Scientific Committee on Health and Environmental Risks

SCHER

Risk Assessment Report on N-CYCLOHEXYLBENZOTHIAZOL-2-SULFENAMIDE

Human Health Part

CAS No.: 95-33-0
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The SCHER adopted this opinion at its 21st plenary on 15 January 2008

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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 N-Cyclohexylbenzothiazol-2-sulfenamide (CBS) and also includes an overview on the toxicology studies on cyclohexylamine and mercaptobenzothiazole, which are hydrolysis products formed from CBS.

3.2 Specific comments

3.2.1 Exposure assessment

Only inhalation of CBS-containing dusts and dermal exposures to CBS or products containing unreacted CBS are considered relevant for the occupational exposure scenarios. The occupational exposure assessment develops two scenarios, production of CBS and use of CBS as vulcanisation accelerator in the rubber industry. Assessment of occupational exposure by inhalation is based on measured data; dermal exposures are modelled using EASE. While inhalation exposures are predicted to be below an 8-h average of 2 mg CBS/m^3, dermal exposures are predicted by EASE to reach up to 420 mg/person/day. In the assessment of dermal exposures by modelling, it needs to be recognized that the EASE system may widely overestimate actual occupational exposures by skin contact to dust.

CBS is not used directly in applications with consumer exposures, but consumers may be exposed to residues of CBS or the hydrolysis product mercaptobenzothialzole. Consumer exposure to CBS and to mercaptobenzothiazole from the use of CBS is considered as very low in the RAR based on data on exposure to mercaptobenzothiazole from other sources. The SCHER agrees with these conclusions.

3.2.2 Effect assessment

Since no studies on CBS regarding dermal application are available and the database for oral administration of CBS is limited, the conclusions on toxicokinetics integrate data for mercaptobenzothiazole and cyclohexylamine, which are hydrolysis products formed from

CBS. The RAR therefore assumes 100 % absorption after oral administration and inhalation and a dermal uptake of 10 % with adequate justification for deviation from the 100 % default due to the very low dermal toxicity of CBS.

SCHER supports the use of these conclusions in the risk characterisation.

SCHER also agrees that CBS only has a low potential for skin and eye irritation. Based on the results of animal and human studies, CBS should be regarded as a skin sensitizer.

For assessment of repeated dose toxicity of CBS, the limited data on CBS are combined with the more extensive information available on mercaptobenzothiazole and cyclohexylamine. For inhalation of CBS, a NOAEC of 0.048 mg/L (only concentration tested) from a 28-day dust inhalation study is derived. The NOAEL for effects after oral application of CBS is derived as 80 mg/kg bw/day with adequate justification.

Genotoxicity studies with CBS in bacteria and mammalian cells were mostly negative, but a weak clastogenic potential may be indicated by a positive in vitro chromosomal aberration test. However, together with the more extensive database on the genotoxicity of mercaptobenzothiazole and cyclohexylamine, which were consistently negative, SCHER agrees that CBS should not be considered as genotoxic.

No adequate carcinogenicity study with CBS is available, but the absence of increased tumour incidences in adequate studies with mercaptobenzothiazole and cyclohexylamine and the negative genotoxicity data on CBS support the conclusions that CBS should not be classified as a carcinogen.

Regarding reproductive and developmental effects, the SCHER agrees with the conclusion of an overall NOAEL of 70 mg/kg bw/day for developmental toxicity used in the risk characterisation. In the RAR, it is proposed to classify CBS regarding reproductive toxicity due to the severity of testicular effects observed after application of cyclohexylamine, testicular effects were not observed in the limited database availalable for CBS itself. The C & L group concluded that classification for reproductive toxicity is not warranted due to slow hydrolysis of CBS to cyclohexylamine in aqueous solution.

The SCHER does not consider the slow hydrolysis of CBS to cyclohexylamine a convincing argument against classification for reproductive toxicity. The hydrolysis of CBS to give cyclohexylamine forms the basis for including toxicity data on cyclohexylamine in the RAR. Conclusions on a number of endpoints in CBS toxicity are based considering studies cyclohexylamine. However, SCHER does not see a science-based need for classification of CBS regarding fertility since no indication for testicular effects were obtained with CBS itself and effect levels with cyclohexylamine correspond to daily CBS-doses of > 700 mg/kg bw with NOAELS for CBS (calculated on the basis of cyclohexylamine data) of 218 mg/kg bw/day. Moreover, other toxicity endpoints for cyclohexlamine showed lower NOAELs in the repeated dose studies indicating that reproductive effects are adequately covered in the extrapolation.

3.2.3 Risk characterisation

The risk characterization performed in the RAR uses the margin-of-safety (MOS) approach and is performed for inhalation and dermal exposures. The SCHER agrees with conclusions iii)[1] for one of the two occupational exposure scenarios regarding inhalation exposures due to low MOS. Conclusion iii) is also supported regarding skin sensitisation

[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.

and combined exposures but agrees with the RAR that the concern for combined exposures is borderline.

Regarding consumer exposure, due to the concluded very low exposure, conclusion ii) is accepted.

The SCHER also supports conclusion ii) for consumers and exposures from the environment.

4. LIST OF ABBREVIATIONS

LOAEL	Lowest Observed Adverse Effect Level
LOAEC	Lowest Observed Adverse Effect Concentration
MOS	Margin of Safety
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
RAR	Risk Assessment Report
TGD	Technical Guidance Document