Scientific Committee on Health and Environmental Risks

SCHER

Risk Assessment Report on Vinyl acetate

Human Health Part

CAS No.: 108-05-4
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The SCHER adopted this opinion at its 26th plenary on 17 November 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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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 very detailed and of good quality; the risk assessment methods used are in compliance with the requirements of the Technical Guidance Document. The most relevant studies and publications are included in the RAR. The SCHER generally agrees with the conclusions made in the RAR.

As described in the RAR, vinylacetate (VA) is a very special compound in that it is genotoxic, induces tumours in 2 animal species at localizations relevant to man. This would require classification as a Category 2 carcinogen. IARC has concluded that there is inadequate evidence in humans for the carcinogenicity of acetaldehyde and that there is sufficient evidence in experimental animals and has classified VA as possible carcinogenic to humans (Group 2B). Instead, the RAR proposes classification as a category 3 carcinogen and labelled as R 40. In September 2007 the TCC&L agreed on this classification and labelling.

This is based on the overall conclusion, that the critical events in vinyl acetate carcinogenesis do fit to the criteria for the exceptional cases where genotoxic action is thought to be thresholded. The RAR refers to the revised chapter 4.13.3 of the Technical Guidance Document on Risk Assessment, Human Health Risk Characterisation, which defines two general cases where mutagenicity may be shown to have a threshold: The RAR refers to the case, where the toxicokinetic considerations clearly demonstrate that mutagenic metabolites will only be produced in vivo at very high exposures to the parent substance which are unlikely to be achieved in realistic human exposure scenarios. The SCHER notes, that this does not apply for VA, because the mutagenic metabolite acetaldehyde is formed even at exposure levels relevant to humans (see below).

Moreover, although the SCHER agrees not to classify VA as a Cat 2 carcinogen, it has to be pointed out, that classification of VA as a Cat. 3 carcinogen is not in accordance with the criteria for classification of carcinogens. At present these are hazard based and do not consider exposure. The deviation should have been clearly indicated in the RAR.

3.2 Specific comments

3.2.1 Exposure assessment

VA monomer is solely used as an intermediate in chemical industry for manufacturing (polymerisation) of vinyl acetate (co)polymers. These polymers are ingredients of a variety of products, which are applied in the manufacture of adhesives, paints, fillers, coating materials, plasters and primers for porous building materials in the construction industry and in finishing agents.

Workplace exposure to VA monomer may result from releases during production of the substance, polymerisation of the monomer, compounding operations involving the polymers, and eventually use of the end products.

There is no direct consumer use of vinyl acetate monomer. However, consumer exposure may result from the use of polymerized vinyl acetate products containing very small amounts of residual monomer such as binders and additives for paints and plasters, glues (e.g. for carpets or structural members), and coatings.

Three scenarios have been identified to estimate occupational exposure: Production and polymerisation, manufacturing of formulations, and use of formulations. Reasonable worst-case exposure estimates via inhalation revealed 3.0, 14.6, and 2.6 mg/m^3, respectively. For the use of suitable gloves low levels of daily dermal exposure are to be expected. Since no measurement results are available, a protection efficiency of 90 % is taken as a default value leading to an exposure level of 42 mg/person/day. However, the short retention time of vinyl acetate on the skin leads to considerably lower dermal exposures than predicted by the EASE model.

For consumers the sum of all types of exposure resulting from residual monomeric vinyl acetate (reasonable worst case) is estimated to be in the range of 5 to about 20 microg/kg bw/d.

The indirect exposure to humans through food, drinking water and air estimated as a worst case scenario revealed a maximum daily intake in the vicinity of a VA production facility of 36 microg / kg bw, whereas the general background exposure is 2.47 E-03 microg / kg bw. In both cases about 90% of the exposure is via air.

The SCHER agrees with the exposure assessment as proposed in the RAR.

3.2.2 Effect assessment

The SCHER agrees with the Member State's Rapporteur on the key health effects of VA (acute toxicity; skin, eye and respiratory tract irritation; repeated dose toxicity and developmental toxicity). The SCHER also agrees that there is no need for labelling VA as a skin sensitizer (R 43). Furthermore no embryo/fetotoxic or teratogenic effects are to be expected as there is no indication of increased endogenous acetaldehyde level during VA exposure.

The SCHER also agrees with the proposed NOAEC of 50 ppm (178.5 mg/m^3) for long term exposure, based on effects on the respiratory tract in rats and mice.

Target organs of repeated VA exposure include the nasal cavity upon inhalation and the gastrointestinal tract upon oral application.

In prokariotic cell systems in vitro (Salmonella mutagenicity test, SOS chromotest) no mutagenic potential was found. On incubation with eukariotic cells dose-dependent effects such as chromosomal aberrations, sister chromatid exchange and micronuclei are observed. Evidence for the occurrence of DNA cross-links was obtained after incubation of very high concentrations of vinyl acetate with human lymphocytes. Under in vivo conditions no stable DNA adducts were found. After single intraperitoneal injections of 1000 or 2000 mg/kg body weight to mice, a weak increase in the micronucleus count in bone marrow cells was found. In the same experiment no micronuclei were found in the

male germ cells (spermatids). The SCHER agrees that this does not warrant classification as a germ cell mutagen.

In 2-year drinking water studies with F344 rats and BDF_1 mice, tumours of the oesophagus and oral cavity (rats, mice) and stomach and larynx (mice) were induced at the highest concentration of 10,000 mg/l.

In 2-year inhalation studies in rats and mice at VA concentrations of 50, 200 or 600 ppm VA affected the upper and lower respiratory tract only. At 200 ppm or more, atrophy, regenerative processes, inflammation and metaplasia in the olfactory epithelium, and basal cell hyperplasia were found in both species. Similar changes were found in the bronchial and bronchiolar airways of rats and mice at 600 ppm. The following NOAELs were obtained: local effects: 50 ppm in rats and mice; systemic effects (end point reduced body weights): 200 ppm in rats, 50 ppm in mice. In the olfactory epithelium of rats papillomas and carcinomas were found, in the respiratory epithelium inverted papillomas. In mice no tumours were found, but irritation of the nasal epithelia was observed.

A large part of the RAR discusses the mechanism by which VA induces local tumours after oral and inhalation exposure.

VA is carcinogenic at portals of entry: the nasal cavity and upper gastrointestinal tract. Following inhalation and oral exposure vinyl acetate is rapidly hydrolysed by carboxylesterases leading to the formation of acetic acid and acetaldehyde which is further converted into acetic acid in the presence of aldehyde dehydrogenases. Intracellular aldehyde dehydrogenase activity is limited, at higher concentrations of vinyl acetate it will not be sufficient for the oxidation of generated acetaldehyde. As a consequence, high vinyl acetate concentrations result in non-physiologically high concentrations of acetaldehyde. Acetaldehyde is a physiological intermediate with low background concentrations. Its adverse effects (genotoxicity and mutagenicity) are limited to non-physiologically high concentrations. Therefore, a threshold mode of action is assumed for vinyl acetate. Above threshold concentrations, cytotoxicity, mitogenic actions and genotoxic actions occurred.

Overall, the SCHER supports the conclusion that the carcinogenic potential of VA is expressed only when tissue exposure to acetaldehyde is high and when cellular proliferation is simultaneously elevated. This mode of action suggests that exposure levels, which do not increase intracellular concentrations of acetaldehyde will not produce adverse cellular responses. As long as the physiological buffering systems are operative no local carcinogenic effect by VA should be expected at the NOAEL for histological changes in respiratory rodent tissues of 50 ppm.

However, the SCHER disagrees with the assumption presented in the RAR that local levels at 50 ppm VA or below are of no carcinogenic risk, although the risk may be negligibly low as has been indicated by SCOEL (2005). Even the RAR correctly describes that acetaldehyde is a genotoxic carcinogen.

3.2.3 Risk characterisation

On the background of cancer risks and repeated dose toxicity, air concentrations of VA at the workplace should be controlled to a level in the range of 17.6 mg/m^3 (critical exposure level). The SCHER agrees to this proposal and refers to the SCOEL, which has proposed an OEL of 5 ppm (17.6 mg/m^3). SCHER also supports conclusion iii) for repeated dose toxicity after inhalation for scenario 2 (manufacturing of formulations and products) to reduce air concentration to the OEL of 5 ppm.

The RAR comes to conclusion iii) for the endpoint of carcinogenicity after dermal contact.

The SCHER disagrees with this conclusion, because there is no indication that VA can cause skin tumours. Instead SCHER propose conclusion ii) for occupational scenarios regarding dermal exposure.

For consumers and men exposed indirectly via the environment, the SCHER agrees with conclusion ii) for acute and repeated exposures.

4. LIST OF ABBREVIATIONS

EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties
IARC	International Agency for Research on Cancer
NOAEC	No Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Level
OEL	Occupational Exposure Limit
RAR	Risk Assessment Report
SCOEL	Scientific Committee on Occupational Exposure Limits
TCC&L	Technical Committee on Classification and Labelling
VA	Vinyl Acetate

5. REFERENCES

SCOEL (2005) Recommendation from the Scientific Committee on Occupational Exposure Limits for Vinyl Acetate. October 2005