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SCIENTIFIC COMMITTEE ON HEALTH AND ENVIRONMENTAL RISKS

SCHER

Opinion on

"Risk Assessment Report on Anthracene Human Health Part"

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Adopted by the SCHER
during the 9th plenary of 27 January 2006

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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 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 most of the studies relevant for exposure and hazard assessment of anthracene. The exposure assessment is focused on the production and use of isolated anthracene. The SCHER underlines that there are numerous other sources of exposure for this compound, and the total human exposure is likely to be larger than that used in the risk assessment.

The RAR proposes the following conclusions:

Workers

Conclusion iii[1]) for dermal phototoxicity

The SCHER agrees with this conclusion.

Conclusion ii) for systemic toxicity

The SCHER agrees with this conclusion.

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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.*

Conclusion i) for measured exposure data and testing to determine the developmental toxicity of anthracene.
The SCHER agrees with this conclusion, but points out that the conclusion i) should also be applied for the reproductive toxicity of anthracene.

The RAR proposes to waive the previous conclusion, and supports this proposal as follows:

"This substance has not been fully tested for reproductive toxicity and consequently this risk assessment does not evaluate the risks to any human populations for this endpoint. The need for a developmental toxicity study to fill this data gap has been identified following OECD 414 (Prenatal developmental toxicity study). However, this risk assessment describes the situation in the EU in 2003, in which there is only one production site in the EU, with 99% of production volume exported outside the EU and only a very minor use in pyrotechnics. There are no consumer exposures to the commercially-produced substance and human environmental exposures are very low. The potential for worker exposure using modelled estimates is low, and limited measured data and control measures, known to be applied at the production site, indicate that the model predictions are probably over-estimates.

On this basis, and taking into account that a) the developmental toxicity of PAHs is at least partly dependent on binding to the Ah receptor, and b) anthracene does not show such binding to any significant extent, the Technical Meeting agreed that there may be grounds on exposure considerations to waive the requirement on the producer to generate such a study, as long as the exposure situation did not change. Further measured exposure data for workers involved in anthracene production from anthracene oil, anthracene packaging and anthracene use in the manufacture of pyrotechnics, would of course increase the level of confidence in this decision. The situation should be closely monitored and if there are any indications that production and use patterns are changing the potential for increasing exposure should be reconsidered and the need to request a developmental toxicity study revisited."

Consumers

The SCHER agrees with Conclusion ii) of the RAR

Man exposed directly via the environment

Conclusion ii)

The SCHER agrees with this conclusions.

The opinion of the SCHER applies for the production and industrial use of the commercial product anthracene.

3.1. Specific comments

Based on Council Regulation 793/93 the RAR assesses human health risks associated with production and use the commercial product anthracene. In addition, the RAR includes also an assessment of production and use of anthracene as part of complex mixtures in coal tar and coal tar derived products, but this is included only for illustrative purposes.

3.1.1. Exposure assessment

Exposure assessment related to manufacture and use of commercial anthracene is based on three occupational scenarios, (1) the manufacture of anthracene from anthracene oil, (2) anthracene packing, and (3) production of pyrotechnics. Additionally, an exposure scenario for anthracene during coal tar distillation is presented for illustrative purposes. Because for most exposure situations no measured data are available, the RAR uses EASE modelling derived exposure estimates for risk characterization. Because EASE tends to overestimate vapour concentrations of chemicals with low volatility (such as anthracene), the used values are likely to be overestimates. Consumer exposure and exposure of the general population via the environment are estimated to be insignificant.

3.1.2. Effects assessment

3.1.2.1. General toxicity, reproductive and developmental toxicity

The toxicology of anthracene is described in detail in the RAR and the conclusions are mainly supported by the toxicology data. The quality of original data is highly variable as a part of the studies are old and poorly reported. Moreover, some areas of the effects assessment are inadequately covered. For example, no inhalation toxicity studies are available, of the repeated dose toxicity studies only one 90-day study in mice has been carried out according to the current standards, and no reproductive and developmental toxicity studies are available. Based on the available data anthracene is a phototoxic compound, and it has a low potential for acute and subchronic toxicity. The SCHER agrees with the conclusion of the RAR in that new data on developmental toxicity of anthracene are needed. However, the SCHER disagrees with the RAR in that lack of effects on organ weights and histopathology of gonads in the 90-day subchronic study in mice would adequately demonstrate a lack of reproductive toxicity of anthracene. Therefore the SCHER concludes that new data on both reproductive and developmental toxicity are needed (conclusion i).

3.1.2.2. Genotoxicity

This chapter, though well written, presents a selection of studies to the reader with mostly negative results. The document would, therefore, benefit from a tabular overview of the relevant studies, including those with positive results (for instance, those reported by the US NTP), and a more thorough discussion on why the positive findings were discredited. It should also be mentioned, that information on genotoxicity of anthracene in humans was unavailable.

Anthracene was not mutagenic in the majority of bacterial reverse mutation tests, but positive results have been reported in single strains in the Ames test, and in the mouse lymphoma assay. It was tested negative for forward mutations in Chinese hamster V79 cells and human lymphoblastoid cells, and no chromosomal aberrations were induced *in vitro*. Equivocal results were obtained in tests for sister chromatid exchanges. Anthracene did not induce DNA damage in CHO and HeLa cells, or in rat hepatocytes.

In vivo, anthracene did not induce micronuclei in peripheral blood lymphocytes of mice 24 h after 4 daily administrations of up to 2500 mg/kg bw/day or in the bone marrow of mice 96 h after a single dose of 344 mg/kg bw. No chromosomal aberrations, sister chromatid exchanges or unscheduled DNA synthesis were induced in bone marrow cells of mice treated with

intraperitoneal injections of anthracene. It was tested negative in the *Drosophila* SLRL test, but positive in the SMART test.

Negative results were reported for most cell transformation tests (in BALB/3T3 cells, guinea pig foetal cells, Syrian hamster embryo cells and mouse embryo cells).

The SCHER supports the member state rapporteur's conclusion that anthracene is not genotoxic and the conclusion (ii) for this endpoint.

3.1.2.3. Carcinogenicity

No reliable information was available on the carcinogenicity of anthracene in humans. Most of the animal data was generated before 1980, and is therefore not up to current standards.

Two tumours (one liver sarcoma, one uterine adenocarcinoma) were found in a group of 28 BDI or BDIII rats that were fed a total dose of 4.5 g anthracene with the diet over 78 weeks and observed until natural death (Druckrey and Schmähl, 1955; Schmähl, 1955). No control group was used.

No evidence of dermal carcinogenicity was found in mice in a series of old studies, all flawed either by low number of animals and/or poor documentation (Kennaway, 1924a,b; Pollia, 1939; Wynder and Hoffman, 1959). There was also no clear increase in the incidence of skin tumours in mice using protocols investigating the skin tumour initiating activity (LaVoie *et al.*, 1979, 1985; Salaman and Roe, 1956; Scribner, 1973). Contradictory results were obtained when anthracene was applied to the skin followed by exposure to UV radiation or visible light. A high incidence of skin tumours was found in mice 5-8 weeks after the start of treatment with 10% anthracene followed by either UV radiation alone or with exposure to visible light (Heller, 1950; no information on purity and dose of anthracene or on the duration of treatment). By contrast, the incidence of skin tumours was not increased in a study by Forbes *et al.* (1976), in which hairless mice received daily topical applications of 4 g anthracene, followed by UV radiation for 2 h, for 38 weeks, and in a limited study by Miescher (1942), using 5% anthracene, followed by UV radiation for 40 or 60 min.

No lung tumours were observed in 60 rats one year after receiving a single lung implant of 0.5 mg anthracene (approximately 2 mg/kg) dissolved in a 1:1 mixture of beeswax and trioctanoin (Stanton *et al.*, 1972). Implants of pellets containing 4-20 mg anthracene into the cerebrum, cerebellum, or eye of nine rabbits did not induce gliomas 20 and 54 months after implantation (Russell, 1947).

The SCHER agrees with the member state rapporteur interpretation that "the available data do not provide evidence of carcinogenicity for anthracene alone or in combination with light" and the conclusion (ii) for this endpoint.

3.1.3. Risk characterization

Risk characterization for systemic toxicity via all routes of occupational exposure uses the NOAEL of 1000 mg/kg/day based on lack of effects at the highest dose tested in the 90-day study in mice. Considering systemic absorption of 50% this corresponds to a daily body burden of 500 mg/kg. The calculated MOS for combined inhalation and dermal exposure are all >1000, even when using the modelled conservative exposure estimates.

Risk characterization for dermal phototoxicity uses a human LOAEL of 25 µg/cm^2 derived from a single dose phototoxicity trial in healthy volunteers, as well as a more realistic NOAEL of 14 ng/cm^2 (LOAEL 140 ng/cm^2) based on a well-reported dose-response study in guinea pigs. The modelled occupational exposure levels are substantially higher than the NOAEL justifying the conclusion iii).

4. LIST OF ABBREVIATIONS

EASE	Estimation and Assessment of Substance Exposure Physico-chemical properties
LOAEL	Lowest Observed Adverse Effect Levels
MOS	Margin of Safety
NOAEL	No Observed Adverse Effect Levels
PAHs	Polycyclic Aromatic Hydrocarbons
RAR	Risk Assessment Report
TGD	Technical Guidance Document

5. REFERENCES

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6. ACKNOWLEDGEMENTS

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