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Derogation and classification proposals

for

acute inhalation toxicity

of

Copper powder

Copper oxide

Copper sulphate pentahydrate

EBRC Consulting GmbH
Zeppelinstr. 8
30175 Hannover
GERMANY

1. Introduction

The current draft of the Voluntary Risk Assessment on Copper and Copper Compounds lacks experimental data on the acute inhalation toxicity of Copper (II) oxide and Copper powder. However, in the meantime, an acute inhalation toxicity study on copper sulphate pentahydrate has recently been made available for inclusion in the VRA.

This document summarises the most relevant facts on the parameters relevant for the assessment of acute inhalation toxicity of copper sulphate pentahydrate, copper (II) oxide and copper powder.

Considering the available toxicokinetic data for various Copper compounds, the particle size distribution of these compounds in airborne matter, the fraction of material likely to become airborne under practical conditions of handling and use (based on dustiness testing), and by read-across from available acute inhalation toxicity data for "similar" Copper compounds, proposals for classification and for derogation from testing were derived for all three Copper compounds.

2. General aspects relevant for classification

This subchapter attempts to summarise relevant criteria for the investigation and evaluation of inhalation toxicity of a compound, and are designed to illustrate the "likeliness of exposure under normal handling and use":

(a) The investigation of acute inhalation toxicity is performed according to the requirements of the TGD by applying the test methods specified in Annex V of Directive 67/548/EEC and the assessment criteria of Directive 93/21/EEC. In Annex VI of Directive 93/21/EC it is expressly stated:

- the aim of a classification is the designation of all physico-chemical, toxicological and ecotoxic properties of a substance….., which may represent a hazard under conditions of normal handling and use (see introduction, 1.1)

(b) For the notification of new chemical substances, Directive 92/32/EEC (Annex VIIA) requires the submission of two acute toxicity tests. Apart from the mandatory oral study, a second route of administration needs to be tested in relation to the most likely route of human exposure. Apart from this, the Directive offers little support for the choice of the most suitable route of exposure.

(c) However, the TGD (2003) itself explicitly offers the following criteria for the choice of inhalation as the relevant route of administration for acute toxicity studies:

- significant vapour pressure of the substance (> 10^{-2} Pa at 20°C) or
- substance as used contains relevant amounts of particles in the inhalable size range
- relevant dust or aerosol formation occurs during handling of the substance.

All three Copper compounds under discussion in this document have negligible vapour pressure.

Particle size is considered to be an intrinsic feature of these compounds.

For all three substances, the subsequent chapters present detailed information on particle size and measures of the fraction of material likely to become airborne upon mechanical agitation under practical handling and use.

(d) The argument may be raised that for example copper sulphate is part of (pesticide) products that are intended for spraying in the agricultural setting, thus necessitating an interest for inhalation toxicity. However, this is not considered to represent a valid argument, for several reasons:

- such pesticide use is outside of the scope of the existing and new chemicals legislation, and of the voluntary risk assessment on copper, because it is dealt with in detail elsewhere; copper sulphate in these applications is in the form of formulated products, not as the pure substance itself.

- it is mandatory to investigate the inhalation toxicity when applying for the registration of a pesticide. This is by all means justified, since such pesticide formulations usually contain a multitude of formulating agents which may mediate toxicity by synergistic effects, or simply by making the substance more bioavailable etc.

- such spraying of dilute solutions/emulsions/suspension in aqueous media is absolutely incomparable to the potential exposure to (solid) crystalline copper sulphate itself.

3. Physico-chemical data and composition details relevant for classification

3.1 Physical particle size of Copper sulphate pentahydrate products as currently placed on the EU market

Apart from being the subject of a voluntary risk assessment under the EU Chemicals Directive, Copper sulphate is currently also subject to regulatory review under the Biocidal Products and the Plant Protection Products. In a recent survey (ECI, 2006), the following information on products size and market share was obtained from the largest producer of $CuSO_4 \cdot 5H_20$ chemicals in Europe. Copper Sulphate Pentahydrate is marketed in 6 different types and crystal sizes, as follows:

	Product Name	Description appearance	Size range (d50)	Market share (approx.)	User sector
1	"Big size"	large crystals (stones)	>50 mm	20%	agro sector, water treatment and other technical applications
2	"Grain size"	medium crystals (coffee beans)	>10 mm	15%	agro sector, fertilizers, and other technical applications
3	"Minute size"	small crystals (rice size)	>5mm	10%	mining industry, and other technical applications
4	"Snow technical grade"	microcrystals (sugar)	220 µm	15%	chemical industry, pharmaceutical, and other technical applications
5	."Snow F.F.G.", Free Flow.Grade	Microcrystals (sugar)	220 µm	35%	exclusively animal feed
6	"Snow H.P.G.", High Purity Grade	Microcrystals (sugar)	220 µm	5%	chemical-electronic applications (circuit boards)

The latter three types are all of similar dimension, and represent microcrystals below 750 microns. Any differences between products merely indicate the presence of an anti-caking agent (FFG), or refer to an especially pure product from selected raw materials (HPG). Products 4 and 5 are produced under the same technical conditions.

Product type 4 is the material that was extensively tested for dustiness and particle size (see subchapters 3.4.1 and 3.4.2, below), because it represents the finest size material that is placed on the market in the EU. The d50 was determined at 220 µm. Product type 5 material is produced under the same conditions, and can therefore be considered equivalent in size.

For Product type 6, a comparative dry sieve analysis was conducted (see table below), confirming the d50 (i.e. in the range between 200-300 µm) and very similar size distribution.

Sieve analysis	Type 4	Type 6
> 0,5 mm	0.8	0,6
0,5 mm - 0,4 mm	3.4	3.0
0,4 mm - 0,3 mm	21.7	18,1
0,3 mm - 0,2 mm	37.7	37,8
0,2 mm - 0,1 mm	26.4	30.0
0,1 mm - 0,05 mm	8.7	9.8
< 0,05 mm	1.3	0,7
Total	100.0	100,0

After conducting a survey of the $CuSO_4 \cdot 5H_20$ producing companies listed on the European chemical Substances Information System (ESIS), ECI has confirmed that those manufacturers that responded, do not place any material of a particle size finer than those listed in the table above on the EU market (ECI; 2006).

ECI is only aware of one producer in the US who for a specialised application provides a material ("instant powder grade") that is finely ground to size corresponding to a median physical particle diameter of approx. 1 µm. This material is <u>not</u> placed on the EU market.

3.2 Relative copper content

The following inorganic copper compounds are covered by the voluntary risk assessment:

Compound	Cu metal	Copper(II) sulphate pentahydrate	Cuprous(I) oxide	Copper(II) oxide	Copper oxychloride
Molecular formula	Cu	$CuSO_4.5H_2O$	Cu_2O	CuO	$Cu_2Cl(OH)_3$
Relative Cu content	100%	25%	89%	80%	60%

To be noted from this tabular summary is the fact that Copper sulphate particles contain a mere 25% of Copper, so that by comparison, the Copper powder or the Copper oxide upon ingestion or inhalation will deliver a 3-4-fold higher dose of Copper to any target organism.

4. Bioavailability considerations

4.1 Bioavailability upon ingestion

In chapter 4.1.2.1.2 (toxicokinetics, oral) the VRA on Copper describes the available studies on oral absorption, which are summarised here in abbreviated format:

- both in humans and in animals (rat), oral absorption of Copper is inversely proportional to the dose, which corresponds to its role as an essential trace element

- true human Cu absorption rates may be as high as 60% at low intake rates (0.007 mg Cu/kg bw/d[1]), but fall to approx. 25% when intakes increase to a range of 0.11 mg Cu/kg bw/d, with a similar tendency in rats

- in a comparative oral bioavailability study (Himmelstein, 2003) for several Copper compounds, the well-soluble Copper sulphate and the poorly soluble Copper (I) oxide were given orally at a dose of 20 mg Cu/kg bw/d. At this comparably high dose level, oral absorption rates for all tested compounds varied only in the range of 10.7 – 12.9%. Whereas this finding may be interpreted as a sign of similar availability at the chosen dose, it does not essential provide information on possible differences at lower, physiologically and practically more relevant uptakes.

- no such data of direct relevance for human health are available for Copper powder and Copper (II) oxide, but data from feeding studies in cattle, pigs and chicken clearly indicate a very limited bioavailability of the Copper (II) oxide compared to soluble forms (sulphate) of Copper.

- by comparison of the water solubilities (see subchapter 3.2 below) of Copper powder with the other compounds discussed here, the lack of solubility supports the assumption of a similarly low oral bioavailability as for Copper (II) oxide.

4.2 Bioavailability upon inhalation

In chapter 4.1.2.1.2 (toxicokinetics, inhalation) the VRAC derives inhalation absorption factors for several Copper compounds base don particle size-dependant deposition modelling, as summarised in table 4-7 of the document as follows:

Proposed inhalation absorption factors for copper compounds using particle size distribution data

Substance	CAS	rel. density [g/cm³]	D50 [µm] MMAD(1)	D50 GSD(1)	predicted fractional deposition			inhalation absorption(2) [%]
					ET	TB	PU	
Copper powder	7440-50-8	5.9	71.7	3.9	49.2	0.9	1.2	14
Copper (I) oxide	1317-39-1	6.3	9.9	3.3	67.5	1.4	3.8	21
Copper (II) oxide	1317-38-0	2.3	60.7	3.8	49.4	0.9	1.1	14
Copper (II) sulphate pentahydrate	7758-99-8	3.6	90.3	5.2	48.6	1.0	1.2	14
Dicopper chloride trihydroxide	1332-40-7; 1332-65-7	8.9	12.2	4.1	56.2	1.4	3.5	18

(1): MMAD/GSD values above the linear range of the model are reset by default to max. values of 20 µm and 4.0 (GSD); (2): rounded values

It may be assumed from the above data that the fractional deposition of Copper powder, Copper (II) oxide and Copper sulphate after inhalation of airborne matter is indeed quite similar, because of the comparatively large (aggregated) particles that are generated when these materials become airborne.

[1] For an adult weighing 70kg

4.3 Water solubility

Despite being a poor surrogate for bioavailability, water solubility is nevertheless often used to describe differences in potential bioavailability. For this reason, the water solubility data of Copper compounds as given in chapter 1.3 of the VRAC are presented below, choosing the pH closest to the neutral region in cases where pH-dependant data were available:

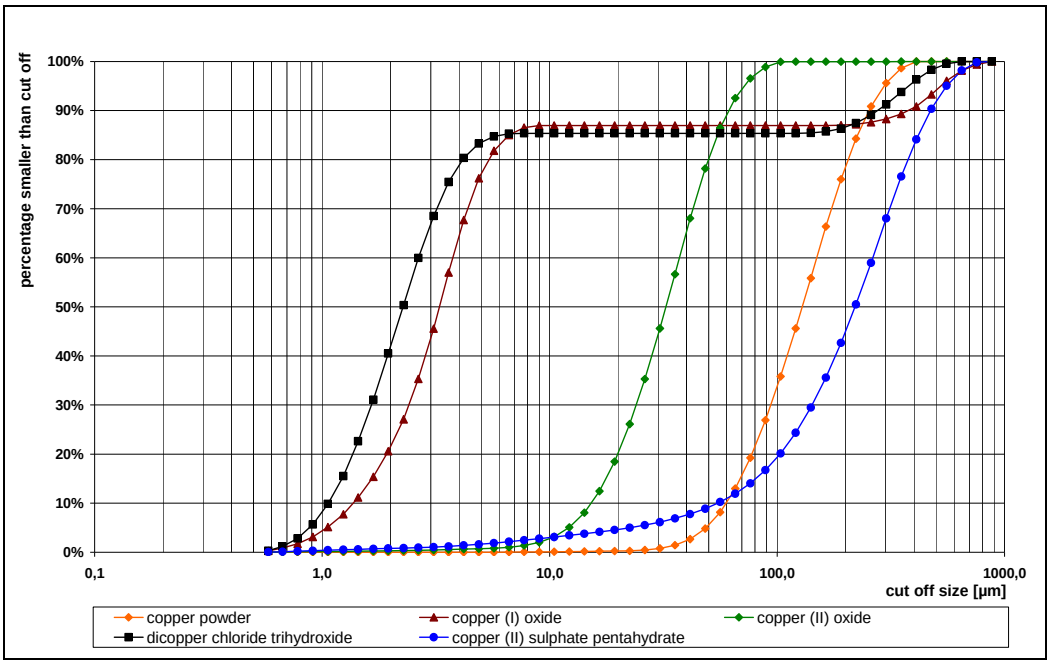
Compound	Water solubility [mg/L]	Remarks/exp. conditions
Copper sulphate pentahydrate	266,000	n.a.
Copper (I) oxide	> 6.39	20℃, pH=6.6
Copper oxychloride	> 1.19	20℃, pH=6.6
Copper (II) oxide	< 0.39	20℃, pH=6.0
Copper metal	insoluble*	*

(*): dissolution testing has yielded max. releases of Copper ions at levels below 0.3 mg/L

5. Particle size data

5.1 Physical particle size of commercially available copper compounds in comparison

The physical particle size distribution of copper compounds was determined with the aid of a dry dispersion technique and subsequent laser-diffraction measurement, in accordance with the guidelines OECD 110, CIPAC MT 187, and ISO13320-1, as presented in the following graph:



From the data above, it is evident that from all copper compounds tested, copper sulphate pentahydrate and copper powder have the largest particle sizes – their median physical diameters are one-hundred-fold larger than the two compounds classified as “harmful via inhalation”, namely Cu(I)oxide and Copperoxychloride. Even Copper (II) oxide exhibits a physical particle size one order of magnitude higher than the two substances classified as “harmful”.

However, the data presented above are merely an indication of the relative dimensions between the various compounds. They are not informative for the purpose of assessing inhalation hazard, because:

- physical particle size is not the determinant of deposition in the respiratory tract, but instead the aerodynamic diameter, which is linked to the physical diameter by the square root of the rel. density; in consequence, particularly for metal compounds of high rel. density, the aerodynamic diameter is much larger that than the physical diameter.

- finally, the data presented above reflect the total composition of the substance in question, but not the fraction that may become airborne – particles of a diameter of > 100 microns can are hardly be suspended in air long enough to become inhaled, and the inhalability of such particles is indeed very low.

As a consequence, the assessment of particle-size dependant inhalation deposition behaviour in the respiratory tract should be based on methods capable of measuring the relevant parameters (see section 3.4.2 below).

5.2 Particle size information relevant for inhalation toxicity assessment

In this context, it is noted that test guideline OECD 403 does not give recommendations on particle size, but draft OECD 433 with reference to SOT (SOT COMMENTARY, 1992: Recommendations for the Conduct of Acute Inhalation Limit Tests, Fundam. Appl. Toxicol. 18, 321-327) states: „*An aerosol with a mass median aerodynamic diameter (MMAD) between 1 to 4 mm and a geometric standard deviation (GSD) in the range of 1.5 to 3.0 is recommended because particles in this range allow exposure of the entire respiratory tract".*

In order to determine whether or not any of the copper compounds in question fulfil this recommendation and to which extent, and also to obtain a measure for the likely composition of airborne matter generated under conditions of "practical handling and use", the following measurements were performed:

<u>Dustiness and particle size testing according to the Heubach rotating drum method:</u>

It is generally recognised that physical particle size distributions have little bearing for the particle size distribution of a compound in an occupational setting. Instead, a variety of factors cause particle agglomeration under conditions of mechanical agitation of any such material, which are reflective of dry manipulation techniques such as bag filling or dumping, mixing, loading and weighing etc.

For this reason, tests according to the DIN norm 55 992 were performed in a rotating drum apparatus according to Heubach. In this test system, the test substance is mechanically agitated in a rotating drum, and the thus generated airborne material is transported from the chamber to a collecting device in a constant stream of air. Two experimental results are obtained from this:

- total dustiness: a parameter that describes the tendency of a particle to become airborne, and is expressed as the fraction of material [in mg/g] that will become airborne under conditions of mechanical agitation.

- particle size distribution: by collecting the material that becomes airborne under these conditions and sampling it with the aid of a cascade impactor, relevant particle size information and in particular a mass median aerodynamic diameter (MMAD) with its corresponding GSD can be determined as an input parameter for the modelling of inhalation deposition patterns.

A validation exercise of this approach with comparisons between dustiness-particle size measurements and actual workplace monitoring data for particle size distributions in zinc oxide and zinc chloride producing or consuming industries is available (Battersby & Boreiko, 2004).

Dustiness data:

Whereas the particle size distribution of various copper compounds under such conditions is presented in the graph further below, the following table gives total dustiness values for various copper compounds:

Compound	Copper (I) oxide	Copper (II) oxide	Copper (II) sulphate pentahydrate	Dicopper chloride trioxide	Copper powder	Zinc oxide
rel. density[(1)] [g/cm³]	5.87	6.32	2.29	3.64	8.9	5.6[(2)]
d50[(3)] [µm]	3.3	32.5	220.4	2.3	129.0	~1[(2)]
total dustiness[(4)] [mg/g]	7.07	363.71	48.75	33.36	45.57	30.1[(5)]

Sources: (1) ECI, producer data; (2) ZOPA; (3) Franke, 2004a-e; (4) Selck, 2004; (5) Armbruster, 2000
Data on zinc oxide included for purposes of comparison with Zinc oxide RAR.

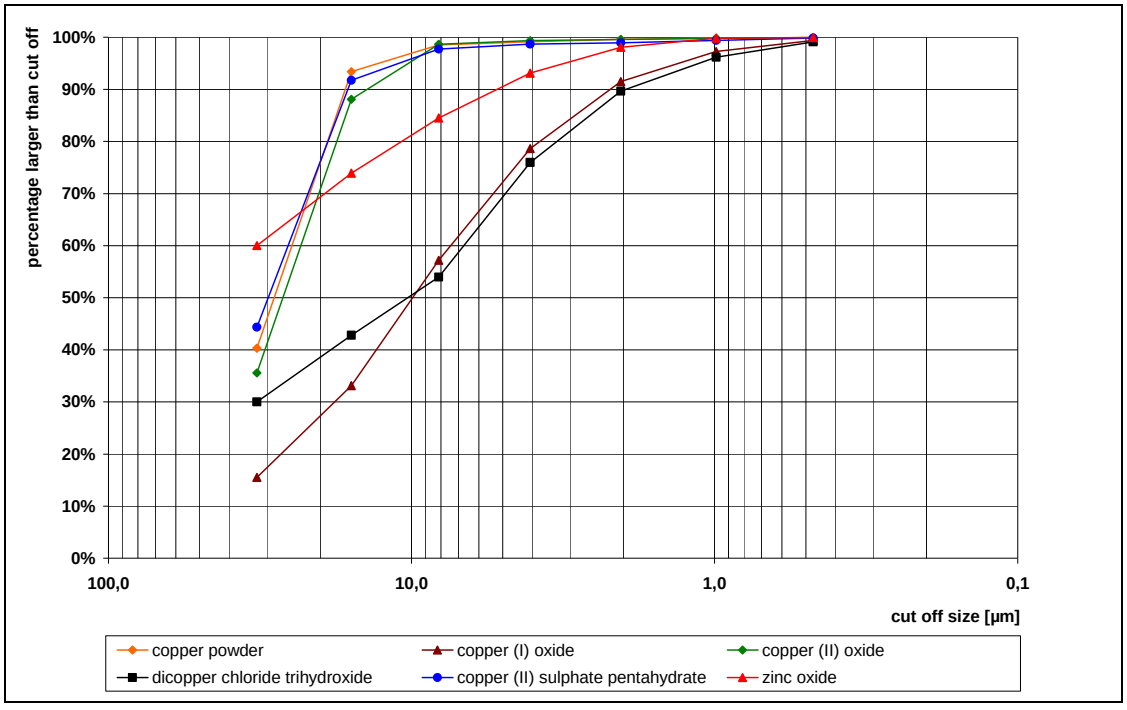
The data above can be interpreted in a way that under conditions of mechanical agitation, only a minor proportion of the materials will have the tendency to become airborne, whereas the remainder of the material will remain fairly immobile. In other words,

- of the total copper sulphate pentahydrate or copper powder present, less than 50 mg per 1000 mg, or in other terms only 5% of the material has the propensity to become airborne.

- for copper (II) oxide, this figure is higher at 36%.

Particle size data (airborne fraction):

The additional resolution of airborne particles in the dustiness test according to particle size with the aid of a multi-stage impaction device is presented in the following graph (zinc oxide merely shown for comparative purposes):



The particle size distribution curves clearly fall into two groups:

- copper(I) oxide and copperoxychloride: both compounds are known to be “harmful via inhalation”, and show a particle size distribution in the airborne fraction that contains a relevant proportion (>70%) of material in the range 1-4 µm, thus able to penetrate to the deep respiratory tract

- copper (II) oxide, copper powder and copper sulphate: all three compounds show a rather similar particle size distribution, with clearly less than 5% of the material capable of penetrating to the tracheobronchial and pulmonary region of the respirator tract, i.e. below 5% of an aerodynamic diameter of than 10 microns or less.

6. Toxicological data for inorganic copper compounds

Data on acute inhalation toxicity

In table 4-15 of chapter 4.1.2.2.1 (acute toxicity, inhalation), the available acute inhalation toxicity data are summarised, of which an extract only is presented here:

Identity	Particle size[b] (µm)	Species (strain)	Sex	LC_{50} value (mg/litre)	Study rating[c]
Copper (I) oxide (Nordox paint grade)	4.4-5.1	Rat (SD)	M+F	5.36	1
Copper (I) oxide (Nordox agro grade)	2.3-2.6	Rat (SD)	M F M+F	2.92 3.69 3.34	1
Copper (I) oxide	NR	Rat (SD)	M+F	>5	2
Copper (I) oxide (Spiess Urania paint grade)	NR	Rat (Wistar)	M+F	>30	2
Copper (I) oxide	NR	Rat	M	>200	3
Copper oxychloride	2.8	Rat (SD)	M+F	LC_{50} (1hr) >11.4	2
Copper oxychloride	3.23-3.65	Rat (SD)	M F M+F	2.83 >2.77 4.74	1
Copper sulphate pentahydrate[d]	1.6	Rat (SD)	M+F	>2.95*	2
Copper sulphate	NR	Hamster (Syrian)	M	n.d.	4
Copper sulphate	NR	Mouse (CD_1)	-	n.d.	4

NR not reported. n.d. not determined. ***a*** unpublished report ***b*** mass mean diameter ***c*** based on Klimisch *et al* (1997) ***d*** recently made available; *: maximum attainable concentration

When comparing the two studies leading to classification proposal as “harmful via inhalation” for copper oxychloride and copper I oxide, then the LC50 values from both tests are quite similar.

This can be explained by particle size considerations and MPPD modelling (see appendix), which yield similar deposition patterns and predicts that approx. 90% of the inhaled material is translocated to the GI tract, from which at this dose level Copper is assumed to be absorbed at a rate between 11 and 13 % (see chapter 3.2.1 above) irrespective of speciation, based on a comparative bioavailability study.

Data on acute oral toxicity

Substance	Reported test method	Species (strain)	Sex	LD_{50} value (mg/kg BW)	Study rating[b]
Copper (I) oxide	Annex V B.1	Rat (SD)	M+F	1340	1
Copper (I) oxide	Annex V B.1	Rat (SD)	M F M+F	1295 1209 1291	1
Copper (I) oxide (Nordox agro grade)	Annex V B.1 (tris); OECD 423	Rat (SD)	M+F	300-500 [c]	1
Copper (I) oxide	Annex V B.1	Rat (Wistar)	M+F	5400	2
Copper (I) oxide	NR	Rat (SD)	NR	>5000	3
Copper (I) oxide	NR	Rat	NR	470	4
Copper (II) oxide	Annex V B.1 (Fixed Dose)	Rat (SD)	M+F	>2500	1
Copper sulphate (pentahydrate)	Annex V B.1	Rat (SD)	M+F	482	1
Copper sulphate (pentahydrate)	Annex V B.1; OECD 401	Rat (SD)	F	666	1
Copper sulphate (anhydrous)	NR	Rat	NR	300	3
Copper sulphate (pentahydrate)	NR	Rat	NR	960	4
Copper oxychloride	US EPA 81-1	Rat (SD)	F M	950 1200	1
Copper oxychloride	Annex V B.1; OECD 401	Rat (SD)	M F M+F	1796 2006 1862	1
Copper oxychloride	Annex V B.1; OECD 401	Rat (SD)	M F M+F	1083 1854 1398	1
Copper oxychloride	Annex V B.1; OECD 401	Mouse (CD-1)	M+F	299	1

NR - not reported. ***a*** unpublished report ***b*** based on Klimisch *et al* (1997) ***c*** estimated range based on Fixed Dose method.

As a brief summary, the study results for copper sulphate, copper (I) oxide and copper oxychloride are consistent with a classification with “harmful via ingestion”.

In contrast, a study in Copper (II) oxide yielded an LD50 > 2000 mg/kg bw, thus requiring no classification.

Derogation from testing for copper powder has been based on poor solubility and a suggestion to read-across from copper (II) oxide.

7. Derogation and classification proposals

7.1 Copper (II) oxide

Copper (II) oxide has a low oral toxicity (LD_{50} > 2000 mg/kg bw), and a low water solubility (< 0.39 mg/L). Although toxicokinetic data in laboratory animals are not available for this compound, investigations in feeding trials with cattle, pigs and chicken indicate a very limited bioavailability compared to other Copper compounds.

Laboratory investigations on the propensity to become airborne suggest a moderate mobility (i.e., total dustiness measured at 364 mg/g). The particle size distribution of airborne matter shows a mass median aerodynamic diameter of more than 60 microns, based upon which the following deposition pattern in humans was derived (see also chapter 3.2.2 above): extrathoracic 49%, tracheobronchial 0.9%, alveolar fraction 1.1%. The corresponding prediction for the rat is given in the appendix, yielding a total deposition of 34%, with 33% deposited in the extrathoracic region, 0.4 % in the tracheobronchial region, and 0.4% in the alveolar fraction.

The following conclusions are drawn from the data presented in this document:

- Copper (II) oxide has a moderate (but not negligible) tendency to become airborne,

- however, based on particle size considerations (MMAD > 60 µm), more than 95% of the material deposited in the respiratory tract will be translocated to the GI tract shortly after inhalation, so that the acute toxicity will be determined by that of the oral route,

- Copper (II) oxide is assumed to have a low bioavailability, based on water solubility and on indicative data from animal feeding studies,

- it has an established low oral toxicity (LD_{50} > 2000 mg/kg bw).

It can therefore be concluded that the inhalation hazard of Copper (II) oxide is very low.

It is therefore proposed to derogate from animal testing.

In consideration of the arguments set forth above, a classification for acute inhalation toxicity is not required.

7.2 Copper powder

Copper powder has not been tested for acute oral toxicity, but by way of read-across from data on Copper (II) oxide and its extremely low water solubility (<< 1 mg/L) has been assigned a low oral toxicity, not requiring classification.

In analogy with Copper (II) oxide, a very limited bioavailability compared to other Copper compounds is similarly assumed.

Laboratory investigations on the propensity to become airborne suggest a very low mobility (i.e., total dustiness measured at 46 mg/g). The particle size distribution of airborne matter shows a mass median aerodynamic diameter of more than 70 microns, based upon which the following deposition pattern in humans was derived (see also chapter 3.2.2 above): extrathoracic 49%, tracheobronchial 0.9%, alveolar fraction 1.2%. The corresponding prediction for the rat is given in the appendix, yielding a total deposition of 34%, with 33% deposited in the extrathoracic region, 0.4 % in the tracheobronchial region, and 0.4% in the alveolar fraction.

The following conclusions are drawn from the data presented in this document:

- Copper powder has a negligible tendency to become airborne (i.e., less than 5%),

- based on particle size considerations (MMAD > 70 µm), more than 95% of the material deposited in the respiratory tract will be translocated to the GI tract shortly after inhalation, so that the acute toxicity will be determined by that of the oral route,

- Copper powder, in analogy to Copper (II) oxide and based on the extremely low water solubility, is assumed to have a low bioavailability,

- it is assumed to have a low oral toxicity (LD_{50} > 2000 mg/kg bw) by read-across from Copper (II) oxide.

It can therefore be concluded that the inhalation hazard of Copper powder is very low.

It is therefore proposed to derogate from animal testing.

In consideration of the arguments set forth above, a classification for acute inhalation toxicity is not required.

7.3 Copper sulphate pentahydrate

Copper sulphate pentahydrate has been tested several times for acute oral toxicity, with resulting LD_{50} values in the rage of 480 – 960 mg/kg bw, resulting in a classification as "harmful via ingestion". Similarly, the anhydrous form has yielded an LD_{50} of 300 mg/kg bw, in line with the slightly elevated relative copper content compared to the hydrate.

Only recently, an acute inhalation toxicity study on a superfine grade (physical particle size d50 approx. 1 µm[2]) copper sulphate pentahydrate has been made available. 5 male and 5 female rats were exposed for 4 hours to a dry aerosol at a maximum attainable concentration of 2.95 mg/L, of which one animal died during the study (day 7 post exposure).[3] The study report does not explicitly mention whether the exposure was full-body or nose-only, but the former can be assumed since in table 2 (page 11) of the study, it is stated that the fur of the test animals was coated with test material during the first five days.. This would imply that some ingestional intake on top of the inhalation exposure will have occurred. Finally, the test material is stated in the report to have been "sifted" prior to exposure. This type of material is not placed on the market in the EU.

The following characteristic properties of Copper sulphate may be summarised here:

- Copper sulphate pentahydrate has a low relative Copper content (25%, compared for example to Copper powder (100%), Copper (I) oxide (89%) and Copper (II) oxide (80%)

- the oral bioavailability of Copper sulphate in comparison to other Copper compounds at dose levels relevant for acute toxicity testing has been assessed as being similar, i.e. 11-13%

- laboratory investigations on the propensity to become airborne suggest a negligible mobility (i.e., total dustiness measured at 49 mg/g). The particle size distribution of airborne matter shows a mass median aerodynamic diameter of more than 90 microns, based upon which the following deposition pattern in humans was derived (see also chapter 3.2.2 above): extrathoracic 49%, tracheobronchial 1.0%, alveolar fraction 1.2%; in this context, it should be noted that the prediction range of the MPPD model is limited to an upper limit of 20 microns, so that the deposition stated here will be an overestimate; finally, particles of a size in the range of 90 microns hardly become airborne, let alone do they have an appreciable tendency to penetrate to the inhalation tract

- the corresponding inhalation deposition prediction for the rat is given in the appendix, yielding a total deposition of 34%, with 33% deposited in the extrathoracic region, 0.4 % in the tracheobronchial region, and 0.4% in the alveolar fraction

- technical considerations render inhalation toxicity testing of commercially available Copper sulphate pentahydrate as it is placed on the market in the EU technically unfeasible: the d50 physical particle size has been determined at 220 µm – thus, in order to make it deliverable for acute inhalation testing, it would have to be reduced in particle size by grinding it down by a factor of more than 100-fold, in order to achieve adequate amounts of particles in the size range 1-4 µm. Even when such micronised material was tested, the maximum attainable concentration was 2.95 mg/L, and only after the test material had previously been sifted presumably to increase the proportion of fine particles.

- without manipulation of particle size (i.e. by micronisation), more than 95% of inhalable Copper sulphate pentahydrate would be deposited in the extrathoracic region, and subsequently and rapidly translocated to the GI tract; however, only approx. 5% of the material present in commercial grades of this substance can at all become airborne

- toxicity from agents other than systemically available Copper cations is not to be expected: any Copper sulphate will deposit almost exclusively in the ET fraction, from where systemic absorption is unlikely to occur; absorption from this region is commonly extrapolated from dermal absorption data, which is known to be low (0.3%).

[2] Corresponding to an experimentally verified MMAD of approx 1.6 µm
[3] More details on study findings are reported in the VRA Copper Human Health Effects chapter (version August 2006)

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- given that Copper sulphate is only moderately irritant and not corrosive, any direct local action is also not anticipated

- the residual very low amounts of copper sulphate that may reach the tracheobronchial region based on the predictions set forth below may at first glance be subject to dissolution; however, any dissolution is effectively counteracted by the high carbonate content (50 mM) of airway fluids, so that any material that becomes available would be rendered insoluble as Copper carbonate

In conclusion, the acute inhalation toxicity of Copper sulphate pentahydrate when tested as a very fine powder is moderate: even with material of a physical particle size of approx. 1 µm, an LC_{50} of > 2.95 mg/L was observed. This concentration level was described as the maximum attainable concentration under the given conditions.

However, Copper sulphate pentahydrate as it is placed on the market in the EU has a lowest median particle size of 220 µm. Detailed particle size testing has shown that this material contains negligible amounts of material of inhalable size.

It is therefore proposed to derogate from animal testing, both on scientific grounds and for lack of technical feasibility.

In consideration of the data and arguments set forth above, a classification for acute inhalation toxicity is not required.

8. References

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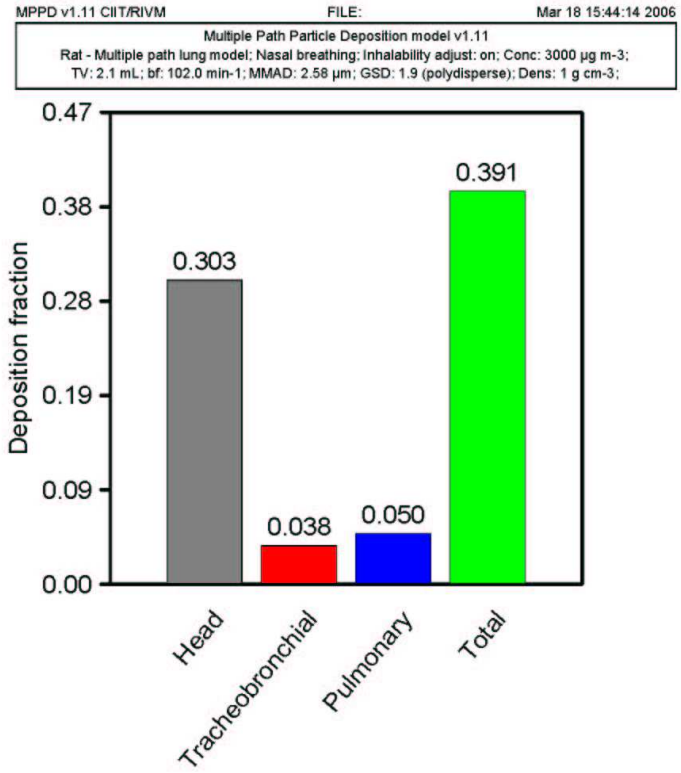
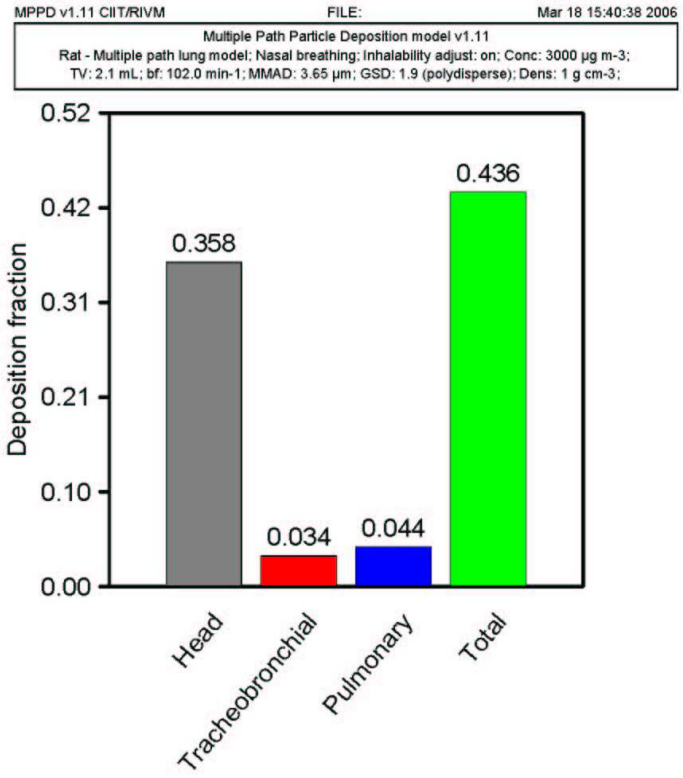
9. Appendix

MPPD model predictions based on MMAD values given in the study summaries of Blagden (2001) and Wesson (2003). For simplification, the model was run with default parameters, and an arbitrary exposure concentration of 3 mg/L (close to the LC50 in both studies) and the same GSD (1.9) for lack of reporting in the later study.

MPPD model run (rat) for Copper (I) oxide (Blagden, 2001)



MPPD model run (rat) for Copper oxychloride (Wesson, 2003)



MPPD model run (rat) for Copper compounds with MMAD > 20 µm
(upper limit of the model prediction range)