuous breeding protocol TCEP treatment revealed impairment of fertility in mice. At 700 mg/kg/day significant reduction of the number of litters produced by the F0 generation was observed. The reproductive system of male mice seemed to be more sensitive to the TCEP treatment than that of female mice. A NOAEL of 175 mg/kg/day is derived from the study. As starting point for MOS calculation the human dose according to the experimental NOAEL is identified as 12250 mg/person/day (175 mg/kg/d x 70 kg), the corresponding occupational air concentration for 8 hours inhalation calculates to 1225 mg/m^3.

The minimal MOS calculates to 75 (7 for metabolic rate scaling from mice to humans x 5 for human intraspecies variation x 5/7 for dosing differences of 7 days per week in the study compared to occupational exposure of 5 days per week x 3 for the uncertainty related to severe nature of the effects the indication for a steep dose response relationship). The according critical exposure level is 160 mg/person/day (12250 mg/person/day / 75) or 16 mg/m^3 (1225 mg/m^3 / 75). It has to be noticed that these values lie above the critical exposure level for repeated dose toxicity

Concern is expressed for all dermal exposure scenarios. With respect to fertility impairment risk reduction measures at the workplace appear to be necessary. However, it should be kept in mind, that as a consequence of risk assessment with respect to repeated dose toxicity and carcinogenicity, risk reduction measures will have to be requested, which efficiently reduce occupational exposures. If these control measures are implemented and complied with, exposures will be brought to a level which is below concern with respect to fertility impairment too.

Developmental effects

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

No significant toxicity to embryo or fetus development has been observed after oral TCEP treatment of pregnant rats. Concerning developmental toxicity the NOAEL from this study is reported as 200 mg/kg/day, a dose which clearly induced maternal toxicity. Based on the available data, the results are interpreted as giving no indication for developmental toxicity of TCEP up to doses which induce chronic toxic effects and/or carcinogenicity. There is no concern with respect to this endpoint for workers.

Summary of occupational risk assessment

Risk estimation for TCEP is mainly based on oral studies. Because no data are available concerning absorption after inhalation or skin contact, route to route extrapolation is based on the default assumption of 100 % absorption at all routes.

For TCEP concern results for carcinogenicity in combination with repeated dose toxicity after inhalation and dermal contact and fertility after dermal contact. On the background of the

exposure assessment and the proposed critical exposure levels, the according health risks are comparably high. This evaluation of risk is based on the assumption that a thresholded mode-of-action might be possible for TCEP tumour induction.

Tables 4.3 (inhalation) and 4.4 (dermal contact) try to visualize the risk profile of TCEP. According to the specific arrangement of exposure scenarios and critical exposure levels for different toxicological endpoints the relatively high risks are placed in the left upper corner, the relatively low risks in the bottom right corner of the tables.

On the background of cancer risks, air concentrations of TCEP at the workplace should be controlled to a level in the range of 0.2 mg/m^3 (critical exposure level for carcinogenicity). By this exposure reduction inhalation risks from other endpoints, as repeated dose toxicity and fertility impairment would similarly and effectively be mitigated too. Special emphasis should be given to reduce skin contact with TCEP (even if dermal absorption proved to be somewhat lower than 100%). Based on cancer risk assessment, dermal exposure should be controlled to levels in the range of 2 mg/person/day. On that background it needs to be carefully considered whether gloves could be able to sufficiently reduce dermal exposure.

Table 4.3: Ranking of the critical exposure levels for TCEP with respect to inhalation exposure at the workplace

Exposure scenario		Exposure level in mg/m³	Carcinogenicity	Repeated dose toxicity, systemic	Fertility	Acute toxicity
			Critical exposure level in mg/m^3			
			0.2 mg/m³	1 mg/m³	16 mg/m³	70 mg/m³
3a	Use of formulations and products with spray application (25% TCEP)	8.3	iii	iii		
1	Production of TCEP	1.2	iii	iii		
2	Production of polymers and formulations	1.2	iii	iii		
3b	Use of formulations and products without aerosol formation (25% TCEP)	1.2	iii	iii		

(1) blank fields: conclusion ii

Table 4.4: Ranking of the critical exposure levels for TCEP with respect to dermal exposure at the workplace

Exposure scenario		Exposure level in mg/p/d	Carcinogenicity	Repeated dose toxicity, systemic	Fertility	Acute toxicity
			Critical exposure level in mg/p/d			
			2 mg/p/d	10 mg/p/d	160 mg/p/d	15000 mg/p/d
3a	Use of formulations and products with spray application (25% TCEP)	2500	iii	iii	iii	
1	Production of TCEP	420	iii	iii	iii	
2	Production of polymers and formulations	420	iii	iii	iii	
3b	Use of formulations and products without aerosol formation (25% TCEP)	210	iii	iii	iii	

(1) blank fields: conclusion ii

Consumers

Oral exposure of consumers to TCEP can result from the intake of dust, due to hand-to-mouth behaviour, or the contamination of articles for daily use, e.g. toys. The estimated amounts (99th percentile) from dust intake are 0.0033 µg/kg bw/d for adults and 0.2 µg/kg bw/d for a three year old child. For babies the most significant source of exposure could be sucking at a toy, which under worst case assumptions is estimated as 240 µg/kg bw/d.

Inhalation exposure occurs by inhaling airborne particles. Assuming 100% absorption, model estimates reveal an uptake (99th percentile) of 0.4 µg/kg bw/d for adults and 0.96 µg/kg bw/d for children.

Dermal exposure can occur from direct contact with products, e.g. furniture coverings, as well as with house dust. Dermal exposure from different sources can be estimated to a total of about 4 µg/kg bw/d for adults. Dermal exposure of children as related to bodyweight can exceed that of adults with an estimated value of 10 µg/kg bw/d.

For female adults, a body burden would account for ~ 4.5 µg/kg bw/d, under reasonable worst case conditions and taking all paths into consideration. The respective value for 1 - 3 year-old children is 11 µg/kg bw/d. For babies of about 3 months a body burden would account up to 240 µg/kg bw/d by sucking on toys, the other paths can be neglected.

Acute Toxicity

Consumers are expected to be exposed to TCEP several orders of magnitude lower than the range of LD50 values derived from acute oral toxicity tests in animals. **Conclusion ii.**

Irritation and corrosivity

Data on human experience with TCEP are not available.
In experiments with rabbits, the substance demonstrated weak skin irritation after occlusive or semi-occlusive patch testing for 4 to 24 hours exposure times. After instillation into the eyes of rabbits, mild conjunctival irritation was detected; this irritation healed within 2 days.
Information on local effects on skin and eyes of humans is not available. TCEP is not a corrosive substance, as judged on the basis of Draize tests with rabbits. **Conclusion ii.**

Sensitisation

Human data on sensitizing properties of TCEP are not available. An animal study (Buehler Test) showed no skin sensitizing potential of TCEP. The read across from sensitisation data of the two other chloroalkyl phosphates TCPP and TDCP indicated that these substances do not possess significant skin sensitisation potential. Based on data on TCEP and structurally related substances it is concluded that there is no concern. **Conclusion ii.**

Repeated dose toxicity

Because kidney effects appear to be the most sensitive endpoint for repeated exposure TCEP the lowest LOAEL for kidney lesions in Scl:ddY mice (12 mg/kg bw/d) was chosen as the basis for risk assessment.

Results of studies give clear evidence that mice were more sensitive to the kidney effects than rats. Thus, the interspecies variation seems to be considerable. The estimated total body burdens from different exposure pathways (with an assumed absorption of 100%) are compared with an oral LOAEL from an 18 month study. Following the exposure considerations there is reason to assume a special risk for babies sucking a TCEP containing textile cube and for children due to TCEP exposure from house dust.

Adults: For all exposure scenarios via different routes the margins of safety are judged to be sufficient taking into account that the absorption figures are reasonable worse case estimates. **Conclusion ii**.

Children: The margins of safety via different routes are judged to be sufficient taking into account that the absorption figures are reasonable worse case estimates. **Conclusion ii.**

Babies: The margin of safety for the scenario sucking on toys is judged to be not sufficient to cover all uncertainties. A NOAEL for kidney effects is not available, and the use of a LOAEL for risk characterisation requires a higher margin of safety. **Conclusion iii.**

Margins of Safety for consumer exposure via different routes

Route	Exposure (µg/kg bw/d)	MOS *)	Conclusion
Inhalation			
Adults	0.4	30000	(ii)
Children	0.96	12500	(ii)
Dermal			
Adults	~4	3000	(ii)
Children	10	1200	(ii)

Oral			
Adults	0.0033	>3106	(ii)
Children	0.2	60000	(ii)
Babies	240	50	(iii)

*) The MOS was derived by using the oral LOAEL of 12 mg/kg bw/d (kidney effects)

Mutagenicity

Bacterial gene mutation tests were negative. In vitro genotoxicity tests with mammalian cells were negative for gene and chromosome mutations. Two in vivo mammalian micronucleus tests and a *Drosophila* test were negative. Very weak effects in an in vitro SCE tests are considered to be without relevance for mutagenicity. **Conclusion ii**.

Carcinogenicity

TCEP induces the formation of benign and malignant tumors at various sites in experimental animals. Renal tubule cell neoplasms were found in rats and mice each in both sexes. At present the mechanism of tumor development in the kidneys of TCEP treated rats and mice remains unclear. Data of gene mutation tests and genotoxicity tests are suggestive to assume that TCEP appears to have no genotoxic potential. Thus it is likely that the tumor formation in the kidney would be mediated by non-genotoxic (epigenetic) mechanisms. A species specific mechanism of tumor formation in the kidney was not identified.

A threshold level for carcinogenicity has not been established due to the lack of relevant data. Renal tumors in male and female F344/N rats, in male B6C3F1 mice and in male Scl:ddY mice may be induced secondary via cytotoxicity followed by cell proliferation. However, a NOAEL for the cytotoxic effects and also for a cell proliferation mechanism could not be derived. The scientific difficulties of establishing a threshold level for the carcinogenicity of TCEP have to be recognized. However, based on the assumption that any of the adverse effects observed in the chronic toxicity studies might be responsible for the induction of tumour development, the LOAEL of 12 mg/kg bw/d for kidney lesions in Scl:ddY mice after feeding in the diet for 18 months might be used as a surrogate LOAEL for the risk characterisation in relation to carcinogenicity using a MOS approach.

The total body burden for female adults estimated for reasonable worst case conditions and taking into account all paths of exposure (inhalation, dermal, and oral) would account for ~ 4.5 µg/kg bw/d. The respective value for 1 - 3 year-old children is calculated to be 11 µg/kg bw/d. Taking into account the underlying worst case exposure scenarios with assumed bioavailabilities of 100% for all exposure routes the margin of safety between the assumed oral LOAEL of 12 mg/kg bw/d (kidney lesions) and the estimated exposure levels is judged to be sufficient (MOS of 2660 and 1090 for adults and children, respectively). **Conclusion ii.**

An oral body burden for babies (3 months) for worst case conditions was calculated to be 240 µg/kg bw/d. It has to be taken into account that a NOAEL for tumour formation is not available. The use of a LOAEL for risk characterisation requires a higher margin of safety. The margin of safety between the assumed LOAEL of 12 mg/kg bw/d and the exposure level is judged to be not sufficient (MOS 50). **Conclusion iii**.

Toxicity for reproduction

TCEP treatment resulted in significant impairment of reproductive capacity and fertility during continuous breeding and for two successive generations in mice of both sexes. The reproductive system of male mice appeared to be more sensitive to TCEP treatment as evidenced by less successive reproduction of treated males in comparison to treated females and further by significant male reproductive organ weight reduction and sperm parameter impairment in mice of two different strains. Reproductive failure was observed at daily doses of 700 mg/kg bw. An oral NOAEL/fertility of 175 mg/kg bw/d was derived from these studies, which is compared with the estimated total body burden with an assumed oral, dermal and inhalative absorption of 100%. Following the exposure scenarios there might be a special risk for babies and children due to group-specific exposure behavior.

The estimated total body burden for female adults for reasonable worst case conditions would account for ~ 4.5 µg/kg bw/d. The respective value for 1 - 3 year-old children is calculated to be 11 µg/kg bw/d. The margin of safety between the oral NOAEL (fertility) of 175 mg/kg bw/d and the estimated exposure levels is judged to be sufficient (MOS 39000 and 16000). **Conclusion ii.**

The oral body burden for babies (3 months) under worst case conditions was calculated to be 240 µg/kg bw/d. The margin of safety between the oral NOAEL of 175 mg/kg bw/d and the estimated exposure level is judged to be sufficient (MOS 730). **Conclusion ii.**

Teratogenic effects of TCEP were investigated up to doses of 200 mg/kg bw/d. Even at maternally toxic doses (NOAEL/maternal toxicity = 100 mg/kg bw/d) no embryo-/fetotoxic or specific teratogenic properties were observed. Therefore, developmental toxicity is not considered to be a relevant endpoint. **Conclusion ii.**

Humans exposed via the environment

Indirect exposure of humans via the environment is calculated as 5.8 µg/kg bw/d for the local scenario and as 1.1 x 10-5 mg/kg bw/d for the regional scenario.

Repeated dose toxicity

Because kidney effects appear to be the most sensitive endpoint for repeated exposure of TCEP the lowest LOAEL for kidney lesions in Scl:ddY mice (12 mg/kg bw/d) was chosen as the basis for risk assessment.

Results of studies give clear evidence that mice were more sensitive to the kidney effects than rats. Thus, the interspecies variation seems to be considerable. There is a single report in humans after high inhalation exposure of a child aged five years.

For the local scenario, the calculated total intake 0.0058 mg/kg bw/d is compared with an oral LOAEL of 12 mg/kg bw/d. The margin of safety of 2069 is judged to be sufficient. **Conclusion ii**.

The regional total intake was calculated as 1.1 x 10-5 mg/kg bw/d. The margin of safety of about 106 is judged to be sufficient. **Conclusion ii**.

Mutagenicity

Bacterial gene mutation tests were negative. In vitro genotoxicity tests with mammalian cells were negative for gene and chromosome mutations. Two in vivo mammalian micronucleus

tests and a *Drosophila* test were negative. Very weak effects in an in vitro SCE tests are considered to be without relevance for mutagenicity. **Conclusion ii**.

Carcinogenicity

TCEP induces the formation of benign and malignant tumors at various sites in experimental animals. Renal tubule cell neoplasms were found in rats and mice each in both sexes. At present the mechanism of tumor development in the kidneys of TCEP treated rats and mice remains unclear. Data of gene mutation tests and genotoxicity tests are suggestive to assume that tris(2-chloroethyl) phosphate appears to have no genotoxic potential. Thus it is likely that the tumor formation in the kidney would be mediated by non-genotoxic (epigenetic) mechanisms. A species specific mechanism of tumor formation in the kidney was not identified.

A threshold level for carcinogenicity has not been established due to the lack of relevant data. Renal tumors in male and female F344/N rats, in male B6C3F1 mice and in male Scl:ddY mice may be induced secondary via cytotoxicity followed by cell proliferation. However, a NOAEL for the cytotoxic effects and also for a cell proliferation mechanism could not be derived. The scientific difficulties of establishing a threshold level for the carcinogenicity of TCEP have to be recognized. However, based on the assumption that any of the adverse effects observed in the chronic toxicity studies might be responsible for the induction of tumour development, the LOAEL of 12 mg/kg bw/d for kidney lesions in Scl:ddY mice after feeding in the diet for 18 months might be used as a surrogate LOAEL for the risk characterisation in relation to carcinogenicity using a MOS approach.

For the local scenario the calculated intake of 0.0058 mg/kg bw/d is compared with an oral LOAEL of 12 mg/kg bw/d (kidney lesions). The margin of safety of 2069 is judged to be sufficient. **Conclusion ii.**

The regional intake was calculated as 1.1 x 10-5 mg/kg bw/d. The margin of safety of about 106 is judged to be sufficient. **Conclusion ii.**

Toxicity for reproduction

TCEP treatment resulted in significant impairment of reproductive capacity and fertility during continuous breeding and for two successive generations in mice of both sexes. The reproductive system of male mice appeared to be more sensitive to TCEP treatment as evidenced by less successive reproduction of treated males in comparison to treated females and further by significant male reproductive organ weight reduction and sperm parameter impairment in mice of two different strains. Reproductive failure was observed at daily doses of 700 mg/kg bw. An oral NOAEL/fertility of 175 mg/kg bw/d was derived from these studies.

For the local scenario the total intake was calculated as 0.0058 mg/kg bw/d. The margin of safety of about 30000 is judged to be sufficient. **Conclusion ii.**

The regional intake was calculated as 1.1 x 10-5 mg/kg bw/d. The margin of safety in the range of 107 is judged to be sufficient. **Conclusion ii**.

Teratogenic effects of TCEP were investigated up to doses of 200 mg/kg bw/d. Even at maternally toxic doses (NOAEL/maternal toxicity = 100 mg/kg bw/d) no embryo-/fetotoxic or specific teratogenic properties were observed. **Conclusion ii.**

5 RESULTS

5.1 ENVIRONMENT

Aquatic compartment (incl. sediment)

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.

This conclusion applies to all life cycle steps to surface water, the functioning of the WWTP and the sediment.

Terrestrial compartment

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

This conclusion applies to all life cycle steps.

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.

This conclusion applies to all life cycle steps.

Secondary poisoning

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.

This conclusion applies to all life cycle steps. No risk characterisation for secondary poisoning was carried out since TCEP does not possess a bioaccumulation potential.

5.2 HUMAN HEALTH

5.2.1 Human health (toxicity)

Workers

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

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

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

ad iii)

For TCEP three occupational exposure scenarios are evaluated. TCEP is produced (scenario 1) and is used for the production of formulations (scenario 2). The use of TCEP-containing formulations (scenario 3) includes spray application (scenario 3a) and applications without formation of aerosols (scenario 3b). The overall result of risk assessment indicates that current exposure levels (inhalation and dermal contact) are too high for all occupational exposure scenarios.

From the toxicological point of view, concern mainly derives from the carcinogenic properties of TCEP. In addition, chronic toxicity and partly fertility impairment gives reason for concern.

Measures selected for risk reduction should be able to substantially reduce TCEP exposure of workers. Special emphasis should be given to the “spray application” scenario (dermal contact and inhalation).

With respect to risk assessment for carcinogenicity inhalation exposure at the workplace should be reduced to a level of 0.2 mg/m^3 or below. It is recommended to establish an occupational exposure limit for TCEP.

Concerning skin contact, exposure should be controlled to levels in the range of 2 mg/person/day. On that background it needs to be carefully considered whether gloves could be able to sufficiently reduce the dermal risks from TCEP.

Consumers

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

This conclusion applies to the exposure of babies through sucking on toys with respect to the carcinogenic properties of the substance and the effects after repeated oral administration.

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.

This conclusion applies to all other exposure scenarios and toxicological endpoints.

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.

This conclusion applies to all exposure scenarios and all toxicological endpoints.