EUROPEAN COMMISSION

Health & Consumer Protection
Directorate-General

Scientific Committee on Health and Environmental Risks

SCHER

Risk Assessment Report on Alkanes, C_{14-17}, chloro

MCCP

Human Health Part

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Scientific Committees
on consumer products
on emerging and newly identified health risks
on health and environmental risks

The SCHER adopted this opinion at its 21st plenary on 15 January 2008

About the Scientific Committees

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.

In addition, the Commission relies upon the work of the European Food Safety Authority (EFSA), the European Medicines Evaluation Agency (EMEA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

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Questions relating to examinations of the toxicity and ecotoxicity of chemicals, biochemicals and biological compound whose use may have harmful consequences for human health and the environment.

In particular, the Committee addresses questions related to new and existing chemicals, the restriction and marketing of dangerous substances, biocides, waste, environmental contaminants, plastic and other materials used for water pipe work (e.g. new organics substances), drinking water, indoor and ambient air quality. It addresses questions relating to human exposure to mixtures of chemicals, sensitisation and identification of endocrine disrupters.

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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 document is of good quality and very comprehensive. The exposure and effects assessment follow the TGD.

MCCPs cover mixtures of alkanes with 14 to 17 carbon atoms and different degrees of chlorination. The degree of chlorination typically ranges from 40 - 63 % for different MCCPs as given in Chapter 1. MCCPs used in toxicological studies were sometimes outside this range (e.g. Darnerud and Brandt, 1982; Erikson and Darnerud, 1985). This information is missing in Chapter 1. Furthermore there is no information on chain length distribution for C14 to C17.

3.2 Specific comments

3.2.1 Exposure assessment

The current production capacity of the medium-chain chlorinated paraffins is 45,000 - 160,000 tonnes/year. The main use is as secondary plasticiser in PVC. Further they are used as metal working fluids, paints and varnishes, adhesives/sealants, flame retardants, leather fat liquors, carbonless copy paper.

Occupational exposure may occur during manufacture of these products.

Measurements of MCPP concentrations in the air were available for several workplaces. As MCCPs are viscous liquids with very low vapour pressures, measured concentrations in the air were below 0.1 mg/m^3 for most workplaces. Higher concentrations were found for spraying (up to 0.19 mg/m^3). As several processes in the production of PVC operate in excess of 100°C vapour may be formed which condenses to form mist. Measurements from these workplaces give a maximum value of 1.2 mg/m^3. Higher values were also obtained during the use of metal working fluids, where aerosols may be created by mechanical agitation. Reasonable worst case 8h TWA values of 2.4 mg/m^3 were determined for oil based metal working fluids, whereas the values for water based metal working fluids were considerably lower. Values obtained by use of EASE were higher than those from the exposure measurements.

Measurements on dermal exposure were only available for the use of metal working fluids, from which exposure to chlorinated paraffins was derived using boron as a marker for MWF contamination. It is not explained in the report, why boron serves as a marker.

The study by Semple et al. (2005) was chosen because it provided the largest available set of information and represents exposure data from workers without using protective gloves. From experience and the observations of other authors it was believed that gloves are not commonly worn in these work situations and they may not be consistently worn throughout the work shift. For water-based MWFs a dose of 180 mg/day of MCCP was derived and for oil-based 25,000 mg/day. The references, however, are missing in the list of references. The EASE prediction is by a factor of 10 lower than the measurements.

For all other scenarios EASE has been used to predict dermal exposure. EASE gives exposure of up to 1 mg/cm^2/day resulting in doses of up to 420 mg MCCP/day for the different scenarios.

MCPPs are not sold directly as consumer products, but they are found in materials, to which consumers could be exposed, such as leather, adhesives and sealants, rubber, plastics and paints, and metal working fluids. Exposure from most applications has been considered as negligible and no exposure estimates have been given. SCHER agrees with this approach. For the use of metal working fluids and wearing of leather clothes worst case exposure concentrations of 0.5 mg/event and 1 mg/day have been derived.

The EUSES model has been used to estimate concentrations of MCCP in food, air and drinking water. For the uptake into root crops from soil the exposure assessment was based on a study with carrots, which gave a bioaccumulation factor of 0.045, which is considerably lower than the factor obtained using TGD/EUSES defaults. The resulting exposure values were 0.032 mg/kg/day for local and 2.6 x10^{-4} mg/kg/day for regional exposure.

Measurements were available for breast milk giving a 97.5th percentile level of 130.9 µg/kg fat to be used in the risk assessment, while for cow's milk the value was 63 µg/kg fat.

Combined exposure was not considered relevant as consumer exposure is an infrequent event rather than repeated daily exposure. SCHER agrees with this conclusion.

3.2.2 Effect assessment

Toxicological studies have been performed with mixtures of different chain length distribution and degree of chlorination. In the introduction it is stated that no qualitative differences in effects have been found in toxicological studies including also chlorinated paraffins of shorter chain length (SCCP), which have been evaluated in an earlier EU RAR. Therefore read across from one MCPP to the other or from SCCP to MCCP has been performed. SCHER supports such an approach. However, SCHER considers the justification insufficient, because no comparison of the physicochemical and toxicological data of different MCPP and SCPP is given to prove the similarity.

Based on a valid in vitro study a dermal absorption of 1 % was derived in a worst case approach. SCHER agrees with this value. SCHER also agrees with 50% absorption for the oral route and for inhalation. Following repeated dietary administration, retention in fatty tissues occurs and it is also found in some human breast milk samples. As metabolites glutathione derived conjugates have been detected and CO_2 is formed, depending on the degree of chlorination. Elimination occurs via the faeces, via exhaled CO_2 and to a limited extent in the urine.

The acute oral toxicity of MCCPs is very low, with no deaths occurring at doses up to 15000 mg/kg bw. MCCPs have only low skin and eye irritating potential and they lack skin sensitisation potential.

The liver (weight increase, enzyme induction, centrilobular hepatocyte hypertrophy, necrosis at higher dose levels), thyroid (follicular hypertrophy and hyperplasia, increased TSH levels, decreased T4 levels) and kidney (increased weight, chronic nephritis, tubular pigmentation) are target organs for repeated oral dose toxicity of MCCPs in rodents.

Overall, from a 90 days study with rats a NOAEL of 23 mg/kg/day was identified based on effects in the kidney. SCHER agrees with this NOAEL.

The MCCPs did not show genotoxicity in bacterial test systems and in mouse bone marrow micronucleus tests. Absence of genotoxicity in eukaryotic test systems in vitro was assumed by cross reading from the SCCPs and it was concluded that MCCPs are not genotoxic.

No carcinogenicity studies are available on the MCPPs. Therefore cross reading from SCCP has been performed, which causes liver, thyroid and kidney tumours in rats. The liver and thyroid tumours were considered as of little relevance to human health due to their species specific mode of action, i.e. peroxisome proliferation in the liver in rats but not in humans and lower T_4 binding capacity in the blood in rats compared to humans. While SCHER accepts the species specificity for the liver, for the thyroid this is considered rather a quantitative than a qualitative difference. For the kidney tumours, a detailed mode of action analysis has been performed, which is acknowledged by SCHER. According to this analysis, for the kidney tumours a mode of action different from α2u-nephropathy could not be completely ruled out, which would indicate relevance for humans.

It was concluded that for classification no cross reading from the SCCPs with respect to carcinogenicity is possible. For hazard identification and for risk assessment, however, cross reading was performed. Therefore the risk characterization for the carcinogenicity endpoint was conducted using the same NOAEL of 23 mg/kg bw/day identified for repeated dose effects on the kidney in rats. A NOAEL approach was chosen due to the lack of genotoxicity. It is not clear to SCHER, why the distinction for classification on the one side and hazard and risk assessment on the other side has been made. Furthermore, the arguments for a non genotoxic mode of action are not sufficient, as there may be specific activation mechanisms in the kidney.

In studies on developmental toxicity with rats and rabbits no embryotoxic or teratogenic effects of MCCP have been detected, and there were also no effects on fertility.

However, severe effects (internal haemorrhaging and deaths) have been observed in newborn rats. The maternal NOAEL for this effect was 47 mg/kg/day. Several studies have investigated the mode of action for this effect and it seems to be due to a MCCP mediated deficiency of vitamin K in the dams´ milk and to effects of MCCP itself in the milk on the pups. Also in the dams, haemorrhages were found at parturition with a NOAEL of 100 mg/kg bw.

There was discussion, whether this effect in newborn rats is rather a developmental effect than repeated dose toxicity, because the development during the neonatal period of rats corresponds to the development period during the last trimester of human pregnancy. As a consequence classification for developmental toxicity was proposed by a minority of member states. SCHER does not share this view. As described in the RAR, the effect in the rats does not occur in uterus, as there is sufficient supply of vitamin K from the dams. It can be assumed that the same holds for humans. However, the severity of the effect has to be considered in the risk assessment.

3.2.3 Risk characterisation

The NOAEL of 23 mg/kg bw/day from a 90 days study has been used for the risk assessment for repeated dose toxicity and carcinogenicity. There are no studies with longer duration. Due to the accumulating properties it is probable, that the NOAEL in studies of longer duration than 90 days would be considerably lower. For effects mediated via lactation the NOAEL of 47 mg/kg bw/day from the 1-generation study has been applied. Again, the NOAEL might be lower after longer application. Further, the severity of this effect has to be considered in the risk characterisation. This might lead to

conclusion iii)[1] instead of conclusion ii for some work place scenarios for repeated dose toxicity.

Conclusion iii) was reached due to high dermal exposure for the use of MCCP in oil-based metal working fluids in relation to repeated dose toxicity, carcinogenicity, effects via lactation and effects at the time of parturition.

For consumers, indirect exposure via the environment, and risks from physicochemical properties conclusion ii was reached. SCHER agrees with these conclusions.

4. LIST OF ABBREVIATIONS

MCCP	Medium-Chained Chlorinated Paraffin
MWF	Metal working fluid
MOS	Margin of Safety
NOAEL	No Observed Adverse Effect Level
PVC	Poly Vinyl Chloride
RAR	Risk Assessment Report
TGD	Technical Guidance Document
TWA	Time-Weighted Average
SCCP	Short-Chained Chlorinated Paraffin
TSH	Thyroid Stimulating Hormone
T4	Thyroxin

[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.*