EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Health and Environmental Risks

SCHER

Risk Assessment Report on (3-CHLORO-2-HYDROXYPROPYL)TRIMETHYLAMMONIUM CHLORIDE (CHPTAC)

Human Health Part

CAS No.: 3327-22-8
EINECS No.: 222-048-3

Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risks

The SCHER adopted this opinion at its 19th plenary on 20 September 2007

About the Scientific Committees

Three independent non-food Scientific Committees provide the Commission with the scientific advice it needs when preparing policy and proposals relating to consumer safety, public health and the environment. The Committees also draw the Commission's attention to the new or emerging problems which may pose an actual or potential threat.

They are: the Scientific Committee on Consumer Products (SCCP), the Scientific Committee on Health and Environmental Risks (SCHER) and the Scientific Committee on Emerging and Newly-Identified Health Risks (SCENIHR) and are made up of external experts.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCHER

Questions relating to examinations of the toxicity and ecotoxicity of chemicals, biochemicals and biological compound whose use may have harmful consequences for human health and the environment.

In particular, the Committee addresses questions related to new and existing chemicals, the restriction and marketing of dangerous substances, biocides, waste, environmental contaminants, plastic and other materials used for water pipe work (e.g. new organics substances), drinking water, indoor and ambient air quality. It addresses questions relating to human exposure to mixtures of chemicals, sensitisation and identification of endocrine disrupters.

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ACKNOWLEDGMENTS

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Keywords: SCHER, scientific opinion, Regulation 793/93, (3-chloro-2-hydroxypropyl)trimethylammonium chloride, CHPTAC, human health, CAS 3327-22-8

Opinion to be cited as:

SCHER, Scientific opinion on the risk assessment report on (3-Chloro-2-hydroxypropyl)trimethylammonium chloride - Human health part, CAS 3327-22-8, 20 September 2007

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1. BACKGROUND

Council Regulation 793/93 provides the framework for the evaluation and control of the risk of existing substances. Member States prepare Risk Assessment Reports on priority substances. The Reports are then examined by the Technical Committee under the Regulation and, when appropriate, the Commission invites the Scientific Committee on Health and Environmental Risks (SCHER) to give its opinion.

2. TERMS OF REFERENCE

On the basis of the examination of the Risk Assessment Report the SCHER is invited to examine the following issues:

(1) Does the SCHER agree with the conclusions of the Risk Assessment Report?

(2) If the SCHER disagrees with such conclusions, it is invited to elaborate on the reasons.

(3) If the SCHER disagrees with the approaches or methods used to assess the risks, it is invited to suggest possible alternatives.

3. OPINION

3.1 General comments

The health part of the document is of good quality, it is comprehensive, and the exposure and effects assessment follow the Technical Guidance Document. The RAR covers all studies relevant for exposure and hazard assessment of (3-chloro-2-hydroxypropyl)trimethylammonium chloride (CHPTAC). From technical point of view it is recommended that the RAR would be carefully checked and edited. For example, some doses given for acute oral toxicity (p. 39) should be in g/kg instead of mg/kg, abbreviations and references should be checked, and some incomplete sentences should be completed.

3.2 Specific comments

3.2.1 Exposure assessment

Dermal contact is considered the most significant route of exposure. Inhalation exposure is insignificant due to low vapour pressure of CHPTAC and because no aerosol forming processes are used. Residual amounts of CHPTAC in final products may lead to indirect exposure via food and the environment. Because CHPTAC is in alkaline conditions hydrolysed to the reactive epoxide 2,3-epoxypropyltrimethylammonium chloride (EPTAC), and the both chemicals are used for cationisation of starch, the exposure assessment for the use scenarios of these two chemicals is closely interrelated.

Occupational exposure assessment of CHPTAC was carried out without considering personal protective equipment and is based on three scenarios: (1) production, (2) loading operations and (3) end uses. Due to lack of measured data the RAR uses EASE modelling for dermal and inhalation exposures. The highest exposure is predicted for dermal exposure related to production of CHPTAC (reasonable worst case scenario 300 mg/person/day), but inhalation exposures for all occupational scenarios are very low. SCHER agrees with this approach, but points out that dermal exposure modelling with EASE generally overestimates the actual exposure (Creely *et al.*, 2005).

CHPTAC is not intentionally used for products directly marketed to consumers, but consumer exposure may occur via residues present in products manufactured with cationic starch or proteins, such as copy paper, newsprint, food contact materials and some cosmetics. The RAR concludes that exposure to CHPTAC from consumer products and via the environment is negligible. SCHER agrees with these conclusions.

3.2.2 Effect assessment

Only a limited database is available for the effect assessment of CHPTAC. No studies on toxicokinetics or reproductive toxicity are available.

An *in vitro* study on percutaneous absorption in mouse and human skin is available and based on this study the RAR uses human dermal uptake of 6% (excluding the contribution of tape stripping) for risk characterisation. The RAR assumes inhalational absorption of 75% and gastrointestinal absorption of 50%. SCHER agrees with these approaches.

SCHER also supports the conclusion of RAR that CHPTAC is not a skin irritant, eye irritant or skin sensitizer.

Two repeated dose toxicity studies are presented: a 28-day oral toxicity study in rats with a limit test (one dose-level) design, and a 108-week dermal study in mice with twice weekly application. The RAR derives a repeated dose LOAEL of 1085 mg/kg/day based on increased (20%) relative kidney weight and vacuolisation of kidney tubule cells of male rats in the former study. In the dermal study in mice a small (15%) but significant decrease in absolute and relative testicular weight was observed at the high dose. The RAR, however, ignores this finding because of (1) uncertainties in definition of a reliable LOAEL due to the twice a week dosing regimen and (2) considering an oral rat study more preferable than a dermal mouse study. SCHER disagrees with this reasoning and regards the data from the dermal mouse study relevant. SCHER therefore derives a repeated dose NOAEL equivalent with estimated systemic dose of 24 mg/kg/day based on decreased testicular weight.

All *in vitro* mutagenicity tests gave positive results while the only *in vivo* test (mouse bone marrow micronucleus test) was negative. The RAR concludes that CHPTAC is an *in vitro* mutagen, but there is uncertainty about *in vivo* mutagenicity, and no definite conclusions can be made without additional testing. Further *in vivo* data, however, is not considered necessary, because most likely new data would not help to refine risk reduction measures. It is also possible that the mutagenic response is associated with the formation of EPTAC from CHPTAC under the conditions of the used test systems. SCHER supports this conclusion in spite of the fact that from the scientific point of view it is necessary to clarify the *in vivo* mutagenicity of CHPTAC.

In the dermal carcinogenicity study in mice with twice weekly dosing no skin carcinogenesis was observed, but a dose-dependently increased incidence of lung adenomas and carcinomas was found both in males and in females. The RAR uses the Benchmark dose (BMD) approach and the multistage model to calculate the carcinogenic potency of CHPTAC based on combined benign and malignant lung tumours. The derived BMDs for 10% increase in tumour incidence are 55 mg/kg/day for workers (5 days per week exposure) and 49 mg/kg/day for consumers (7 days per week exposure). The RAR also classifies CHPTAC as Category 3 carcinogen, R40. SCHER supports these conclusions.

In the absence of reproductive toxicity studies the only effect of CHPTAC observed in reproductive organs was the decreased testicular weight after long-term dermal exposure in mice (NOAEL 24 mg/kg/day). For consumer exposure and indirect exposure via the environment the RAR proposes a systemic NOAEL of 5 mg/kg/day for gonad toxicity derived from 28-day oral rat study with EPTAC, but points out that this NOAEL is higher than the value derived for repeated dose toxicity for EPTAC (LOAEL 3.16 mg/kg/day). The RAR concludes that in spite of the fact that the formal data requirements for reproduction toxicity are not met, additional testing is not of high priority. This is because in the CHPTAC production scenario all risk reduction measures are already applied because of the use of Category 2 carcinogen epichlorohydrin as a starting material. In addition, in all CHPTAC use scenarios the principal concern is the formation EPTAC, which is a genotoxic carcinogen and requires a strict worker protection. SCHER agrees with these approaches.

3.2.3 Risk characterisation

The risk characterization presented in RAR uses the margin-of-safety (MOS) approach for inhalation and dermal exposures. For the production scenario the RAR uses data on CHPTAC. On the other hand, for the use scenarios the RAR uses the formation of EPTAC as the main risk component, because most of the CHPTAC is hydrolysed to EPTAC during cationisation process, and EPTAC is a genotoxic carcinogen and a potent human sensitizer. SCHER supports this approach.

SCHER agrees with conclusions iii)[1] for all occupational use scenarios due to intentional conversion of CHPTAC to EPTAC. SCHER also agrees with the conclusion ii) for the production scenario. In the production of CHPTAC a Category 2 carcinogen epichlorohydrin is used as a starting material for synthesis, and therefore sufficient risk reduction measures need to be in used. Consequently, conclusion ii) is substantiated.

SCHER also agrees with conclusion ii) for all consumer scenarios and exposures from the environment because of only negligible risk for all endpoints due to very low exposures.

4. LIST OF ABBREVIATIONS

BMD	Benchmark dose
CHPTAC	(3-chloro-2-hydroxypropyl)trimethylammonium chloride
EASE	Estimation and Assessment of Substance Exposure
EPTAC	2,3-epoxypropyltrimethylammonium chloride
LOAEL	Lowest Observed Adverse Effect Level
MOS	Margin of Safety
NOAEL	No Observed Adverse Effect Level
RAR	Risk Assessment Report
TGD	Technical Guidance Document

5. REFERENCES

Creely KS, Tickner J, Soutar AJ et al (2005) Evaluation and further development of EASE model 2.0 Ann Occup Hyg 49: 135-145.

[1] *According to the Technical Guidance Document on Risk Assessment – European Communities 2003:*

- *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 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.*