Scientific Committee on Health and Environmental Risks

SCHER

Risk Assessment Report on

Bis(hydroxylammonium)sulfate

CAS No.: 10039-54-0

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The SCHER adopted this opinion at its 21st plenary on 15 January 2008

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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.

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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.

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http://ec.europa.eu/health/ph_risk/risk_en.htm

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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 human health part of the document is of good quality and well structured. The exposure and effects assessment follows the TGD and covers the studies relevant for exposure and hazard assessment of bis(hydroxylammonium)sulfate.

3.2 Specific comments

3.2.1 Exposure assessment

Bis(hydroxylammonium)sulfate is produced in about 500 000 t/a. Its major use (> 90 %) is as intermediate in the production of caprolactam. Other uses (2 %) include use as intermediate for the production of oximes, ingredients in plant protection products and pharmaceuticals. Minor uses are in textile and metal finishing and as developers in the photographic industry. Exposure scenarios have been developed for the production of bis (hydroxylammonium) sulfate, the formulation of photo-developing chemicals and as an auxiliary in different industry, for the use in photographic laboratories and in different other industries, e.g. electroplating industry.

For exposure by inhalation in the production of bis(hydroxylammonium)sulfate a maximum value of 0.9 mg/m^3 inhalable dust has been measured. For the other scenarios EASE gave exposure concentrations from 0.05 to 1.25 mg/m^3. Dermal exposure, assessed with EASE ranged from negligible to 420 mg/person/day, the highest value was obtained for the dermal contact with bis(hydroxylammonium)sulfate dust in the formulation as an auxiliary in different industries. It is discussed, that this value should be much lower in reality due to the large particle size of bis(hydroxylammonium)sulfate (95 % > 200 µm).

SCHER supports the approach to estimate the exposure to bis (hydroxylammonium) sulfate during acid pickling in analogy to sulphuric acid. The justification, however, is somewhat confusing. The reasons obviously are 1) sulfuric acid is used for the same purpose, 2) both compounds have similar physicochemical properties i.e. low vapour pressure??, and 3) measurements are available on sulfuric acid.

Concerning consumer exposure the exposure to bis(hydroxylammonium)sulfate as developer in photography was evaluated and considered as negligible due to incidental and short exposure. SCHER, however, notes that in single cases exposure may be similar to professional use in photographic laboratories with a worst case dermal exposure estimate of 12.6 m/person/day.

3.2.2 Effect assessment

In case of few or missing data read across from hydroxylamine hydrochloride has been performed. In principle SCHER supports read across, however, the justification is insufficient. Why is the hydroxylamine moiety only considered as the toxic species?

No specific data were available on the toxikokinetics, metabolism and distribution of bis(hydroxylammonium)sulfate. The conclusions on the absorption rates (100 %) for oral exposure and exposure by inhalation are accepted by SCHER. However, concerning dermal exposure a distinction should be made between exposure to bis(hydroxylammonium)sulfate solutions and bis(hydroxylammonium)sulfate dust, because it can be assumed that the particles are rather large (95 % > 200 µm according to data from production of bis(hydroxylammonium)sulfate), which will not be taken up easily by the skin. Therefore for particles an uptake of 1 % could be assumed in contrast to solutions, where 10 % can be assumed.

In the section on acute inhalation toxicity the conclusion that bis(hydroxylammonium)sulfate did not cause severe toxic effects is not correct, because no effects at all were detected in inhalation risk tests. Nevertheless, no relevant conclusions can be drawn, because of the presumably low exposure concentrations due to the low vapour pressure of the compound.

The major effect of bis(hydroxylammonium)sulfate is methaemoglobinaemia, which was detected in rats, rabbits and cats after oral exposure and in rats and rabbits after dermal exposure. Dermal acute toxicity was higher in rabbits than in rats, and higher under occlusive then under semi-occlusive conditions. The description of the tests with rabbits is confusing. One study shows severe necrosis of the skin under occlusive conditions. Necrosis and subsequent better dermal uptake is most probably the reason for the higher systemic toxicity after occlusive exposure. This aspect is not discussed in the RAR.

SCHER agrees to the proposal for classification with R21/22 (harmful in contact with skin and if swallowed). And also supports the R36/38 (irritating to eyes and skin).

Bis(hydroxylammonium)sulfate was clearly sensitizing in a Magnusson and Kligman test, but not in a Buehler test. Human experience also shows sensitizing properties, therefore SCHER supports labelling as R43 (may cause sensitisation by skin contact).

Several repeated dose toxicity studies with up to 2 years exposure are available in rats and mice. Major targets were the blood, spleen, liver, kidney and the bone marrow. The findings in these organs were consistent with the haematotoxic effects of bis(hydroxylammonium)sulfate. The severity and incidence of the hematotoxic effects were dose-related and time-related. The overall NOAEL was derived from a 2-year drinking water study with rats and was 5 ppm (equivalent to about 0.2 mg/kg bw/d in males and 0.4 mg/kg bw/d in females). For local effects in the digestive tract the NOAEL was 80 ppm. SCHER agrees to these NOAELs.

No genotoxicity data in vitro were available with bis(hydroxylammonium)sulfate. Therefore read across from hydroxylamine hydrochloride was performed, which was negative in most bacterial test systems, but positive in the mouse lymphoma assay, chromosome aberration and SCE tests and in tests with drosophila. In most cases, the positive results were only weak or the methodology was inadequate. SCHER recommends analysing also the sulfate ion with respect to its genotoxic properties for supporting read across. Two micronucleus tests were available investigating the genotoxicity in vivo of bis(hydroxylammonium)sulphate. Both were negative, but have deficiencies. In conclusion, SCHER considers the database on genotoxicity as insufficient to justify the conclusion that bis(hydroxylammonium)sulphate is a non genotoxic carcinogen.

In a 24 month drinking water study a dose related increase of haemangiosarcomas and haemangiomas of the spleen has been observed in male and female rats, respectively. The LOAEL was 5 ppm. Also in drinking water studies with mice vascular neoplasm of the spleen and the lymph nodes have been found. . SCHER agrees to R40 (limited evidence of a carcinogenic effect).

No guideline studies on fertility were available. In a subchronic repeated dose toxicity study with rats, no effects on the reproductive organs have been found up to a dose level of 21 mg/kg bw. In a guideline study on developmental toxicity in rats no embryo-, foetotoxic or teratogenic potential was observed. The NOAEL was 3 mg/kg bw for maternal toxicity and 20 mg/kg bw for embryo-/foetotoxicity. SCHER agrees that no classification as toxic for reproduction is needed.

3.2.3 Risk characterisation

A reference MOS has been derived for the evaluation of the MOS obtained. Furthermore critical exposure levels were derived by dividing the NOAEL by the reference MOS.

SCHER does not agree on a threshold approach for the risk characterisation for carcinogenicity, because the database on genotoxicity is insufficient. Therefore conclusion iii) would be obtained for all workplace scenarios for the endpoint carcinogenicity.

For workers conclusion iii)[1] has also been obtained for skin sensitisation and repeated dose toxicity (inhalation, dermal and combined routes) for most scenarios, which is accepted by SCHER. SCHER disagrees, however, on conclusion iii for acute toxicity for one scenario, based on a MOS of 83 for dermal exposure and 64 for combined exposure, because of dermal exposure to dust. Based on a dermal absorption of 1 % instead of 10 %, a MOS above the MOS_{ref} would result.

No risk was identified for consumers, because exposure was considered as negligible. As indicated above, SCHER considers exposure in photographic laboratories also a possible consumer exposure scenario, which would require a risk assessment for consumers.

SCHER notes that the risk characterisation for man exposed via the environment has yet to be completed.

4. LIST OF ABBREVIATIONS

LOAEL	Lowest Observed Adverse Effect Level
MOS	Margin of Safety
NOAEL	No Observed Adverse Effect Level
RAR	Risk Assessment Report
SCE	Sister Chromatid Exchange
TGD	Technical Guidance Document

[1] [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