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SCIENTIFIC COMMITTEE ON TOXICITY, ECOTOXICITY AND THE ENVIRONMENT (CSTEE)

Opinion on the results of the Risk Assessment of:

SODIUM PERBORATE

Human Health part

CAS N°: 11138-47-9

EINECS N°: 234-390-0

Carried out in the framework of Council Regulation (EEC) 793/93 on the evaluation and control of the risks of existing substances[1]

Adopted by the CSTEE during the 43rd plenary meeting of 28 May 2004

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[1]   Regulation 793/93 provides a systematic framework for the evaluation of the risks to human health and the environment of those substances if they are produced or imported into the Community in volumes above 10 tonnes per year. The methods for carrying out an in-depth Risk Assessment at Community level are laid down in Commission Regulation (EC)1488/94, which is supported by a technical guidance document.

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Terms of Reference

In the context of Regulation 793/93 (Existing Substances Regulation), and on the basis of the examination of the Risk Assessment Report the CSTEE is invited to examine the following issues:

1.   Does the CSTEE agree with the conclusions of the Risk Assessment Report

2.   If the CSTEE disagrees with such conclusions, the CSTEE is invited to elaborate on the reasons for this divergence of opinion.

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.

INTRODUCTION

The RAR preferentially addresses local effects of the compound whereas systemic effects have not been sufficiently evaluated due to insufficient data. Since perborate is rapidly degraded to hydrogen peroxide and boric acid it is concluded that adverse effects of sodium perborate are chiefly related to these two degradation products. . A RAR on boric acid is not available so far, and CSTEE agrees with the conclusion that the risks for workers and consumers cannot be evaluated without such information.

GENERAL COMMENTS

The human health part of the document is comprehensive and written in accordance with the principles of the Technical Guidance Documents. Inconsistencies in the effects assessment part have to be resolved, however, and there are still many typographical errors. Additional exposure scenarios, and further studies, which should have been included in the RAR, were identified in the open literature.

SPECIFIC COMMENTS

Exposure assessment

Sodium perborate is mainly used as a bleaching agent in laundry detergents, in dishwashing agents, in stain removers and in denture cleansers. It is also used as preservative in ophthalmic solutions, and as tooth bleaching agent. Minor quantities are used in polysulfide-sealants production and the textile bleaching industry (less than 10 tons per year for each).

Eleven occupational exposure scenarios are described in the RAR: four are for the production, six are for processing and production of formulations and one is for the exposure of personnel in laundries. Exposure scenarios were not presented for the textile bleaching industry and for polysulfide-sealants production; instead it was assumed that exposure scenarios would be similar to the ones presented. It would improve transparency if the rationale for this assumption is given in the RAR. The RAR does not address exposure of health care professionals handling perborate containing formulations.

Inhalation exposure is highest during production for filling, emptying, transferring, weighing, mixing, and transport operations with a "worst case" 90th percentile of 12.1 mg/m^3 (area measurement, inhalable dust, TWA; no information on respirable dust concentration, or particle size distribution available). In detergent factories, 90th percentiles of the overall dust concentrations range from 0.18 mg/m^3 for packing areas to 0.93 mg/m^3 for dosing/tipping operations (again, no information on respirable dust concentrations, or particle size distribution available). Highest dermal exposures were identified during production for filling, emptying, transferring, weighing, mixing, and transport operations, and during processing for dosing, tipping, and transport of bags with an estimated 0.1-1 mg/cm^2 per day (corresponding to 12 mg/kg bw/day) as a "worst case" based on EASE calculations.

As occupational exposure in laundries is reported to be up to "12 times higher than consumer exposure" (i.e. up to 12 mg/kg bw/day for the dermal route), it is unclear, why this is considered "negligible" with respect to the dermal route.

Five consumer exposure scenarios are described (laundry detergents/handling of powder, laundry detergents/handwashing, automatic dishwashing detergents/handling of powder, denture cleansers, stain removers). The RAR should mention that, in addition, sodium perborate is a common preservative in ophthalmic solutions and artificial tears (cf., for instance, Noecker, 2001), and that sodium perborate is used for bleaching teeth.

Perborate concentrations in consumer products range between 4 and 31%, with a maximum at 50% in stain removers. During a machine wash about 70% of the sodium perborate is degraded. Inhalation exposure of consumers is negligible (less than 0.008 µg/m^3). Dermal exposure is highest during handwashing with heavy duty detergents and is calculated from use data as 1 mg/kg bw/day.

Because of hydrolysis, an indirect exposure to sodium perborate through drinking water is not expected; however, a maximum of about 0.2 mg boron / litre drinking water may stem from the use of sodium perborate.

Effects assessment

Toxicokinetics

No information on absorption, distribution, metabolism and excretion was available for the inhalation and dermal exposure routes.

In limited studies with 4-5 volunteers, 2-3 fold increases in blood boron levels were found 2 hours after single or repeated mouthwashes with solutions containing 1.2 g of sodium perborate. At 48 hours the blood boron levels were at background concentrations again. The RAR notes that "excretion is not terminated after one week". It is unclear from which data this conclusion was drawn.

Degradation of sodium perborate to sodium metaborate and hydrogen peroxide is mentioned under the toxicokinetics section of the RAR, whilst degradation to boric acid and hydrogen peroxide is mentioned in other sections. This should be clarified.

Acute toxicity

In animal studies, the monohydrate (but not the tetrahydrate) was irritant upon oral administration with LD_{50} between 1700 and 2700 mg/kg. Inhalation induced respiratory irritation at 39 and 74 mg/m^3. In humans, accidental oral intakes of household and dishwashing formulations were described as non-specific injuries. The dermal LD_{50} for the monohydrate was greater than 2000 mg/kg bw.

Irritation/corrosion

Moistened sodium perborate was not or only slightly irritating to the skin of rabbits. The RAR should mention cases of irritant dermatitis in hospital cleaning women (Hansen, 1983).

Sodium perborates may induce irreversible effects on the corneal tissue of rabbits. The CSTEE notes that a rabbit low-volume eye test with sodium perborate monohydrate is not included in the RAR (Maurer et al, 2001). In this test, sodium perborate monohydrate was shown to be mildly irritating, but corneal opacity and neovascularization were present in single animals at study termination.

In humans, incidents of mild and transient eye and upper respiratory tract (nose) irritation were reported. The RAR states that these effects may have been related to peak exposures, but does not provide corresponding exposure levels. A "limit for respiratory irritation" was reported as 21 mg/m^3.

Sensitization

Sodium perborate was not sensitizing in a limited Buehler test (only 10 animals in the treatment group) and there are no reports on skin sensitization in humans. Data on related boron compounds (boric acid, sodium borate and tetraborate decaborate) are negative but no details are given in the report.

Repeated-dose toxicity

There were no valid animal inhalation studies available. No systemic effects were seen in a 13-week dermal study on rabbits with a 2.5% sodium perborate solution (corresponding to about 50 mg/kg bw/day). In a 28-day oral study on rats 1000 mg/kg bw/day given daily by gavage (only tested dose) irritant effects on the stomach, reduced spleen size, haematological effects have been observed. No effects were seen in male rats after 200 mg/kg given by gavage for 6 d and 3 d

post treatment and in the teratogenicity study at 100 mg/kg after rats received 100, 300 and 1000 mg/kg by gavage at days 6-15 of pregnancy.

Lung function measurements in about 100 workers from different production plants and workplaces over a period of 20 years did not indicate an adverse effect of sodium perborate (as only for 16 workers quantitative data on exposure levels were available, this information is of limited value).

Genotoxicity

In vitro, sodium perborate induced point mutations in *Salmonella typhimurium* strains TA100 and TA102 in the absence, but not in the presence of a metabolic activation system (S-9 mix). No response was seen in TA98. Positive results were found in a chromosomal aberration test in Chinese Hamster Ovary Cells, and in a test for the induction of DNA damage. Addition of catalase reduced or even abolished the genotoxic and cytotoxic activities of sodium perborate, indicating that the effects were caused by oxidative damage, most probably through the degradation product hydrogen peroxide.

The CSTEE notes that there is additional mutagenicity data available which should be included in the RAR (Watanabe et al., 1988; report on the mutagenic activity of sodium perborate tetrahydrate in *Salmonella typhimurium* TA102, and in *Escherichia coli* WP2/pkM101 and WP2uvrA/pKM101; all tests performed without metabolic activation). In this study these bacterial strains have been used to demonstrate their specific sensitivity to various oxidative (and crosslinking) agents.

There were no *in vivo* data available. Under *in vivo* conditions sodium perborate is rapidly degraded to hydrogen peroxide and borate. Hydrogen peroxide is an *in vitro* genotoxicant, but has no significant genotoxic activity *in vivo* CSTEE agrees with the conclusion that a genotoxic risk of borates in humans at the exposure scenarios described is unlikely.

Carcinogenicity

There were no epidemiology data and no data from animal carcinogenicity studies available. Sodium perborate induced hyperplasia in the stomach mucosa of rats after high and locally irritating oral doses (1000 mg/kg bw/day for 28 days).

Toxicity for reproduction

A decrease in absolute testes weight was found in an oral 28-day toxicity study on rats at the only tested dose level of 1000 mg/kg bw/day (corresponding to about 70 mg/kg bw/day boron). There were no histopathological changes in the testes. Because the histological methods were not very sensitive, and because of known effects of other borates (not specified in the RAR) an adverse effect of sodium perborate cannot be dismissed, and the member states rapporteur postpones the final decision on this endpoint until a targeted risk assessment on the reproductive effects of other boron compounds is finalized.

Sodium perborate tetrahydrate was not considered as a developmental toxicant in a study performed according to OECD TG 414 (NOAEL for maternal and developmental toxicity: 100 mg/kg bw/day). The RAR notes that external malformations were seen at 100 mg/kg bw/day. These were statistically significant but considered incidental due to a lack of dose-response by the authors of the study. CSTEE notes that there is a discrepancy between the description of the results in the effects assessment part, the risk characterization part, and in Table 4-22.

Risk characterisation

The risk characterization was carried out with data on the tetrahydrate, or, for some consumer exposure scenarios, with data for the degradation products boric acid and hydrogen peroxide.

The inhalation and dermal routes of exposure were taken into account for the risk characterization.

Workers

The CSTEE agrees with conclusion (ii) for acute toxicity, skin irritation, and sensitization for all exposure scenarios. The chemical may cause serious eye damage; as the risk is minimized by prescribed protective equipment, the CSTEE is in agreement with conclusion (ii).

For upper airway irritation, conclusion (iii) was drawn based on data on hydrogen peroxide (NAEC, rat: 14 mg/m^3; NAEC human: 7 mg/m^3), the observation of nose/respiratory irritation at some production sites, and a "worst case" exposure level of 12 mg/m^3 in production plants. The CSTEE supports this conclusion.

For repeated dose toxicity a LOAEL of 1000 mg/kg bw/day was derived from a 28-day oral rat study (irritant effects on stomach, effects on spleen and haematological parameters). Although the site of contact irritant action makes a route-to-route extrapolation difficult, if not inappropriate, a human inhalation NAEC of 3480 mg/m^3 was calculated by route-to-route and interspecies extrapolation from the oral study with a LOAEL of 1000 mg/kg bw/day. With the argumentation of a "worst case" inhalation exposure level of 12.1 mg/m^3, the available data on hydrogen peroxide, and the information from workplace surveillance, conclusion (ii) was reached for all scenarios. Data on the systemic toxicity of boric acid were not taken into account. The CSTEE does not support this conclusion, and finds that further data is necessary to fully evaluate this endpoint (conclusion (i)) because of the following reasons: (1) Inhalation is likely to be an important route of occupational exposure, (2) there is no data on the toxicokinetics and metabolism of sodium perborate after inhalation exposure (3) if degradation to hydrogen peroxide and boric acid is assumed, the systemic effects of boric acid have to be included as well.

Sodium perborate is genotoxic *in vitro,* with greatly reduced or even abolished activities if a metabolic activation system or catalase were added to the cell cultures. It was therefore assumed that the mechanism of action is through oxidative damage by hydrogen peroxide, a degradation product of sodium perborate. Although there were no *in vivo* genotoxicity data available, it was further assumed, based on the available *in vitro* data and on data for hydrogen peroxide, that effective detoxification mechanism are in place which prevent that the activity *in vitro* is expressed *in vivo*. The CSTEE is in agreement with this view and therefore supports the proposed conclusion (ii) for all scenarios.

There were no carcinogenicity data available. At concentrations that cause irritation, the chemical may induce cell proliferation. Taking also into account the information available for hydrogen peroxide and borates, there are, however, no concerns for carcinogenicity at non-irritating concentrations. The CSTEE agrees with conclusion (ii) for all scenarios.

For fertility and developmental toxicity the conclusions will depend on the outcome of the targeted risk assessment of the boron compounds (conclusion (i)). The CSTEE is in agreement with this conclusion.

Consumers

The CSTEE agrees with conclusion (ii) for acute toxicity, sensitization, repeated dose toxicity, genotoxicity and carcinogenicity for all endpoints.

The CSTEE notes that no risk characterization is presented for irritation/corrosivity and skin absorption which also requires information on the stability of perborate on the skin and mucous membranes. Such information should be provided.

For fertility and developmental toxicity the conclusions will depend on the outcome of the targeted risk assessment of the boron compounds (conclusion (i)). The CSTEE is in agreement with this conclusion.

Man exposed indirectly via the environment

The CSTEE notes that the proposed conclusion (ii) for humans exposed indirectly via the environment is in contradiction with the text of the RAR itself (chapter 4.1.3.4), where further information relating to boric acid and boron compounds is requested for a final risk assessment. The CSTEE therefore recommends a change into conclusion (i).

<u>References</u>

Hansen KS (1983) Occupational dermatoses in hospital cleaning women. Contact Dermatitis 9, 343-351.

Maurer JK, Molai A, Parker RD, Li L, Carr GJ, Petroll WM, Cavanagh HD, Jester (2001) Pathology of ocular irritation with bleaching agents in the rabbit low-volume eye test. Toxicol Pathol. 29(3):308-19.

Noecker R (2001) Effects of common ophthalmic preservations on ocular health. Adv. Ther. 18(5): 205-125 (review).

Watanabe K, Sakamoto K and Sasaki T (1998) Comparisons on chemically-induced mutation among four bacterial strains, *Salmonella typhimurium* TA102 and TA2638, and Escherichia coli WP2/pKM101 and WP2 uvrA/pKM101: collaborative study II. Mutat. Res. 412(1):17-31.