



Scientific Committee on Health and Environmental Risks

SCHER

Copper, Copper II sulphate pentahydrate, Copper(I)oxide,
Copper(II)oxide, Dicopper chloride trihydroxide

Human health part

CAS No: 7440-50-8, 7758-99-8, 1317-39-1, 1317-38-0, 1332-65-6

EINECS No. 231-159-6, 231-847-6, 215-270-7, 215-269-1, 215-272-9



The SCHER adopted this opinion at its 24th plenary on 15 July 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 (EMA), the European Centre for Disease prevention and Control (ECDC) and the European Chemicals Agency (ECHA).

SCHER

Questions relating to examinations of the toxicity and ecotoxicity of chemicals, biochemicals and biological compounds 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.

Scientific Committee members

Herman Autrup, Peter Calow, Wolfgang Dekant, Helmut Greim, Wojciech Hanke, Colin Janssen, Bo Jansson, Hannu Komulainen, Ole Ladefoged, Jan Linders, Inge Mangelsdorf, Marco Nuti, Anne Steenhout, Jose Tarazona, Emanuela Testai, Marco Vighi, Matti Viluksela

Contact:

European Commission
Health & Consumer Protection DG
Directorate C: Public Health and Risk Assessment
Unit C7 - Risk Assessment
Office: B232 B-1049 Brussels

Sanco-Sc8-Secretariat@ec.europa.eu

© European Commission 2008

The opinions of the Scientific Committees present the views of the independent scientists who are members of the committees. They do not necessarily reflect the views of the European Commission. The opinions are published by the European Commission in their original language only.

http://ec.europa.eu/health/ph_risk/risk_en.htm

ACKNOWLEDGMENTS

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

Dr. Hannu Komulainen, National Public Health Institute, Department of Environmental Health, Finland

Keywords : SCHER, scientific opinion, risk assessment, Regulation 793/93, Copper, Copper II sulphate pentahydrate, Copper(I)oxide, Copper(II)oxide, Dicopper chloride trihydroxide, human health part, CAS No: 7440-50-8, 7758-99-8, 1317-39-1, 1317-38-0, 1332-65-6

Opinion to be cited as: SCHER, scientific opinion on the risk assessment on Copper, Copper II sulphate pentahydrate, Copper(I)oxide, Copper(II)oxide, Dicopper chloride trihydroxide, human health part, CAS No: 7440-50-8, 7758-99-8, 1317-39-1, 1317-38-0, 1332-65-6, 15 July 2008

TABLE OF CONTENTS

ACKNOWLEDGMENTS 3

1. BACKGROUND 5

2. TERMS OF REFERENCE..... 5

3. OPINION..... 5

 3.1. General comments 5

 3.2. Specific comments 5

 3.2.1. Exposure assessment 5

 3.2.2 Effect assessment 6

 3.2.3 Risk characterisation..... 8

4. LIST OF ABBREVIATIONS..... 8

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 Reports the SCHER is invited to examine the following issues:

- (1) Does the SCHER agree with the conclusions of the Risk Assessment Reports?
- (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 risk assessment (RA) is a Voluntary Risk Assessment (VRA) managed by European Copper Institute and reviewed by a Member State. The RA follows basically the Technical Guidance Document (TGD). Place to place the RA goes beyond the routine practice, on scientific basis. The deviations from the TGD have been justified in the risk assessment report (RAR).

The RAR is transparent and individual studies have been described in detail. The experimental effect data were ranked for quality according to the published criteria and more weight was put to studies fulfilling the formal guideline criteria.

The RA contains different copper compounds. Most effect data have been available for copper sulphate. In the absence of data for other compounds, data were read across when possible, in a conservative way. The SCHER agrees the approach. Free ionic copper was considered active and the bioavailability from other compounds is less than from copper sulphate.

Because copper is an essential element, the concentration of copper in the body is strictly and efficiently regulated. Copper is highly toxic if protective mechanisms are bypassed (i.v., i.p. dosing). Data based on oral, dermal and inhalation exposures are most relevant for RA.

The RA is overall of good quality and comprehensive.

3.2. Specific comments

3.2.1. Exposure assessment

Regarding occupational exposure, data for twelve industrial processes, from copper smelting to production of copper chemicals and other copper products (excluding biocides and pesticides) have been compiled from the recent period 1998-2006, from several industrial sites. Sources of exposure were further characterized by site visits, including dust measurements and particle size determinations in selected sites. Typical and reasonable worst case (RWC) exposures were determined via inhalation and dermal routes.

Inhalation exposure assessment was based on measured personal exposure data and included also acute inhalation exposure (short-term peak values) as a separate assessment. Use of respiratory protection equipment (RPE) was noted when having been used consistently. Some exposure data was corrected by correction factors for differences in samplers used for data collection which may be regarded at this step somewhat unusual. However, the corrections were justified.

About 80 % of copper (I) oxide and copper oxychloride particles are below 10 µm. The particle size of other copper compounds is larger. Over 80 % of the total workplace copper aerosols were reported to consist of particles larger than 10 µm. The fractional deposition of the compounds was predicted in the respiratory tract by a model and the data used for risk characterisation.

In the absence of dermal exposure data for copper, data on zinc (zinc oxide) was used by “analogous substance” principle for workers. The use of zinc data was justified by a similar industrial process of handling, dustiness and particle size with the most copper compounds and inadequacy of the EASE model in exposure assessment for hot metal processes. Since copper does not cause skin irritation and the dermal absorption is low, the approach may be regarded acceptable.

Altogether, the data indicate that workers engaged in the manufacture of copper compounds are exposed highest.

As to consumer exposure, typical and RWC external exposures were assessed/calculated for a number of consumer products (cigarettes, cosmetics and toiletries, hare care products, coins, jewellery, some paints, dietary supplements), also as a separate extra source (copper in cigarettes, coins, hare care products) for workers.

The human exposure via the environment was calculated both for local (inhalation exposure, exposure in food) and regional scenarios (water and food). Due to limited data, inhalation exposure was modelled by EUSES from stack emissions of copper refineries and smelters. Soil levels of copper were determined from continuous deposition of the last 10 years, modelled by EUSES and added to the regional background. Some true measured concentrations around smelters and refineries have been much higher than the modelled concentrations but they were omitted from the RA as uncertain data, without clear justification. As an estimation of dietary intake, additional external exposure was calculated from consumption of locally produced lettuce (as a surrogate of plants and vegetables). The calculation was presented as a RWC estimate but only the lower end of soil copper data was used without clear justification.

The regional exposure assessment was based on published literature. Separate estimates were made for acute and chronic effects in water. The combined exposure was calculated separately for general population and workers (on the top of occupational exposure). In the RAR, it remains unclear, which oral intake data was finally used in the RWC assessment in the regional scenario. The same summary table (by contents) is presented as estimated typical oral copper intake for children and adults (Table 4-70) and as 90P-RWC oral copper intake for children and adolescents (Table 4-72).

3.2.2 Effect assessment

The concentration of copper in the body is strictly and efficiently regulated by homeostatic mechanisms. Systemic effects ensue but the capacity of the homeostasis is exceeded. The major control mechanism is gastrointestinal absorption and biliary excretion into faeces. Liver has an important role in the maintenance of the copper homeostasis. The failure to maintain homeostasis may lead to adverse effects resulting either from deficiency or excess.

Copper deficiency causes more and far severe adverse health effects than copper toxicity.

Few data were available on inhalation absorption. For estimating absorption via inhalation, based on particle size distribution the deposition in different parts of the respiratory tract was modelled. For the pulmonary fraction 100 % was assumed, for the other fractions the value for absorption in the gastrointestinal tract was taken. This led to the assumption of an overall absorption of 14 %. For dermal absorption, 0.3 % was taken as the best estimate absorption factor from unpublished in vitro studies. For dry copper substances 0.03 % was used, as a default.

Copper absorption from the gastrointestinal tract is dose-dependent, decreasing with increasing dose. The absorption factors for oral exposure were drawn from true pooled fitted data (exposure-specific absorption). For animals, the average 25 % was used for all repeated dose studies, for humans the range was 60-30 %. The SCHER agrees with the approach. However, the functions used in calculation of the human absorption factor need more detailed description. What does each function represent and why the calculation is based on two functions? The mean of their (close) results was taken for risk characterisation.

The SCHER agrees with the classification of copper (I) oxide and copper oxychloride harmful after acute inhalation exposure (Xn, R20). A derogation of classification is proposed for copper (II) oxide and copper powder due to poor bioavailability, large particle size and low toxicity and for copper sulphate due to large particle size of the current products (d50 220 µm). This may be accepted, pertaining that products with smaller particle size will not come to market. Acute dermal toxicity of the compounds is low. SCHER agrees with the classification of the compounds harmful after acute oral exposure (Xn, R22).

Nausea and other gastrointestinal irritation effects due to high copper concentration in drinking water (leached from the distribution system, "corrosive" water) may be regarded as the main adverse effect in humans (a repeated acute effect). An external NOAEL 4 mg/l was derived for the gastrointestinal effect from human studies and may be accepted for RA. No data have been available on skin irritation in humans. The compounds have not caused skin irritation in animals. The SCHER supports the classification of copper (I) oxide and copper sulphate as eye irritants (Xi) but milder similar effects have been observed also with other compounds. Copper is not considered to cause skin sensitisation. Respiratory sensitisation is not known.

The repeated dose toxicity data is mainly based on copper sulphate but read across for other compounds. No relevant animal data have been available after inhalation and dermal exposure. After repeated oral dosing, liver, forestomach and kidneys are target organs of toxicity in rats. There is some indication in animals that daily ingestion of dietary copper causes tolerance to high doses.

Both human and animal data were available for assessment of systemic oral repeated dose toxicity. Proper dose-response data were available only in animal studies (feeding studies in rats and mice). Therefore, an external NOAEL, 16.3 mg Cu/kg/day, was derived from a feeding study in rats for risk characterisation and may be supported.

Copper (sulphate) has been negative in bacterial mutagenicity tests but has caused chromosome aberrations in mammalian cells in vitro, at high concentrations. Chromosome aberrations have been observed also in vivo after an i.p. administration but no genotoxicity after peroral administration. The assumed mechanism(s) of genotoxicity are generation of reactive oxygen species and/or inhibition of DNA-repair enzymes. The RA concludes that copper (sulphate) is not mutagenic. The proper conclusion would be that it is not mutagenic after peroral exposure (and evidently by other routes when the homeostatic mechanisms are not bypassed). The SCHER agrees that there is no need for classification of copper sulphate as mutagenic and that further testing of other copper compounds for genotoxicity is not required, as concluded in the RA.

Though no proper data exist to evaluate carcinogenicity of copper in animals, and the human data is limited, the SCHER agrees that carcinogenicity is not a concern for copper.

Excess risk of lung cancer has been consistently detected in copper smelters but the causative factor is plausibly arsenic in the ore.

The SCHER agrees that there is no need to classify copper for reproductive effects. Though severe developmental effects have been observed after an i.v. and i.p. administration in animals, specific developmental effects have not been detected below maternally toxic doses after peroral administration.

3.2.3 Risk characterisation

Adverse effects due to copper deficiency in animals and man have been described in the RAR qualitatively. No conclusive Deficiency Effect Level (DEL) was derived but dietary intake of 1 mg Cu/day has been shown to be sufficient to maintain the copper balance.

The risk characterisation for toxicity uses the margin-of-safety (MOS) approach. Internal (absorbed) dose (the sum of oral, inhalation and dermal dose, as relevant) and internal NOAELs were used for calculation. The use of internal dose(s) is a scientifically valid exercise for accurate assessment but is demanding, presumes comprehensive data and contains uncertainty in the form of absorption factors. Because rather much data have been available for copper, the selected approach and the MOSrefs may be accepted.

Regarding the risk characterisation for workers, the SCHER agrees with the conclusions made. The conclusion is generally ii)¹ except iii) for acute effects in production of copper powder and copper compounds and maintenance operations without RPE in melting and casting. The conclusion is also iii) for repeated dose effects in some sites of copper powder production. For the sites which have not provided data, i) was proposed.

The SCHER agrees with the conclusion (ii) regarding consumer exposure.

As to indirect exposure through the environment, copper in drinking water leached from the distribution system ("corrosive" drinking water) to cause acute effects seems to be the most common risk. The RA does not stress enough that point. Acute effect is a daily problem as far as the water contains excess copper. The calculated MOSs (5.6 for typical scenario, 1.9 for RWC) have lead to ii). Though SCHER accepts the ii), it notes that the margin of safety at high copper concentrations is low. The MOSs for other effects due to indirect exposure justify conclusion (ii).

Conclusion (ii) was reached for typical combined exposure of the general population (indirect and consumer exposure), and also for RWC using moderately corrosive drinking water in the assessment. The conclusion was (ii) also for workers (occupational RWC, typical consumer and typical indirect exposure) in other work scenarios than production of copper powder (iii), where the exposure is highest and site specific. For the reason (i) was recommended for the sites which have not presented exposure data. The SCHER agrees the conclusions for the defined scenarios but reminds again that in the worst case drinking water may be "corrosive" (high copper concentration) and alone cause an acute adverse effect regardless other exposures.

4. LIST OF ABBREVIATIONS

d50	Diameter of 50 % of particles
DEL	Deficiency Effect Level
i.p.	intraperitoneal

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.*

i.v.	Intravenous
MOS	Margin of Safety
MOSref	reference Margin of Safety
NOAEL	No Observed Adverse Effect Level
RA	Risk assessment
RAR	Risk assessment report
RWC	Reasonable worst case
TGD	Technical Guidance Document