Scientific Committee on Health and Environmental Risks

SCHER

Risk Assessment Report on PROPAN-1-OL

Human Health Part

CAS No.: 71-23-8

EINECS No.: 200-746-9

SCHER adopted this opinion at its 25th plenary on 9 September 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.

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.

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ACKNOWLEDGMENTS

The rapporteur is acknowledged for his valuable contribution to this opinion:

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Keywords: SCHER, scientific opinion, risk assessment, Regulation 793/93, propan-1-ol, human health, CAS 71-23-8

Opinion to be cited as:

SCHER, scientific opinion on the risk assessment report on propan-1-ol, human health part, CAS 71-23-8, 9 September 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 human health part of the RAR is of good quality, it is transparent and comprehensive, and the exposure and effects assessment follow the Technical Guidance Document (TGD). SCHER, however, disagrees with some conclusions of the RAR on effect assessment because of insufficient justification. The RAR covers most available studies relevant for exposure and hazard assessment of propan-1-ol, but lacks two case reports on propan-1-ol intoxication (Blanchet et al. 2007; Vujasinovic et al. 2007). These case reports, however, do not influence the conclusions of the RAR.

3.2 Specific comments

3.2.1 Exposure assessment

Propan-1-ol is a high production volume chemical that is mainly used as a solvent for a wide variety of chemical industry applications, such as formulation of disinfectants, pharmaceuticals, cleaning products, paints, coating materials, printing inks and cosmetics. It is also used as an intermediate for production of n-propylacetate, n-propylformiate and reactive resins. In addition, propan-1-ol is notified as an active substance within the scope of the Biocide Directive 98/8EC.

Occupational exposure to propan-1-ol takes place by inhalation and through the skin, but for consumers oral exposure is also possible from mouth hygiene products.

Occupational exposure assessment of propan-1-ol was carried out for six scenarios: (1) production of propan-1-ol and further processing as an intermediate, (2) preparation of formulations, (3) use of paints, (4) use of cleaning formulations, (5) use of printing inks, and (6) use of disinfectants. Highest exposures are estimated for scenarios 3 and 4. In order to establish reasonable worst case (RWC) exposure levels the RAR uses mainly measured data for inhalation exposure assessment and, due to lack of measured data, EASE modelled data for dermal exposure assessment. SCHER agrees with these approaches.

Consumer exposure by inhalation was assessed for six scenarios: (1) use if disinfectants, (2) use of household cleaners, (3) use of paints, (4) use of hardener solutions, (5) use of wall paper removers, and (6) cleaning of kitchen floor. Highest estimates were for scenario 1. Inhalation exposure was estimated using CONSEXPO program for calculating the means per event and the averages per year. The mean per event value tends to overestimate the exposure, because it refers to the personal volume, which is only of

relevance during working and does not take into account the declining exposure after active use of the product. Therefore this value was only used for characterization of acute risks. Dermal exposure was estimated for the use of cosmetics and for the use of disinfectants using formulas presented in TGD. The SCHER agrees with these approaches.

3.2.2 Effect assessment

Limited amount of toxicokinetic data is available on propan-1-ol, and there is no data on systemic bioavailability of propan-1-ol after inhalation or dermal exposure. Based on human data on ethanol and butan-1-ol the RAR estimates that the bioavailability of propan-1-ol is within the range of 30-76% after inhalation exposure. Considering the uncertainties the RAR uses bioavailability of 75% as an RWC assumption for risk characterisation. Considering the physicochemical properties of propan-1-ol and the available gastrointestinal bioavailability data the RAR assumes 100% absorption through dermal and oral route for risk characterisation. SCHER agrees with these estimates.

The RAR concludes that the acute toxicity of propan-1-ol after oral, inhalation and dermal exposure is low. The compound is not corrosive and the findings do not justify classification as skin irritant, but based on repeated exposure trials in humans the RAR proposes classification with R66 (Repeated exposure may cause skin dryness or cracking). The outcome of eye irritation studies results in classification as “Xi, Irritant” and labelling as R41 (Risk of serious damage to eyes). Propan-1-ol is not skin sensitizer. SCHER agrees with these conclusions.

Availability of repeated dose toxicity studies with propan-1-ol is very limited, and the database includes no studies carried out according to the OECD Guidelines. Moreover, no acceptable repeated dose studies with inhalational or dermal exposure are available. Therefore the RAR proposes conclusion i)[1] with regard to 90-day inhalation study in rats. SCHER agrees with this conclusion.

The database for genotoxicity of propan-1-ol is limited and there are no valid studies on bacterial or mammalian cell mutagenicity, or in vivo genotoxicity. There are some positive findings in the bacterial mutagenicity tests and increased frequency of chromosomal aberrations was reported in rat bone marrow cells in vivo. Overall, the results are inconclusive due to deficiencies in study design and inadequate reporting. The RAR concludes that there is no relevant concern with respect to mutagenicity and that propan-1-ol should not be classified as a mutagen. SCHER is of the opinion that the available database on genotoxicity of propan-1-ol is insufficient to justify the conclusion on lack of concern for mutagenicity, and proposes therefore conclusion i) for this endpoint.

No valid carcinogenicity studies with propan-1-ol are available. However, increased incidences of malignant liver tumours, myeloid leukaemia and a variety of benign tumours were observed in a published lifetime study in rats with twice weekly oral dosing of propan-1-ol at 240 mg/kg bw but with an insufficient number of animals. Although clearly inconclusive, these data raise some concern about possible carcinogenic potential of propan-1-ol. The RAR concludes that the risk assessment for carcinogenicity cannot be performed, but because of negative results of mutagenicity studies carcinogenicity should not be an endpoint of concern. SCHER disagrees with this conclusion due to insufficient justification.

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[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.*

No guideline studies are available for the assessment of reproductive or developmental toxicity of propan-1-ol, and the RAR uses inhalation exposure studies published in peer-reviewed literature. Fertility studies indicated that exposure of male rats to propan-1-ol during spermatogenesis results in severely impaired fertility at the highest exposure level of 7000 ppm (17460 mg/m^3) 7 h/day for 6 weeks (LOAEC 17460 mg/m^3, NOAEC 8730 mg/m^3). Using this LOAEC, a rat respiratory rate of 0.8 l/min/kg and assuming that 100% of the inhaled propan-1-ol is systemically absorbed during the 7 h exposure period the RAR calculates that the systemic exposure associated with impaired male fertility is 5800 mg/kg/day. On the basis of this estimate the RAR concludes that impaired male fertility is observed at so high exposure level that classification and labelling as toxic for reproduction is not justified.

SCHER disagrees with this conclusion for the following reasons:

- First, the current classification and labelling criteria are based upon the presence of a hazard rather than a risk, and therefore should not be driven by the exposure level.
- Second, SCHER acknowledges the high exposure levels in the fertility study, but points out that because of the high vapour pressure of propan-1-ol the air concentrations in workplaces can be high. The 90th percentile of the 8 h TWA representing the RWC for the occupational scenario 3 is only 18 times lower than the NOAEC of this study. Accordingly, the risk characterisation of propan-1-ol uses reproductive and developmental toxicity as the critical endpoint of toxicity that results in conclusion iii) for several exposure scenarios.
- Third, the assumption of complete systemic absorption of propan-1-ol from the inhaled air during the 7 h exposure period is likely to overestimate the systemic exposure in the fertility study. The 100% absorption also contradicts the risk assessment itself, because the conclusion of the toxikokinetics section proposes 75% absorption. Moreover, the estimated daily exposure level is so high that on the basis of acute oral toxicity data it should have resulted in mortality.

Developmental toxicity studies revealed developmental defects in foetuses at the two higher exposure levels (LOAEC 17460 mg/m^3, NOAEC 8730 mg/m^3, 7 h/day on gestational days 1-19). Also in this case the RAR does not consider classification and labelling justified because of high estimated systemic exposure levels. For the same reasons as above SCHER disagrees with this conclusion of the RAR.

3.2.3 Risk characterisation

Risk characterization uses the margin-of-safety (MOS) approach for inhalation and dermal exposures of workers and for inhalation, dermal and oral exposures of consumers.

Regarding several occupational exposure scenarios the RAR proposes conclusion iii) for respiratory depression as well as local effects related with repeated dose toxicity by inhalation and dermal exposure, fertility impairment by inhalation, dermal and combined exposure, and developmental toxicity by inhalation and combined exposure. For repeated dose toxicity by inhalation, dermal and combined exposure the RAR proposes conclusion i).

Regarding consumer exposure scenarios the RAR proposes conclusion iii) for oral exposure to mouth hygiene products, and aggregated exposure to mouth hygiene products, cosmetics, disinfectants and general cleaning products because of concern for fertility impairment and developmental toxicity. Conclusion iii) applies also for sensory irritation.

The RAR also points out that in several cases scientifically sound risk assessment is not possible due to limitations of data, and therefore the results of requested studies may influence the outcome of risk characterisation. SCHER agrees with these conclusions.

4. LIST OF ABBREVIATIONS

EASE	Estimation and Assessment of Substance Exposure
LOAEC	Lowest Observed Adverse Effect Concentration
MOS	Margin of Safety
NOAEC	No Observed Adverse Effect Concentration
RAR	Risk Assessment Report
RWC	Reasonable worst case
TGD	Technical Guidance Document
TWA	Time-Weighted Average

5. REFERENCES

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