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SCHER

Opinion on

"Risk Assessment Report on Phenol Human Health Part"

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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

The human health part of the document is comprehensive and covers all relevant exposure routes and potential adverse health effects following acute and chronic exposure. The evaluation is based upon both experimental animal and epidemiological studies.

Human exposure to phenol is based upon three main scenarios, occupational exposure based upon inhalation and dermal contact in 3 different occupational settings, and consumer exposure. Consumer exposure is based upon inhalation and dermal contact with waxes and cleaners, and the use of cosmetics. Information on occupational exposure for waxes and cleaners, professional cleaners, is missing. Human exposure indirectly via the environment was also evaluated for oral and inhalation exposure.

Hazard identification

Signs and symptoms of acute toxicity in man and experimental animals are similar regardless of the route of administration. Phenol caused severe chemical burns and influenced the nervous system. However large interspecies differences in sensitivity were observed.

Chronic exposure to phenol has shown effects on the nervous system and liver (humans and animals) and on the haematopoietic and immune system (animals).

Genotoxicity

No information on the genotoxicity of phenol in humans is available.

Phenol is not mutagenic in the vast majority of bacterial reverse mutation tests. It can, however, cause chromosome aberrations and induce micronuclei in mammalian cells both in the absence

and in the presence of metabolic activation. Phenol induced sister chromatid exchanges, unscheduled DNA synthesis, and DNA strand breaks *in vitro*.

In vivo, phenol induced slightly increased frequency of bone marrow micronuclei at myelotoxic doses in mice (100-300 mg/kg bw i.p.), whereas tests in rat a similar high doses were negative. This high dose effect in mice may suggest that the effect is due to overwhelmed metabolic inactivation or to hyperthermia. Significant phenol-induced hypothermia was generally associated with the dose levels at which positive results were found in the micronucleus studies, and it was therefore hypothesized that the micronuclei were not due to a direct mutagenic effect of phenol, but were secondary to low body temperature which could result in an inhibition of spindle function with disturbance of the mitotic apparatus and resulting aneuploidy. The presence of kinetochores in micronuclei from phenol-treated mice (300 mg/kg bw, single i.p. dose) was indeed demonstrated in a recent study (Spencer at al., 2004) and provides evidence for the disruption of the spindle apparatus which could be linked to hypothermia and for which a mutagenic threshold could be assumed (it is noted that no group of phenol-treated animals maintained at normal body temperature was investigated, and that no dose-response experiments were performed to support the hypothesis).

Other indicators for in vivo genotoxicity were inconclusive, e.g. no DNA adducts lack of LacZ mutations (HSE, 1999).

For the oral route of exposure a threshold for mutagenicity could further be assumed because of the rapid detoxification of any active phenol metabolites in vivo following ingestion and because of the negative findings in the oral carcinogenicity studies. However, metabolites of phenol like catechol and hydroquinone were shown to be clastogenic, and there is at present no data available to support a mutagenicity threshold for other routes of exposure (inhalation, dermal).

Concerns regarding the *in vivo* mutagenicity of phenol therefore still remain. Data from germ cell studies *in vivo* are inadequate.

The SCHER therefore supports the RAR's conclusion, that phenol should be regarded as an *in vivo* somatic cell mutagen. Because the possibility of a direct mutagenic effect cannot be excluded on basis of the currently available data, thus conclusion i)[1] would be warranted for mutagenicity for workers and consumers.

Carcinogenicity

Epidemiology data are inadequate and were generally confounded by co-exposure to carcinogens. No conclusion could be drawn from a nested case-control study on respiratory cancer of workers

[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.

exposed to phenol due to co-exposure by pesticides.

In a 2-years carcinogenicity study on F344 rats and B6C3F1 mice (NIH, 1980), phenol was administered via drinking water (2500 or 5000 ppm, equivalent to a dose of 200 and 450 mg/kg bw/d for rats and 281 and 375 mg/kg bw/d for mice). An increased incidence of leukaemia, pheochromocytoma and c-cell carcinomas was reported in male rats treated with the lower dose but not in high-dose rats or in mice or female rats. Phenol was a promoter of mouse skin carcinogenesis in two-stage protocols. A medium-term dermal study in a transgenic mouse model did not give any indication on treatment-related proliferative responses.

Recently, elevated levels of phenol and its metabolite hydroquinone in the human body have been hypothesized to be associated with leukaemia (McDonald et al., 2001). It is further noted that phenol has been shown to inhibit topoisomerase II, and that secondary leukaemia has been reported from topoisomerase II-inhibitor drugs (Felix, 1998).

SCHER disagree with conclusion ii) for genotoxicity and carcinogenicity in the RAR.

Considering the fact that a direct mutagenic action cannot be excluded from the available data, the SCHER considers that conclusion iii) is warranted for workers and consumers for carcinogenicity.

3.1. Exposure assessment

For the risk assessment purposes the rates of oral and inhalation absorption were assumed to be 100%, whereas for dermal exposure the rate was set to 80%.

In workers, the exposure was assessed in three different scenarios, and a sub-scenario. The internal body burden was based upon ambient air levels and using standard physiological parameters and dermal exposure is assessed with the EASE model. The body burden following inhalation exposure has been validated using urinary phenol as a biomarker. The exposure was assessed individually for the two routes of exposure and the combined body burden. Contribution via oral route was not considered.

Relevant oral exposure has not been assumed for consumers. Consumer exposure excurses during the application of floor waxes, polishes and disinfectants, inhalation and dermal contact. Furthermore, dermal contact occurs during the use of cosmetics. Yearly average dose rates by inhalation were estimated to be 0.48 mg/kg bw/d for women and 0.7 mg/kg bw/d for children (10 years). Dermal exposure was estimated to be 0.44 mg/kg bw/event and 0.3 mg/kg bw/d for use of waxes etc and cosmetics, respectively.

Indirect exposure for phenol via the environment occurs during oral intake via plant shoot and drinking water. Exposure at two different scenarios were estimated to be 0.0464 mg/kg bw/d (point source) and 1.5x10-4 mg/kg/bw/d (regional sources), respectively. Levels of phenol in ambient air at both scenarios were considered too low to be of any concern.

3.2. Risk characterization

LOAEL for oral administration was based upon a mouse study on sub-acute toxicity; for inhalation N(L)OAECs were used for local effects, based upon a rat study, and systemic effects based upon human data; for dermal exposure the NOAEL for both systemic and local effects was

derived from a rabbit study. The appropriateness for using N(L)OAEC for human risk is questionable.

MOS values were estimated for both acute and chronic dermal and inhalation exposure, and local and systemic effects. Most of the MOS calculated for the occupational exposure are small.

SCHER agrees with the recommendations:

iii) for combined dermal and inhalation exposure during the formulation and use of phenolic resins using spraying techniques for both acute and repeated exposure.

iii) for repeated inhalation exposure and systemic effects for workers employed with the production and further processing of phenol resins.

Due to its extreme corrosive properties, conclusion iii) was recommended for single dermal exposure and contact to the eyes.

SCHER agrees that all other occupational exposure scenarios and effects should be classified ii).

For consumer exposure, SCHER agrees with conclusion in the RAR), that there is no concern for acute toxicity following oral and dermal exposure. However, due to the corrosive properties of phenol, SCHER agrees with the RAR that conclusion iii) is justified for direct skin and eye contacts. SCHER also agrees with conclusion iii) for chronic dermal and inhalation exposure and systemic effects.

SCHER agrees that all other exposures and effects should be classified ii).

For indirect exposure via the environment the intake was mainly via consumption of plant shoot and drinking water. SCHER agrees with conclusion iii) for oral exposure at the local scenario and conclusion ii) for all other scenarios and route of exposures.

4. REFERENCES

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McDonald TA et al. (2001) Hypothesis: Phenol and hydroquinone derived mainly from diet and gastrointestinal flora activity are causal factors in leukemia. Leukemia 15, 10-20.

Health and Safety Executive (HSE) (1999) Phenol: Induction of LacZ-mutations in tissues of treated Muta-TM mice. Covance Laboratories Ltd. Report No. 501/2-D5140 (August 23)

Spencer PJ et al. (2004). Potential for phenol to disrupt the spindle apparatus as evaluated in the mouse bone marrow micronucleus test (MNT). Toxicologist 78(1-S), p. 29.

5. LIST OF ABBREVIATIONS

EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties
LOAEL	Lowest Observed Adverse Effect Levels

MOS	Margin of Safety
N(L)OAEC	No (Low) Observed Adverse Effect Concentration
NOAEL	No Observed Adverse Effect Levels
RAR	Risk Assessment Report
TGD	Technical Guidance Document

6. ACKNOWLEDGEMENTS

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