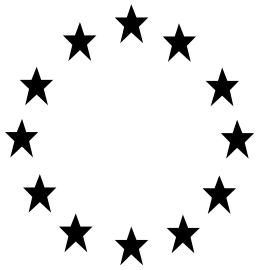
Directive 98/8/EC concerning the placing of biocidal products on the market

Inclusion of active substances in Annex I or IA to Directive 98/8/EC

Assessment Report



Copper (II) Hydroxide

Product-type 8
(Wood preservatives)

September 2011

Annex I - France

Copper (II) hydroxide (PT 8)

Assessment report

FINALISED IN THE STANDING COMMITTEE ON BIOCIDAL PRODUCTS AT ITS MEETING ON 22/09/2011 IN VIEW OF ITS INCLUSION IN ANNEX I TO DIRECTIVE 98/8/EC

CONTENTS

1 – STATEMENT OF SUBJECT MATTER AND PURPOSE

This assessment report has been established as a result of the evaluation of copper (II) hydroxide as product-type 8 (wood preservative), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market[1], with a view to the possible inclusion of this substance into Annex I to the Directive.

Copper (II) hydroxide (CAS no 20427-59-2) was notified as an existing active substance, by Spiess Urania, hereafter referred to as the applicant, in product-type 8.

Commission Regulation (EC) No 1451/2007 of 4 December 2007[2] lays down the detailed rules for the evaluation of dossiers and for the decision-making process in order to include or not an existing active substance into Annex I or IA to the Directive.
In accordance with the provisions of Article 7(1) of that Regulation, the Commission designated France as Rapporteur Member State to carry out the assessment of copper hydroxide on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for copper hydroxide as an active substance in product-type was 28 March 2004, in accordance with Article 9(2) of Regulation (EC) No 1451/2007.

On 29 March 2004, the French competent authority received a dossier from the applicant. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation, taking into account the supported uses, and confirmed the acceptance of the dossier on 30 September 2004.

On 19 February 2008, the Rapporteur Member State submitted, in accordance with the provisions of Article 14(4) and (6) of Regulation (EC) No 1451/2007, to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report. The Commission made the report available to all Member States by electronic means on 9 April 2008. The competent authority report included a recommendation for the inclusion of copper (II) hydroxide in Annex I to the Directive for product-type 8.
In accordance with Article 16 of Regulation (EC) No 1451/2007, the Commission made the competent authority report publicly available by electronic means on 9 April 2008. This report did not include such information that was to be treated as confidential in accordance with Article 19 of Directive 98/8/EC.
In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organised by the Commission. Revisions agreed upon were presented at technical and competent authority meetings and the competent authority report was amended accordingly.
On the basis of the final competent authority report, the Commission proposed the inclusion of copper (II) hydroxide in the Annex I of Directive 98/8/EC and consulted the Standing Committee on Biocidal Products on 22/09/2011.
In accordance with Article 15(4) of Regulation (EC) No 1451/2007, the present assessment report contains the conclusions of the Standing Committee on Biocidal Products, as finalised during its meeting held on 22/09/2011.

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[1] Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing biocidal products on the market, OJ L 123, 24.4.98, p.1

[2] Commission Regulation (EC) No 1451/2007 of 4 December 2007 on the second phase of the 10-year work programme referred to in Article 16(2) of Directive 98/8/EC of the European Parliament and of the Council concerning the placing of biocidal products on the market. OJ L 325, 11.12.2007, p. 3

Purpose of the assessment report

This assessment report has been developed and finalised in support of the decision to include copper (II) hydroxide in the Annex I of Directive 98/8/EC for product-type 8.

The applicant is not currently placing nano forms of copper hydroxide on the market. Therefore, the submitted dossier and the finalised assessment report don't cover potential nanoforms of this copper compound, should such forms exist.

The aim of the assessment report is to facilitate the authorisation in Member States of individual biocidal products in product-type 8 that contain copper (II) hydroxide. In their evaluation, Member States shall apply the provisions of Directive 98/8/EC, in particular the provisions of Article 5 as well as the common principles laid down in Annex VI.
For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report, which is available at the Commission website[3], shall be taken into account.
However, where conclusions of this assessment report are based on data protected under the provisions of Directive 98/8/EC, such conclusions may not be used to the benefit of another applicant, unless access to these data has been granted.

Overall conclusion in the context of Directive 98/8/EC

The overall conclusion from the evaluation is that it may be expected that there are products containing copper hydroxide for the product-type 8, which will fulfil the requirements laid down in Article 5 of Directive 98/8/EC. This conclusion is however subject to:

i. compliance with the particular requirements in the following sections of this assessment report,

ii. the implementation of the provisions of Article 5(1) of Directive 98/8/EC, and

iii. the common principles laid down in Annex VI to Directive 98/8/EC.

Furthermore, these conclusions were reached within the framework of the uses that were proposed and supported by the applicant (see Appendix II). Extension of the use pattern beyond those described will require an evaluation at product authorisation level in order to establish whether the proposed extensions of use will satisfy the requirements of Article 5(1) and of the common principles laid down in Annex VI to Directive 98/8/EC.

[3] http://ec.europa.eu/comm/environment/biocides/index.htm

2 – OVERALL SUMMARY AND CONCLUSIONS

2.1 General substance information/general product information

The main identity and the physical/chemical properties of Copper hydroxide are given in Appendix 1 (Listing of endpoints). The active substance shall comply with the specification given in Appendix 1 of this report.The evaluation has established that for the active substance notified by Spiess-Urania, traces of metals of toxicological concern (arsenic, cadmium and lead) were identified among the manufacturing impurities.

The applicant is not currently placing nano forms of copper hydroxide on the market. Therefore, the submitted dossier and the finalised assessment report don't cover potential nanoforms of this copper compound, should such forms exist.

2.1.1 Identity, physico-chemical properties of the active substance

The active substance as manufactured is copper dihydroxide $Cu(OH)_2$ (CAS-No. 20427-59-2) with a minimum purity of 96.5%. It is also known as copper (II) hydroxide or copper hydroxide. The active substance is cupric ion Cu^{2+}, released from copper hydroxide. Traces of metals of toxicological concern (arsenic, cadmium and lead) were identified among the manufacturing impurities.

The source of copper hydroxide submitted in the dossier is accepted. See the confidential part for the specifications. However, to confirm the data presented in the dossier, a new 5-batch analysis is required at the product authorization stage to check the compliance of current production to these specifications.

Copper hydroxide is a odourless light blue powder. It has a relative density of 3.98 and decomposes above 200°C before melting. It is not volatile (its vapour pressure has been theoretically assessed to be $< 1.0 \times 10^{-5}$ Pa). Solubility in water is pH dependant and increases with acidic concentrations due to release of cupric ion. It does not have any flammable, explosive or oxidising properties.

An adequate analytical method is available for the determination of copper. As the method was collaborately validated and is very widely used, limited validation data were accepted. It must be highlighted that methods of analysis for the relevant impurities were not provided and must be provided before the product authorization stage.

The analyses of copper in environmental matrices and body fluids and tissues are routinely performed in many laboratories. As these methods were collaborately validated and are very widely used, they were accepted but validation data must be provided before the product authorization stage.

2.1.2 Identity, physico-chemical properties of the biocidal product

The trade name of the biocidal product is “SPU-01860-F”. It contains 15.8% of copper hydroxide (10.3% of cupric ion).

The biocidal product is a dark lilac liquid with a fishy odour. Its pH is basic (pH = 10.9). It has a density of 1.128 g/mL. It has neither explosive nor oxidising properties. It has a flash point of 43°C and an auto-ignition temperature of 385°C.

An appropriate analytical method is available for the determination of Copper hydroxide in the biocidal formulation.

2.1.3 Intended use and efficacy

- **Field of use / Function/ Mode of action**

  - **Field of use**

Product type 8 (PT): wood preservative

Copper hydroxide is intended to be used as a preventive wood preservative for wood in Use class 1, 2, 3 4-1 as defined in the EN 335[4]

The active substance is restricted to industrial use only, in timber treatment plants operated by trained personnel. The representative biocidal product presented in this dossier (SPU-01860-F) is supplied as a liquid, water-miscible wood preservative concentrate and is applied by vacuum pressure or by dipping.

The representative biocidal product in this dossier (SPU-01860-F) is an amine copper product; copper hydroxide for wood preservatives is used solely in combination with other active substances. Therefore, no efficacy data with copper hydroxide as sole exist. The formulated concentrated wood preservative SPU-01860-F contains 10.3% copper and some QAV's.

The use concentration for vacuum pressure treatment proposed in the dossier is from 1% up to max. 4 % of the product SPU-01860-F in aqueous solution, and for dipping treatment from 5% up to max. 15% of the product SPU-01860-F in aqueous solution.

  - **Function**

The active substance Copper (II) hydroxide acts as a fungicide and as an insecticide use for preventive wood preservation (product type 8).

  - **Mode of action**

As the active substance is the Cu^{2+} ion, copper hydroxide is therefore described as the precursor to release of the cupric ion. As a consequence, most copper-containing formulations are described in terms of total copper.

Fungi:
It is considered that the fungicidal properties of copper compounds are dependent on the affinity of the copper ion (Cu^{2+}) for different chemical groups within cells, particularly thiol groups, resulting in the non-specific denaturation of proteins and enzymes. In addition, it is thought that the ion can interfere with the activity of the pyruvate dehydrogenase system inhibiting the conversion of pyruvate to acetyl CoA within mitochondria. Copper reacts with most essential elements within a cell. It also reacts with ligands on the cell surface and this can interfere with membrane function. Copper may also act extra-cellulary in the case of fungi and inhibit the production of fungal extracellular enzymes.

Insects:
Copper in toxic doses acts as a stomach poison.

- **Objects to be protected, target organism**

The fact is that no single active substance based wood preservative formulations are placed on the market because of the range of organisms to be controlled. As the exact composition of a formulation

[4] Since 2007 and the revision of the EN335-1, use classes had replaced hazard classes.

depends on the end use of the treated timber, a reading across of data had to be done in assessing the efficacy of the active substance.

Copper efficacy was examined for the following target organisms:

Application mode	**Target organism**	**Active substances rate**
Vacuum pressure timber impregnation and dipping	Fungi: Wood rotting basidiomycetes and soft rot fungi Insects: Wood boring beetles	Although the request of the applicant for a target concentration at 0.5 kg Cu^{2+}/m^3 (claimed in the dossier), **the evaluation based on the trials produced showed a minimum target concentration at 1.29 kg Cu^{2+}/m^3 sapwood loading (12.5 kg SPU-01860-F per m^3 wood) (EN113+EN84).** Please note that these data do not take into account the expected service life of wooden elements treated with copper based product and should be considered as an indicator only.

- **Resistance**

According to the data submitted, no development of resistance from the target fungi has been reported, knowing that there are strains of some species of wood destroying fungi that exhibit tolerance to copper. Additional biocides are used where necessary to control copper-tolerant strains of fungi.

According to the data submitted, the applicant, no formation of resistance has to be expected regarding target insects. There is no evidence of insects being naturally tolerant or being able to develop resistance to copper at the level of copper used for biocidal purposes in wood preservation.

2.1.4 Classification and labelling

On the basis of a review of the submitted data, the following classification and labelling is proposed:

- Active substance

Directive 67/548/EEC	
Class of danger:	T-Toxic, N-Dangerous to the environment
Risk phrases:	R22: Harmful if swallowed, R23: Toxic by inhalation, R41: Risk of serious damage to eyes R 50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Safety phrases:	S22: Do not breathe in dust S25: Avoid contact with eyes S 26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice S37/38: Wear suitable gloves and eye/face protection S45: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible) S57: Use appropriate container to avoid environmental contamination S60: This material and its container must be disposed of as hazardous waste S61: Avoid release to the environment. Refer to special instructions/safety data sheets
Regulation 1272/2008	
Classification and hazard statements	Acute Tox. 4/H302 – Harmful if swallowed Acute Tox. 3/H331 – Toxic if inhaled Eye Dam. 1/H318 - Causes serious eye damage Aquatic Acute/H400 – Very toxic to aquatic life Aquatic chronic/H410 - Very toxic to aquatic life with long lasting effects

- Biocidal product

Directive 67/548/EEC	
Class of danger:	Xn - Harmful, N - Dangerous to the environment
Risk phrases:	R10: Flammable R20/21/22: Harmful by inhalation, in contact with skin and if swallowed R37/38: Irritating to respiratory system and to skin R41: Risk of serious damage to eyes R50/53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Safety phrases:	S22: Do not breathe in dust S25: Avoid contact with eyes S 26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice S37/38: Wear suitable gloves and eye/face protection S45: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible) S57: Use appropriate container to avoid environmental contamination S60: This material and its container must be disposed of as hazardous waste S61: Avoid release to the environment. Refer to special instructions/safety data sheets
Regulation 1272/2008	
Classification and hazard statements	Flam; Liq. 3/H226 - Flammable liquid and vapour Acute Tox. 4/H302/312/332 - Harmful if swallowed / in contact with skin / if inhaled STOT Single 3/H335 - May cause respiratory irritation Skin Irrit. 2/H315 - Causes skin irritation Eye Dam. 1/H318 - Causes serious eye damage Aquatic chronic/H410 - Very toxic to aquatic life with long lasting effects

2.2 Summary of the risk assessment

2.2.1 Human health risk assessment

2.2.1.1 Hazard identification and effects assessment

Foreword

Copper is an essential metal for life and is employed in all human cells. The main daily dietary intake for copper in adults ranges between 1.5 and 3 mg/person/day of copper. Most human diets naturally include between 1 and 2 mg/person/day of copper, with some containing up to 4 mg/person/day

Copper is regulated by a homeostatic mechanism. Homeostasis can be described as the maintenance of a constant internal environment in response to changes in internal and external environments. Homeostatic maintenance requires the tightly coordinated control of copper uptake, distribution and efflux in cells and the organism as a whole. The ability of the body to control the uptake and excretion of copper makes this an important factor in considering the exposure and effects of essential elements like copper.

Copper is involved in the reactions and functions of many enzymes, including angiogenesis, neurohormone release, oxygen transport and regulation of genetic expression. In this scope, copper hydroxide can be considered as a precursor, releasing cupric ion, which is the actual active substance. This explains that, while several endpoints were documented by studies directly performed with copper hydroxide (acute toxicity, skin and eye irritation, sensitisation), other endpoints were documented by other copper salts (mainly copper sulphate).

In mammalian toxicity, it is also considered that the most toxic moiety of any copper salt is the Cu^{2+} ion. This can be shown through the comparison of the most soluble salt (copper sulphate) with other relatively insoluble copper salts, where the solubility, bioavailability and hence toxicity of these salts can vary – with copper sulphate representing the worst-case scenario. When the acute oral toxicity of this salt is compared with copper hydroxide, the data indicate that copper sulphate is more toxic and thus more bioavailable. Therefore all the properties described below for copper will also be applicable to copper hydroxide.

This has also been confirmed in comparative bioavailability studies where copper sulphate was shown to be more or equally bioavailable in relation to the copper carbonate in poultry and swine.
Moreover, as presented in the table below (**Table 2.2.1.1-1**) the Copper sulphate is more toxic than the other copper compounds, and then using studies performed with copper sulphate could be considered as a worst-case.

Table 2.2.1.1-1: Comparative toxicity of the different Copper Salts

Copper salts	Solubility	Acute toxicity (LD_{50})		Irritation
		oral	dermal	
$CuSO_4$	317 g/L	482 mg/kg	>1000 mg/kg	R36/38
$CuCO_3$	1,5 mg/L	1400 mg/kg	>2000 mg/kg	NC*
CuO	0,3 mg/L	>2000 mg/kg	>2000 mg/kg	NC*
$Cu(OH)_2$	6.6µ/L	763 mg/kg	>2000 mg/kg	R41

*NC: No Classification

Consequently, it is considered appropriate to adopt a conservative approach and read-across from copper sulphate to basic copper carbonate, recognising that this may result in over-estimation of effects of less bioavailable soluble substances.

Toxicokinetics

- Absorption

Oral absorption of copper has been investigated in human volunteer studies. Absorption of copper occurs primarily in the small intestine. Oral absorption rates have been shown to vary between 12.4 % for subjects with high copper diet and 55.6 % for subjects with a low-copper diet. Absorption rate for subjects with adequate diet is 36 %. Rats have been shown to absorb 30 to 50 %, although studies in rats have also shown that absorption can be reduced to 10 % at high dietary intakes, as in humans (A6.2/01). Based on these studies, an oral absorption factor of 36 % is used in risk characterisation for humans and 25 % for animals. These values were agreed at the TMIII08.

Quantitative *in-vitro* measurements of human percutaneous copper absorption have been in the range 0.66 to 5.04% of the applied dose. For the purpose of risk assessment, a percutaneous absorption level

of copper of 5% was chosen as the worst case value of copper penetration, under the optimum condition including when emulsifiers were added. This value has been agreed at the TMIII08 and is in line with the EU-VRAR for Copper.

No animal or human studies were available to supply an inhalation absorption level. Thus, the default absorption factor for pulmonary fraction of 100 % is used in risk characterisation as worst-case value of copper salts penetration.

- Distribution

Once absorbed by oral route, copper is bound to albumin and transcuprein and then rapidly transported to the liver where it is incorporated to ceruloplasmin, a transport protein that circulates in the organism and deliver the copper to other organs. It should be however noted that a minor fraction of the absorbed dose can directly be distributed to peripheral organs. In both humans and animals, copper is tightly regulated at a cellular level, involving metallothionein and metallochaperones. These regulating molecules prevent from the accumulation of potentially toxic, free copper ions within the cell. In addition to the liver, the brain is another organ which contains relatively high concentrations of copper.

- Metabolisation

Copper hydroxide dissociates in cupric ion and hydroxyl ion. The latter ion will eventually combine with a proton and will end as water.

- Elimination

Biliary excretion, with subsequent elimination in the faeces, represents the main route of excretion for copper in animals (rats) and humans, with an excretion rate approximately of 1.7 mg Cu/day in humans. Available data show that copper is excreted in the bile in a relatively inabsorbable form. Consequently, little enterohepatic absorption takes place. Biliary excretion of copper and elimination in the faeces is recognised to be essential to the homeostatic regulation of copper in animals and humans. A small amount of copper is also excreted in urine and sweat

Acute toxicity

The acute oral toxicity of Copper hydroxide in the rat was investigated (LD_{50} = 878 mg/kg bw for male and 657 mg/kg bw for female) (A6.1.1). The LD_{50} was determined to be 763 mg/kg bw for the combined sexes. By dermal route, LD_{50} was > 2000 mg/kg for rats (both sexes) (A6.1.2). In an acute inhalation toxicity study the LC_{50} via inhalation was determined in the range of 0.205 to 1.08 mg/l (A6.1.3). Based on these data the test compound requires classification as **toxic by inhalation** (**T; R23**) and **harmful if swallowed** (**Xn; R22**). No classification is required for the dermal route.

Local toxicity

Copper hydroxide was slightly irritating when applied to the skin of 3 New Zealand white rabbits (A6.1.4.1). But, according to the requirements specified by Directive 67/548/EC and subsequent regulations, copper hydroxide is not classified as a skin irritant.

A single application of the substance to the eye of three rabbits produced a severe irritation in non-rinsed eyes (A6.1.4.2). A classification **Xi; R41 "severely irritant to the eyes**" is warranted. Results obtained with eyes rinsed only 4 seconds after application cannot be taken into account. Moreover, the test observation period was only 72 hours, as non reversibility of the effects were seen after the observation period of three days, the lesions were not reversible at the end of the study. As no other data is available for copper hydroxide, this result is also in favour of a classification as a severe irritant to the eyes: Xi; R41.

With regard to skin sensitisation, available animal data (A6.1.5) indicated that copper hydroxide did not induce any sensitisation reactions in the guinea-pig. So, copper hydroxide does not meet the criteria requiring classification as a sensitizer.

Repeated-dose toxicity

With regard to oral repeated dose toxicity, the 90-day dietary study (A6.4.1/01-02) was considered to be the pivotal study for Cu^{2+} presented as copper sulphate pentahydrate. Based on kidney damages, consisting in an increase of cytoplasmic protein droplets, a NOAEL of 1000 ppm (16.3 and 17.3 mgCu/kg bw/day in male and female rats respectively) was determined. Other findings such as liver inflammation and lesions of the forestomach were also reported at 2000 ppm and above (corresponding to doses from 34 mgCu/kg bw/day). These NOAEL of 16.3 mg/kg bw/d was used for the risk characterisation.

There were no dermal repeated dose toxicity studies. However, these studies are not required considering the ability to read-across from the above oral study. Moreover, due to the lack of toxicity observed in the acute dermal toxicity of copper hydroxide and the weak rate of dermal penetration, a toxic effect is not expected.

For repeated-dose toxicity, it was considered that due to the low inhalation exposure during the use of copper-containing wood preservative products, no sub-acute, sub-chronic and/or chronic inhalation studies was necessary.

Mutagenicity

- *In vitro* tests

There was no evidence of mutagenic activity in Salmonella typhimurium strains in the presence or absence of the metabolic activation system when tested with copper sulphate pentahydrate (A6.6.1).
Although limited, these *in vitro* data were deemed sufficient and no further *in vitro* assays were required, considering the results of the *in vivo* tests.

- *In vivo* tests

In vivo studies, conducted with copper sulphate pentahydrate, induced neither micronuclei in the polychromatic erythrocytes from the bone marrow of mice (A6.6.4), nor DNA damage in a rat hepatocyte UDS assay (A6.6.5).
Equivocal results of additional *in vivo* genotoxicity studies from the public domain (Bhunya and Pati, 1987; Agarwal *et al*., 1990; Tinwell and Ashby, 1990), but these studies do not meet the higher reliability criteria (1 or 2) under the BPD.

Copper is therefore considered as non genotoxic.

Carcinogenicity

No carcinogenic potential of copper sulphate was detected in rats and mice. However, all available data are of limited value to evaluate the carcinogenic potential of copper compounds. Study durations are in particular too short (<2 years) and group sizes are small for drawing formal conclusions. However, due to the lack of genotoxicity and considering that the expected level of exposure (as described in paragraph 2.2.1.2) is significantly lower than the usual dietary intake of copper (2-3 mg/day), there is no need to conduct new carcinogenicity studies according to OECD guideline 451/453.

Reproductive toxicity

- Developmental toxicity

Copper administered as copper hydroxide was not teratogenic in rats, mice and rabbits treated during the phase of organogenesis (A6.8.1/04-05). In rabbits, a decreased food consumption and body weight loss occurred in dams receiving 9 mg Cu/kg bw/day. An increased incidence of a common skeletal variant was also observed in foetuses of dams administered with 9 mg Cu/kg bw/day. The NOAEL for

maternal and developmental effects was established at 6 mg Cu/kg bw/day for rabbits and at 30 mg/kg bw/day for rats and mice.

- Fertility

According to the two-generation oral reproduction study in rats administered with copper sulphate (A6.8.2/06), the NOAEL for reproductive toxicity for parental males was 1500 ppm (the highest concentration tested corresponding to 23.6 mg/kg bw/d), The NOAEL for parental females was only 1000 ppm (15.2-35.2 mg/kg bw/d), based on the reduced spleen weight at 1500 ppm. This reduction also occurred in F1 and F2 generations at the same dose level in both males and females. However the reduced spleen weights were not considered a reproductive endpoint as it did not affect growth and fertility.

Therefore as the results of this study do not indicate specific reproductive toxicity at the highest dose level tested, it is proposed that copper sulphate and copper hydroxide should not be classified as reprotoxic compounds.

Neurotoxicity

A neurotoxicity study was not performed since there are no indications for neurotoxic effects from other toxicity tests.

Human data

Human data are based on both clinical studies and poisoning cases.
Clinical studies were performed in healthy volunteers in order to explore the effect of copper gluconate supplementation in the diet. Even if liver functions were identified as the critical endpoints, no evidence of hepatic damage was reported at 10 mg/day.
Poisoning cases consisted in suicide attempts, food and water contamination (cases of India Childhood Cirrhosis, cases of Childhood Idiopathic Toxicosis) and occupational diseases (through Bordeaux mixture exposure).
Acute symptoms resulted in metallic taste, salivation, epigastric pain, nausea, vomiting and diarrhoea. Anatomo-pathological examinations after self-poisoning (ingestion varying between 1 and 100 g of copper dissolved in water) revealed ulcerations of gastro-intestinal mucosa, hepatic damages (dilatation of central vein, cell necrosis and bile thrombi) and kidney lesions (congestion of glomeruli, swelling or necrosis of tubular cells and sometimes haemoglobin casts).
Chronic symptoms, occurred in a voluntary intoxication by daily ingestion of 30 mg of copper for 2 years and 60 mg during the third year, were malaise, jaundice, hepatomegaly and splenomegaly. Liver examination revealed micronodular cirrhosis. In the particular case of vineyard sprayers' intoxication by the Bordeaux mixture (unknown doses), lung lesions with focal distribution were observed: alveoli filled with desquamated macrophages, granuloma in the alveoli septa and fibro-hyaline nodules.

2.2.1.2 Exposure assessment

Primary exposure

Copper product is intended for use by professionals in industrial timber treatment only. Therefore, primary exposure of non-professionals and the general public is not expected.

SPU 01860 F is supplied as a concentrate for dilution before use. It is an aqueous solution containing Copper (II) complexes (corresponds to 15.8% Copper dihydroxide or 10.3% Copper) and other active or non-active ingredients (detailed composition is confidential).

It is intended for use in industrial wood preservation to protect freshly cut wood against insects and fungal infestation. The process is carried out by specialised professionals through:

- mechanical dipping, application solution with 1.545 % of Copper (or 15% aqueous solution of SPU 01860-F), and
- vacuum pressure impregnation (between 10 and 14 bar) with an application solution comprised of 0.412% Copper (or 4% aqueous solution of SPU 01860-F).

As a first tier approach for primary exposure (i.e. exposure of workers at treatment facilities), no Personal Protective Equipment (PPE) is taken into account (except gloves when models give only exposure under gloves).
A second Tier was introduced with the following refinements: Tier 2 estimates are appropriate where the product is used by a specialised industrial /user group. This is the case with timber treatment plant operators who are required to have adequate knowledge and skill in handling hazardous chemicals they use. This is also true where protective measures such as instruction, training, exposure control and PPE are required by health and safety law to be in place.

The results of the human exposure assessments for each use/scenario are reported in following tables:

Table 2.2.1.2-1: Summary of exposure estimates for industrial workers during industrial dipping of wood

Industrial dipping (including mixing and loading, and post-application)					
Users :	Trained industrial workers				
Frequency :	5 cycles/day, 2.5 hours/day, daily				
Model :	**TNsGs Dipping model 1**				
Tier - PPE	**Inhalation exposure**		**Dermal exposure**		**Total exposure**
	Inhaled uptake mg as/day	Systemic dose mg as/ kg bw	Deposit on skin mg as/day	Systemic dose mg as/ kg bw	Systemic dose mg as/ kg bw
Tier 1 : gloves, minimal clothing, no RPE	4.83 x 10^{-2}	8.05 x10^{-4}	621.17	5.18 x10^{-1}	5.18 x10^{-1}
Tier 2 : gloves, protective clothing, no RPE	4.83 x 10^{-2}	8.05 x10^{-4}	141.64	1.18 x10^{-1}	1.19 x10^{-1}

Table 2.2.1.2-2: Summary of exposure estimates for industrial workers during vacuum-pressure impregnation of wood

Vacuum-pressure impregnation (including mixing and loading, and post-application)					
Users :	Trained industrial workers				
Frequency :	3 cycles/day , 5 hours/day, daily				
Model :	**TNsGs handling model 1**				
Tier - PPE	**Inhalation exposure**		**Dermal exposure**		**Total exposure**
	Inhaled uptake mg as/day	Systemic dose mg as/ kg bw	Deposit on skin mg as/day	Systemic dose mg as/ kg bw	Systemic dose mg as/ kg bw
Tier 1 : gloves, minimal clothing, no RPE	4.89 x 10^{-2}	8.15 x 10^{-4}	119.27	9.94 x 10^{-2}	1.00 x 10^{-1}
Tier 2 : gloves, protective clothing, no RPE	4.89 x 10^{-2}	8.15 x 10^{-4}	26.06	2.17 x 10^{-2}	2.25 x 10^{-2}

Secondary exposure

The secondary human exposure estimates consider the potential for the exposure of adults (workers and consumers), infants and children in which they may come into contact with copper treated timber.

Results of the exposure assessment are reported in the following table:

Table 2.2.1.2-3: Summary of estimates for indirect exposure scenarios

Scenario	Route	Estimate *	PPE	Uptake mg as/day	Systemic dose mg as/ kg bw
Adults (professional) - Chronic Handling, cutting and sanding treated timbers	inhalation	1	None	0.163	0.0027
			RPE	0.0163	0.00027
	dermal	2	None	0.17	0.00014
			Gloves	0.017	0.000014
	TOTAL	2	None	0.33	0.0028
			RPE +	0.033	0.00028
Adults (consumers) - Acute Handling, cutting and sanding treated timbers	inhalation	1	None	0.163	0.0027
	dermal	2	None	0.17	0.00014
	TOTAL	2	None	0.33	0.0028
Children – Chronic Playing on playground structure outdoors	dermal	2	None	0.08	0.00027
Infants - Chronic Playing on playground structure outdoors and mouthing	dermal	2	None	0.08	0.0004
	oral	2	None	0.10	0.0036
	TOTAL	2	None	0.18	0.0040
Infants - Acute Chewing preserved timber off-cuts	oral	2	None	0.096	0.0035

*: The different estimates are due to refinements used for the estimation of the dislodgeable copper concentration. Estimate 1 = 68µg/cm² (unrealistically conservative). Estimate 2 = 2µg/cm². Only the more relevant estimate for each scenario/route is reported here. The use of PPE (protective gloves and mask) is considered additionally only for professional users.

2.2.1.3 Risk characterisation for human health

The human health risk characterisation is performed using both the AEL and the MOE approaches.

AELs determination

For each exposure scenario, an appropriate AEL is determined on the basis of the exposure frequency. Accordingly, three types of AELs are classically derived: $AEL_{short\text{-}term}$, $AEL_{medium\text{-}term}$ and $AEL_{long\text{-}term}$ corresponding to short-, medium- and long-term exposures respectively.
AELs are usually derived by applying the following formula:

$$AEL = \frac{NOAEL}{Assessment\ \ factors}$$

In the case of copper hydroxide, all AELs ($AEL_{short\text{-}term}$, $AEL_{medium\text{-}term}$ and $AEL_{long\text{-}term}$) were derived on the basis of the NOAEL of 1000 ppm, corresponding to 16.3 mgCu/kg bw/day obtained in the 90-day oral rat study with copper sulphate (A6.4.1). An oral absorption rate of 25% was taken into account for calculating the systemic NOAEL as follows:

$$NOAELsystemic = 16.3\ x\ 0.25 = \ 4.1\ \ mgCu/kg\ bw/d$$

Although copper hydroxide induced local effects (eye irritation) and copper sulphate induced a minimal to moderate hyperplasia of the squamous mucosa in the forestomach, no local AEC was derived as far as no local effect was detected in the absence of systemic effects. Local effects are therefore covered by systemic AELs.

Regarding the assessment factors, after refinement, a value of 50 (including an inter-species factor of 5 and an intra-species factor of 10)[5] was applied for deriving $AEL_{short-term}$ and $AEL_{medium-term}$. An additional factor of 2 was integrated for taking into account the duration extrapolation from subchronic to chronic exposures. An overall assessment factor of 100 was therefore adopted for deriving $AEL_{long-term}$. These refined assessment factors were agreed by the technical meeting.
These values are used as the reference margin of exposure (MOE_{ref}).

The following AELs were therefore derived:

- $AEL_{short-term}$ = 4.1 / 50 = 0.082 mgCu/kg bw/day
- $AEL_{medium-term}$ = 4.1 / 50 = 0.082 mgCu/kg bw/day
- $AEL_{long-term}$ = 4.1 / 100 = 0.041 mgCu/kg bw/day

In the AEL approach, a risk is considered as acceptable if AEL > exposure.
In practice, exposure is expressed as a percentage of the AEL (%AEL). The risk is therefore considered as acceptable if %AEL < 100.
In the MOE approach, a risk is considered as acceptable if MOE > MOE_{ref} (where $MOE = \frac{NOAEL}{Exposure}$).

ADI Determination

As no food risk assessment was deemed necessary because of the negligible exposure through food, no ADI was derived.
An ADI value of 0.15 mgCu/kg bw/d is nevertheless available in the literature (EFSA, 2008).

Risk characterisation for primary exposure scenarios

- Professional users

The %AELs and the Margins of Exposure (MOE) were calculated for long-term exposures as reported in the table below:

[5] Although the inter-species factor is usually set at 10, it was agreed at TM I09 it could be reduced from 10 to 5 in the case of copper compounds. This factor is composed of an allometric scaling subfactor (which is 4 for rats) and a residual subfactor of 2.5 accounting for the other interspecies variability. Whereas the allometric scaling subfactor was kept unchanged, it was proposed to reduce the residual subfactor from 2.5 to 1.25 on the basis of the extensive toxicokinetic data set in both humans and animals (rats) which demonstrates similarities between the two species in absorption, distribution and excretion of copper compounds.
This approach was accepted by the TCNES and subsequently agreed during the review process by SCHER.
The Biocides Technical Meeting adopted it as a refined tier in order to harmonise with the overall assessment factor used in the VRA.

Table 2.2.1.3-1: Summary of risk assessment after assessment factors refinement for professional users during long-term exposure

Exposure scenario	systemic total dose [mgCu/kg bw/day]	MOEref	AEL long-term	% AEL	MOE
Industrial uses – Primary exposure, dipping process					
All phases of exposure : Tier 1 (mixing and loading + application + post-application)	5.18×10^{-1}	100	0.041	**1263**	**7.9**
All phases of exposure : Tier 2 (mixing and loading + application + post-application)	1.19×10^{-1}	100	0.041	**290**	**34.4**
Industrial uses – Primary exposure, simple vacuum pressure impregnation process					
All phases of exposure : Tier 1 (mixing and loading + application + post-application)	1.00×10^{-1}	100	0.041	**244**	**41**
All phases of exposure : Tier 2 (mixing and loading + application + post-application)	2.25×10^{-2}	100	0.041	**55**	**182**

The % of AEL in the first tier assessment during long-term exposure is >100 and the MOE is <100 for the "dipping process application scenario with handling model 1" and the "simple vacuum pressure impregnation process". However, this tier does not take into account the Personal Protective Equipment (PPE). When PPE (protective clothing and new gloves) are worn, it can be seen that the % of AEL and MOE are acceptable for the "simple vacuum pressure impregnation process" but is still unacceptable for the "dipping process"[6].

Conclusion: the risk for industrial or professional users under the conditions specified above is not acceptable for the "dipping process" whereas the risk is acceptable for the simple-vacuum process when PPE are worn.

- Non-professional users

The biocidal product is foreseen to be used by trained professionals only. Thus, a risk characterisation for non-professionals is not relevant.

Risk characterisation for secondary (indirect) Human Exposure

The %AELs and the Margins of Exposure (MOE) were calculated for secondary exposure scenarios as reported in the tables below:

6 Even when assuming that industrial users, wearing PPE, would be acutely exposed, the risk remains unacceptable (%AEL = 145%, MOE = 34.4).

Table 2.2.1.3-2: Summary of risk assessment for secondary exposure

Scenario	Exposure path	Estimate *	Systemic dose mg as / kg bw	MOE_{ref}	MOE	AEL (mgCu/ kg bw/d)	Expo as % AEL
Adults (professional) - Chronic Handling, cutting and sanding treated timbers	Inhalation and dermal	2 RPE + gloves	0.0028 0.00028	100	**1464** **14636**	0.041	**6.8** **0.68**
Adults (consumers) – Acute Handling, cutting and sanding treated timbers	Inhalation and dermal	2	0.0028	50	**1464**	0.082	**3.41**
Children - Chronic Playing on playground structure outdoors	dermal	2	0.00027	100	**15185**	0.041	**0.66**
Infants – Chronic Playing on playground structure outdoors and mouthing	Dermal and oral	2	0.0040	100	**1025**	0.041	**9.8**
Infants - Acute Chewing preserved timber off-cuts	oral	2	0.0035	50	**1171**	0.082	**4.3**

*: The different estimates are due to refinements for the estimation of the dislodgeable copper concentration. Estimate 1 = 68µg/cm² (unrealistically conservative). Estimate 2 = 2µg/cm².Only the more relevant estimate for each scenario/route is reported here. The use of PPE (protective gloves and mask) is considered additionally only for professional users.

For all these scenarios, %AEL and MOE values show that no unacceptable risk are anticipated for people secondarily exposed.

Overall assessment of the risk for the use of the active substance in biocidal products

Application of copper hydroxide as an approx. 0.4 % aqueous solution (elemental copper) in preventive wood protection (dipping/immersion and vacuum pressure process) is considered to induce an unacceptable risk for professional facility workers on Tier 1 level except for one scenario "cutting and sanding". Higher tier (Tier 2) reflecting actual measures of occupational safety further reduce any potential hazards and result in a satisfactory protection level for workers for the "simple vacuum pressure impregnation process" but **the "dipping process" still represents an unacceptable risk for workers even if PPE are worn long-term exposure.**

Secondary (indirect) human exposures are considered to be devoid of unacceptable risk.

2.2.2 Environment risk assessment

Copper is applied in wood preservatives in the form of aqueous solutions of copper salts. The environmentally relevant moiety and the active principle of Copper hydroxide is the cupric ion (Cu^{2+}), which may be released to the environment at a low rate.

2.2.2.1 Fate and distribution in the environment

As a result of the unique fate of copper in water, soil, sediment and sludge, many of the data requirements listed in Section A7 of the Technical notes for Guidance are not applicable for inorganic compounds and metals in particular e.g. hydrolysis, photodegradation and sediment degradation. It is not applicable to discuss copper in terms of degradation half-lives or possible routes of degradation.

Copper hydroxide as an inorganic compound is not subjected to biological degradation in any environmental compartment. The substance is non-volatile, hydrolytically stable and not biodegradable. Phototransformation in water is not expected. The strong adsorbance to organic carbon, manganese and iron oxides increases in soil with increasing pH.
The most important parameters determining the distribution of copper in the aquatic and soil compartment is adsorption onto solid materials and therefore the copper partitioning coefficients.
Partition coefficient in suspended matter

Kpsusp = 30,246 l/kg (log Kp (pm/w) = 4.48) (50th percentile)

Partition coefficient in sediment

Kpsed = 24,409 l/kg (log Kp(sed/w) = 4.39) (50th percentile)

Partition coefficient in soil

Kpsoil = 2 120 l/kg (log Kp (soil/w) = 3.33) (50th percentile)

As all metals, copper becomes complexed to organic and inorganic matter in waters, soil and sediments and this affects copper speciation, bioavailability and toxicity.

Because of the homeostasis of metals, BCF values are not indicative of the potential bioaccumulation. There is therefore limited evidence of accumulation and secondary poisoning of inorganic forms of metals, and biomagnification in food webs.

2.2.2.2 Environmental effect assessment

The risk assessment is carried out on the basis of total concentrations of copper in the environment taking into account the background plus added amount of copper. It was stated that this approach may be more reliable. The PEC values, initially calculated as “added values” were corrected in order to integrate the background concentrations in copper. Total copper concentrations were calculated in taking into account of the natural/pristine or the regional copper background concentrations (as agreed under the Council Regulation (EEC) 793/93 on Existing Substances - EU-RAR).

2.2.2.2.1 Freshwater compartment

For the freshwater pelagic compartment, 139 individual NOEC/EC10 values resulting in 27 different species-specific NOEC values, covering different trophic levels (fish, invertebrates and algae) were used for the PNEC derivation**.** The large intra-species variabilities in the reported single species NOECs were related to the influence of test media characteristics (e.g., pH, dissolved organic carbon, hardness) on the bioavailability and thus toxicity of copper. Species-specific NOECs were therefore calculated after normalizing the NOECs towards a series of realistic environmental conditions in Europe (typical EU scenario’s, with well defined pH, hardness and DOC). Such normalization was

done by using chronic copper bioavailability models (Biotic Ligand Models), developed and validated for three taxonomic groups (fish, invertebrates and algae) and additional demonstration of the applicability of the models to a range of other species. The species-specific BLM-normalized NOECs were used for the derivation of log-normal Species Sensitivity Distributions (SSD) and HC5-50 values (the median fifth percentile of the SSD), using statistical extrapolation methods.
The HC5-50 values of the typical EU scenarios ranged between 7.8 to 22.1 µg Cu/L. Additional BLM scenario calculations for a wide range of surface waters across Europe further demonstrated that the HC5-50 of 7.8 µg Cu/L, is protective for 90% of the EU surface waters and can thus be considered as a reasonable worst case for Europe in a generic context.

Copper threshold values were also derived for three high quality mesocosm studies, representing lentic and lotic systems. The mesocosm studies included the assessment of direct and indirect effects to large variety of taxonomic group and integrate potential effects from uptake from water as well as from food.
BLM-calculated HC5-50 values (Assessment Factor (AF)=1) were used as PNEC for the risk characterisation.

The AF=1 was chosen due to the certainty concerning 1) the mechanism of action; 2) the overall evaluation of the database; 3) the robustness of the HC5-50 values; 4) corrections for bioavailability (reducing uncertainty); 5) the sensitivity analysis with regards to DOC and read-across assumptions; 6) the factor of conservatism "built in into" the data and assessment (such as no acclimation of the test organisms and no pre equilibration of test media); 7) results from multi-species mesocosm studies and 8) comparison with natural backgrounds and optimal concentration ranges for copper, an essential metal.

The HC5-50, with an AF=1, was used to derive a $PNEC_{freshwater}$ of 7.8 µg Cu/l for Europe in a generic context in absence of site-specific information on bioavailability parameters (pH, DOC, hardness).

2.2.2.2.2 Sediment compartment

The sediment PNEC included using a weight of evidence approach considering different sources and tiered approaches of information: (1) sediment ecotoxicity data, (2) pelagic ecotoxicity data in combination with Kd values derived through different approaches, (3) soil ecotoxicity data and soil bioavailability models and (4) mesocosm/field ecotoxicity.

High-quality chronic benthic NOECs for six benthic species, representing 62 NOEC values were retained for the PNEC derivation. NOEC values were related to sediment characteristics (e.g., Organic Carbon (OC) and Acid Volatile Sulphides (AVS)), influencing the bioavailability and thus toxicity of copper to benthic organisms. The derivation of the freshwater HC5-50sediment for copper was therefore based on the OC-normalized dataset, containing only low-AVS sediments. Using the log-normal species sensitivity distribution a freshwater HC5-50sediment of 1741 mg Cu/kg OC was derived through the statistical extrapolation method.

Using the equilibrium partitioning (EP) approach, the derived HC5-50sediment (EP) values were comparable or higher than the HC5-50 derived from whole sediment tests. The comparison between the sensitivity of soil and benthic organisms added weight to the HC5-50 from whole sediment tests. The same did sediment threshold values and benthic NOECs that were obtained from four mesocosm studies and one field cohort study.

The AF of 1 was chosen due to the certainty concerning 1) weight of evidence provided; 2) the overall quality of the database; 3) the robustness of the HC5-50 values; 4) corrections for bioavailability (reducing uncertainty); 5) the conservative factor built into the system (no acclimation of the test

organisms and only low AVS sediments retained); 6) validations from multi-species mesocosm studies and field studies and 7) comparison with natural backgrounds and optimal concentration ranges.
In case of natural sediments both the amount of AVS and organic carbon present in the sediment has dictated the observed effect levels for copper and were used for the risk characterisation. In absence of AVS data, a default AVS value of 0.77 µmol/kg dry weight was used. This value corresponded to the 10th percentile of the AVS obtained from a wide Flemish monitoring database and additional AVS data from other European countries.

The HC5-50, with an AF=1, was used to estimate a $PNEC_{sediment}$ of 1741 mg Cu/kg OC, for Europe in a generic context. This corresponding to 87 mg Cu/kg dry weight for a sediment with 5 % O.C.(TGD default value)

2.2.2.2.4 Terrestrial compartment

A high-quality dataset of 252 individual chronic NOEC/EC10 values from 28 different species and processes representing different trophic levels (i.e., decomposers, primary producers, primary consumers) has been retained for the PNEC derivation. The observed intra-species differences in toxicity data were related to differences in bioavailability, the latter related to differences in soil properties and to differences in ageing and application mode and rate.
The soil property best explaining the variability in toxicity for most of the endpoints was the eCEC (effective Cation Exchange Capacity).
For the normalisation of the ecotoxicity data, the respective Cu background concentrations were added on all NOEC/EC10 values which were subsequently normalised to representative EU soils using the relevant regression (bio)availability models, generating soil-type specific HC5-50 values.
Species Sensitivity Distributions were constructed using the normalised NOEC/EC10 data. HC5-50 values from log-normal distributions ranging between 13.2 and 94.4 mg Cu/kg dry weight were obtained. A total of eight single species studies were available in which the toxicity of Cu to microorganisms, invertebrates and plants in field-contaminated aged soils was investigated for a wide range of European soil types (peaty, sandy, clay). A total of five multi-species studies were available, three of which studied the effects of copper in freshly spiked soils and 2 in field contaminated aged soils. Invertebrates, plants and micro-organisms were studied. Single species and multi-species field studies indicate that effects did not occur at an exposure level at the HC5-50-value.

Normalized HC5-50 values (AF=1) were used as $PNEC_{soil}$ for the risk characterisation.

The uncertainty analysis that provides arguments for the AF=1 was based on: 1) the overall quality of the database and the end-points covered; 2) the diversity and representativeness of the taxonomic groups covered by the database; 3) corrections for differences in bioavailability (soil properties); 4) the statistical uncertainties around the 5th percentile estimate; 5) NOEC values below the HC5-50 and 6) field and mesocosm studies and comparisons of their results with the HC5-50.

To account for the observed difference between lab-spiked soils and field-contaminated soils, a conservative leaching-ageing factor of 2 was agreed based on test data from the mechanistic research on ageing and ionic strength (leaching) effects.

For the PT08 biocidal product dossiers, unlikely to the VRA, a leaching ageing “L/A” factor of 2 was not used to derive the PNECsoil but it was taken into account in the assessment of the PEC soil (PEC divided by 2). Indeed it was stated that decrease of Cu toxicity with ageing has to be taken into account but rather in the exposure assessment than in the hazard assessment. Since this factor was determined over a period of 18 months, it can be applied for PEC calculation over the same amount of time (i.e. TIME 2 only in the PT08). The L/A factor of 2 was used in the PEC (PEC/2), while for VRA, the L/A factor was used in the PNEC (PNEC/2). In the VRA, the NOEC added were fisrt multiplied by the L/A factor (2). The background concentrations from corresponding control soil were then added. All the individual aged NOECtotal were then normalized and finally the HC5-50 was derived; The AF of 1 was applied on the HC5-50.

The HC5-50, with an AF=1, was used to derive a $PNEC_{soil}$ of 45.6 mg Cu/kg dry weight for Europe in absence of site-specific information on soil properties.

2.2.2.2.5 STP compartment

For the STP compartment, high-quality NOECs from respiration or nitrification inhibition studies, relevant to the functioning of a Sewage Treatment Plant (STP), resulted from biodegradation/removal studies and NOECs for ciliated protozoa were used to derive the PNEC for STP micro-organisms.

The lowest reliable observed NOEC value was noted for the inhibition of respiration = 0.23 mg/l expressed as dissolved copper and carried forward as $PNEC_{STP}$ to the risk characterisation.

2.2.2.2.6 Summary of PNECS

Compartment	PNEC	Unit
STP	0.23	[mg.L-1]
Freshwater	7.8	[µg.L-1]
Sediment	87 18.9	[mg.kgdwt-1] [mg.kgwwt-1]
Soil	45.6 40.35	[mg.kgdwt-1] [mg.kgwwt-1]

2.2.2.3 Risk characterisation for the environment

The intended uses of the representative biocidal product are industrial treatments of wood by dipping/immersion and vacuum pressure impregnation for use classes 1 – 3 (dipping/immersion) and use classes 1 – 4-1 (vacuum pressure impregnation).

No quantitative exposure assessment has been carried out for the life cycle stages “production” and “formulation of the biocidal product” for the following reasons:

- Environmental exposure due to manufacturing of the active substance is covered by other legislation and will therefore not be considered here.

- Concerning the formulation stage, the following information has been provided by the applicant:” The biocidal product is manufactured in a closed formulation facility. Any rinsing solutions are re-introduced into the manufacturing process. A given formulation device is specifically allocated to the manufacturing of one product (here: the respective wood preservative containing copper). During maintenance operations, rinsing solutions are

temporarily stored and re-used quantitatively. The described procedure is standard technology in wood preservative formulation plants and therefore applies to any product to be marketed."

No exposure assessment has been performed for the life cycle stage "service life of the treated wood" intended for use classes 1 and 2 (indoor use) assuming negligible emissions to the environment.

The concentrations of copper in the environment were estimated following the recommendations given in the currently available Guidance Documents. Stages of the wood life considered for the exposure assessment are industrial wood treatment, storage of treated wood and wood in-service for use class 3 and use class 4-1 (vacuum pressure treatment only).

The emissions to the environment from the stages of storage and wood in-service were calculated on the basis of the results of leaching tests with treated wood in contact with water.

As cooper is a natural endogenous compound, the releases due to its use as wood preservative have been added to the background environmental concentration. In a first step, the added predicted concentrations of copper were calculated, in line with the equation given by the ESD. In a second step, the added values were corrected in order to integrate the natural/pristine or the regional background concentrations in copper (as agreed under the Council Regulation (EEC) 793/93 on Existing Substances - EU-RAR):

- Natural/pristine background Cu concentrations in water, sediment and soil were taken from the FOREGS Geochemical Baseline Programme (FGBP) database published in March 2004 (http://www.gsf.fi/foregs/geochem/),
- Regional background Cu concentrations in water, sediment and soil were taken from the EU Existing Chemical Regulation.

Compartment	Natural/pristine background concentration	Regional background concentration	Unit
Surface water	0.88	2.9	[$\mu g.L^{-1}$]
Ground water	0.88	2.9	[$\mu g.L^{-1}$]
Soil	12 10.6	24.4 21.6	[mg kg_{dwt}^{-1}] [mg kg_{wwt}^{-1}]
Sediment	21 4.56	67.5 14.7	[mg kg_{dwt}^{-1}] [mg kg_{wwt}^{-1}]

In the specific case of copper release to soil, the applicant presented studies on copper toxicity in aged contaminated soils. Results from these studies have been reviewed and discussed by RMS. They show that, after 18 month ageing, NOECs increased for plants and invertebrates corresponding to a decrease of copper toxicity threshold. For micro-organisms, NOECs increased also but this is also probably due to an adaptation to copper. 18 month ageing tests were however not long enough to show a total remove of toxicity.

The applicant used these data to derive a lab to field factor reflecting the decrease in bioavailability of copper after 18 months, and proposed to apply this factor for the PNEC derivation. RMS considers that decrease of Cu toxicity with ageing has to be taken into account, but rather in the exposure assessment than in the hazard assessment. Since this factor was determined over a period of 18 months, it can be applied for PEC calculation over the same amount of time or higher (*i.e.* TIME 2 only).

Therefore, an ageing factor of 2 was applied on the total copper concentrations in soil for the values calculated in TIME 2, in order to consider the phenomenon of copper ageing in soil. This strategy was validated at TMIII08.

2.2.2.3.1 Aquatic compartment (including sediment)

- Dipping/immersion

Estimated risks from **industrial treatment by dipping/immersion process** indicate an unacceptable risk to sediment considering a natural and a regional background concentration. Therefore, during the application process, the product must be re-cycled within the facility or collected and disposed of according to local authority regulations in order to minimise the release to the environment.

Estimated risks from **storage** of wood treated by dipping/immersion indicate an unacceptable risk to sediment considering a natural background concentration and to surface water and sediment considering a regional background concentration. All timbers treated by industrial process will have to be stored on impermeable hard standing to prevent direct losses surface water and to allow losses to be collected for disposal.

Concerning **wood-in-service** releases for use class 3, the noise barrier and the bridge over the pond are the only scenarios that foresee emissions to the aquatic compartment. These scenarios indicate an acceptable risk for surface water and sediment when releases from wood treated by dipping/immersion are directed to a sewage treatment plant (noise barrier scenario) but show unacceptable risk when surface treated wood is located above a water body (bridge scenario) even when removal processes are considered (adsorption onto suspended matter and sediment and time-weighted averaging of concentrations). Since an unacceptable risk is identified where direct loses to water are possible there should be a labelling against applications where direct losses to water are possible, thereby preventing use in these situations.

- Vacuum pressure impregnation

Estimated risks from **industrial treatment by vacuum pressure impregnation** indicate an unacceptable risk to sediment considering a regional background concentration. Therefore, during the application process, the product must be re-cycled within the facility or collected and disposed of according to local authority regulations in order to minimise the release to the environment.

Estimated risks from **storage** of wood treated by vacuum pressure impregnation indicate an unacceptable risk to sediment whatever the background considered. All timbers treated by industrial process will have to be stored on impermeable hard standing to prevent direct losses surface water and to allow losses to be collected for disposal.

Concerning **wood-in-service** releases for use class 3, the noise barrier and the bridge over the pond are the only scenarios that foresee emissions to the aquatic compartment. These scenarios indicate an acceptable risk for surface water and sediment when releases from wood treated by vacuum pressure impregnation are directed to a sewage treatment plant (noise barrier scenario) but show unacceptable risk when surface treated wood is located above a water body (bridge scenario) even when removal processes are considered (adsorption onto suspended matter and sediment and time-weighted averaging of concentrations). Since an unacceptable risk is identified where direct loses to water are possible there should be a labelling against applications where direct losses to water are possible, thereby preventing use in these situations.

2.2.2.3.2 Sewage treatment plant organism

PEC/PNEC ratios indicate acceptable risks to sewage treatment plant either from industrial application by dipping/immersion or vacuum pressure impregnation, or from wood-in-service releases (noise barrier scenario).

2.2.2.3.3 Atmosphere

From copper-treated wood, there would be no exposure via the atmosphere due to the very low vapour pressure of copper and copper compounds. Therefore, copper-treated wood would not pose an unacceptable risk to the air compartment.

2.2.2.3.4 Terrestrial compartment

- Dipping/immersion

The dipping application scenario considers the exposure of the soil compartment via the application of contaminated sludge to soil. No risk to terrestrial organisms is expected. However, due to the risk identified for sediment in this scenario, releases via STP during industrial application should not be allowed.

The outdoor storage of treated wood (class 3) following dipping industrial treatment on bare soil is expected to pose a risk to soil organisms. Storage on bare soil should not be allowed. The emissions from treated wood to soil should be substantially reduced by covering the storage area with protective roof or covering the soil with impermeable coating e.g. concrete. Leachates should be collected and treated appropriately (e.g. incineration).

Industrial treatment for use class 1 and 2 and subsequent covered storage should not cause a risk to the terrestrial organisms. As above, however, due to the risk identified for surface water in these scenarios, releases via STP during industrial application should not be allowed.

The PEC/PNEC ratios calculated for wood in service treated by industrial dipping are above 1 for the house scenario considering a natural or a regional background concentration and an ageing factor of 2, which indicates an unacceptable risk for terrestrial organisms. The wood treated by dipping/immersion process should not be allowed for a use in class 3.

- Vacuum pressure impregnation

As for dipping/immersion, the vacuum pressure impregnation application scenario considers the exposure of the soil compartment via the application of contaminated sludge to soil. No risk to terrestrial organisms is expected. However, due to the risk identified for sediment in this scenario (considering a regional background concentration), releases via STP during industrial application should not be allowed.

The outdoor storage of treated wood on bare soil (class 3) following the industrial vacuum pressure impregnation is expected to pose a risk to soil organisms, even in considering an ageing factor of 2. Storage on bare soil should not be allowed. The emissions from treated wood to soil should be substantially reduced by covering the storage area with protective roof or covering the soil with impermeable coating e.g. concrete. Leachates should be collected and treated appropriately (e.g. incineration).

Industrial treatment for use class 1 and 2 and subsequent covered storage should not cause a risk to the terrestrial organisms. As above, however, due to the risk identified for surface water in these scenarios, releases via STP during industrial application should not be allowed.

Concerning the use class 3 and 4-1, the PEC/PNEC ratios calculated for wood in service treated by industrial vacuum pressure impregnation are below 1 for all the corresponding scenarios (house, fence,

noise barrier, fence post and transmission pole) considering a natural or a regional background concentration, which indicates an acceptable risk for terrestrial organisms. The wood treated by vacuum pressure impregnation should be allowed for a use in class 3 and 4-1.

2.2.2.3.5 Ground water

Copper is strongly absorbed and immobile in soil. Therefore, no copper is expected to reach groundwater, and copper hydroxide as a wood preservative is not expected to pose a risk for groundwater contamination.

2.2.2.3.6 Secondary poisoning

Copper is an essential trace element, well regulated in all living organisms. Differences in copper uptake rates are related to essential needs, varying with the species, size, life stage, seasons, etc. Mechanisms to regulate copper homeostasis are applicable across species with specific processes being active depending on the species, life stages etc. Simple estimations on secondary poisoning are therefore not adequate.

There is several evidence to showing the absence of copper biomagnification across the trophic chain in the aquatic and terrestrial food chains. Differences in sensitivity among species are not related to the level in the trophic chain but to the capability of internal homeostasis and detoxification. Field data have further provided evidence on the mechanisms of action of copper in the aquatic and terrestrial environment and the absence of a need for concern for secondary poisoning.

2.2.2.3.7 Assessment of drinking water criterion

According to Directive 98/83/EC Annex I, part B, the limit value for Copper in water is 2 mg/L. This value is not exceeded in any scenario. This means that Copper hydroxide complies with the drinking water criteria.

2.2.2.4 PBT assessment

Being an inorganic compound, the persistence criteria of DT90, field < 1 year and DT50 at 20°C < 6 months that are laid down in paragraph 85 of Annex VI to the Biocides Directive and in the TNsG on Annex I inclusion are not applicable to copper (II) hydroxyde. According to the latter, the degradation triggers do not necessarily apply if the active substance is included in Annex I with regard to areas of use where a long lasting service-life of the treated material is essential and it is scientifically demonstrated that under field conditions there is no unacceptable accumulation in soil (e.g. that the PEC/PNEC < 1 in soil during storage and the service-life of the treated article)

The application as a wood preservative can be considered as such. It was shown above that for storage the PEC/PNEC ratio is above 1. Copper hydroxide meets the criteria for persistence in soil, and can be therefore considered as persistent.

Due to the homeostatic regulation process of invertebrates and fish of copper, bioaccumulation and biomagnification of cooper are considered as not applicable for copper.

Considering the HC5-50 value of 7.8 µg/L for the aquatic compartment, Copper (II) hydroxide fulfils the T criterion.

Copper hydroxide does not fulfil the PBT-criteria. Therefore inclusion in Annex I is not restricted by these criteria.

2.2.3 Overall summary

SCENARIO		Human primary exposure		Human secondary exposure		Aquatic compartment	STP	Terrestrial compartment	Ground water	Air	Secondary poisoning
		Professional	Non professional	Worker	Consumer						
INDUSTRIAL APPLICATION DIPPING/IMMERSION											
Application		**Not acceptable***	NR	Acceptable	Acceptable	**Not acceptable**	Acceptable	Acceptable	NR	NR	NR
Storage						**Not acceptable**	NR	**Not acceptable**	NR	NR	NR
Wood in-service	Classes 1-2	NR	NR	Acceptable	Acceptable	NR	NR	NR	NR	NR	NR
	Class 3 **without** direct release to water					Acceptable	Acceptable	**Not acceptable**	NR	NR	NR
	Class 3 **with** direct release to water					**Not acceptable**	NR	NR	NR	NR	NR
Overall conclusions: Dipping process should not be allowed because of unacceptable risks for industrial workers (short-term and long-term exposure), even if PPE are worn. Moreover, risks are deemed unacceptable for the environment (soil and surface water) during *in-service* phase of wood used in class 3.											
INDUSTRIAL APPLICATION VACUUM PRESSURE IMPREGNATION											
Application		Acceptable*	NR	Acceptable	Acceptable	**Not acceptable**	Acceptable	Acceptable	NR	NR	NR
Storage						**Not acceptable**	NR	**Not acceptable**	NR	NR	NR
Wood in-service	Classes 1-2	NR	NR	Acceptable	Acceptable	NR	NR	NR	NR	NR	NR
	Class 3 **without** direct release to water					Acceptable	Acceptable	Acceptable	NR	NR	NR
	Class 3 **with** direct release to water					**Not Acceptable**	NR	NR	NR	NR	NR
	Class 4-1					NR	NR	Acceptable	NR	NR	NR
Overall conclusions: Vacuum pressure impregnation process should be allowed due to acceptable risk for uses in classes 1 to 4-1 with the following mitigation measures: • During industrial treatments, collective protective equipment shall be ensured when appropriate, and the operators must wear the appropriate personal protective equipments. • During industrial application the emissions to surface water have to be forbidden. Appropriate mitigation measures such as waste recycling or incineration have to be performed. • All timbers treated by industrial process will have to be stored on impermeable hard standing or under a protective roof to prevent direct losses to soil and surface water and to allow losses to be collected and treated appropriately (e.g. incineration) • Pre-treated timber must not be in contact with or above surface water.											

NR: Non relevant

* Considering the wearing of PPE

3 – PROPOSAL FOR THE DECISION

3.1 Background to the proposed decision

On the basis of the proposed and supported uses and the evaluation conducted as summarised in chapter 2 of this document, it can be concluded that copper (II) hydroxide fulfils under the conditions listed in 3.2 the requirements laid down in Article 5(1) (b), (c), and (d) of Directive 98/8/EC.

The applicant is not currently placing nano forms of copper hydroxide on the market. Therefore, the submitted dossier and the finalised assessment report don't cover potential nanoforms of this copper compound, should such forms exist.

Article 10 of the Biocides Directive 98/8/EC addresses the inclusion of an active substance in the Annexes I, IA or IB. For the decision of inclusion or non-inclusion, it has to be examined if the criteria of article 10 (1) are fulfilled.

Use class 1 to 3 is claimed by the applicant for wood treated by dipping.

Use class 1 to 4-1 is claimed by the applicant for wood treated by vacuum pressure.

The physicochemical properties of copper hydroxide are deemed acceptable for the appropriate use, storage and transportation of the biocidal product.

The submitted information on copper hydroxide proves a sufficient efficacy against wood destroying fungi (wood rotting basidiomycetes and soft rot fungi and insects (wood boring beetles)).

The health effects of copper hydroxide are well documented for acute and irritation endpoints. In contrast, all the chronic data are based on copper sulphate. However, considering that copper hydroxide is a precursor releasing cupric ion, which is the actual active element, it was accepted to base the risk assessment on the provided studies. Toxicological profile in the light of exposure resulting from the use of this substance is of no concern. The conclusion of the toxicological assessment is that the risk for professional users is negligible when safe operational procedures are established and appropriate PPE are used, only when wood is treated by a simple vacuum pressure process. Risks to indirectly exposed persons (including infants) is also negligible.

With regard to environmental exposure and effects, based on the risk assessments conducted for the industrial application phases, it is considered that safe uses can only be identified if the possibility of STP exposure during treatment (dipping and vacuum pressure impregnation) is excluded. It is recommended that this should be a condition of Annex I inclusion.

The environmental risk assessment indicates that all mode of industrial application result in an unacceptable risk to the aquatic and terrestrial environment during storage (class 3 and class 4-1).

The environmental risk assessment indicates that, for wood treated by dipping immersion, only noise barrier and fence scenarios investigated for wood in service used in class 3 results in acceptable risk to the aquatic and terrestrial environment. For the house and bridge over the pond scenarios, the trigger value of 1 for the PEC/PNEC ratio is exceeded. The wood treated by dipping/immersion should be restricted to use classes 1 to 2.

The environmental risk assessment indicates that, for wood treated by vacuum pressure, all scenarios investigated for wood in service used in class 3 and 4-1 result in acceptable risk to the aquatic and terrestrial environment.

3.2 Proposed decision regarding the inclusion in Annex I

It is proposed that Copper (II) hydroxide (CAS-No 20427-59-2) be included in Annex I of Council Directive 98/8/EC as an active substance in wood preservative products (product type 8), subject to the following specific provision:

1. The active substance copper (II) hydroxide, as manufactured, shall have a minimum purity of 96.5% w/w, equivalent to 62.9% w/w copper.

2. The identity and the maximum content of impurities have to comply with the confidential part of the dossier.

3. In view of the risk identified for industrial workers during dipping treatment, products shall be authorised only for industrial use by vacuum pressure impregnation, unless it is demonstrated in the application for product authorisation that risks to human and environment demonstrate acceptable levels for other types of application in accordance with Article 5 and Annex VI.

4. In view of the assumptions made during the risk assessment, products authorised for industrial use must be applied with appropriate personal protective equipment and safe operational procedures should also be established, unless it can be demonstrated in the application for product authorisation that risks to industrial users can be reduced to an acceptable level by other means.

5. In view of the risks identified for the aquatic and soil compartments, appropriate risk mitigation measures must be taken to protect those compartments. In particular, labels and/ or safety data sheets of products authorised for industrial use shall indicate that freshly treated timber must be stored after treatment under shelter or on impermeable hard standing to prevent direct losses to soil or water and that any losses must be collected for reuse or disposal.

6. In view of the risks identified for the aquatic compartments, products shall not be authorised for treatment of wood that will be used in outdoor constructions near or above water, unless data is submitted to demonstrate that the product will meet the requirements of Article 5 and Annex VI, if necessary by the application of appropriate mitigation measures.

Specific provisions n°3 and 4 are necessary due to risks identified for industrial users (see section 2.2.1.3).
Specific provision n°5 is necessary due to risks identified for the aquatic and soil compartments, during the industrial treatment phase and wood in service (see section 2.2.2.3.1 and 2.2.2.3.4).
Specific provision n°6 is necessary due to risks identified for the aquatic compartment, during service-life of wood continuously exposed to water (see section 2.2.2.3.1).

3.3 Factor to be taken into account by Member States when authorising products

1. The assessment was made for products containing copper hydroxide only for dipping treatment and for industrial treatments by vacuum pressure impregnation, with limited inhalation exposure. Other uses will have to be considered at the product authorisation stage.
2. The efficacy data do not take into account the expected service life of wooden elements treated with copper based product and should be considered as an indicator only. Additional data should be provided at the product authorization stage. Regarding termites, a full efficacy data should be

provided at product authorisation stage. As copper based wood preservative is used in conjunction with other biocides, full efficacy data should be provided at product authorisation stage including data performed with copper hydroxide.

3. No repeated-dose inhalation study was submitted due to the negligible exposure by this route. A negligible inhalation exposure must therefore be checked when authorising products. Otherwise adequate inhalation data will have to be submitted.
4. Concerning environmental risk assessment, Biotic Ligand Modelling (BLM)-calculated HC5-50 values were used as PNEC for risk characterization. Under product authorization, Member States will have to investigate if the BLMs can be applied under their specific conditions. Moreover, the national natural background should be compared to the background level used for the risk assessment.

3.4 Demand for further information

The submitted dossier satisfies the requirements of Annexes IIA, IIIA, IIB and IIIB of Directive 98/8/CE and is sufficient to recommend Annex I inclusion for copper hydroxide as wood preservative.

Nevertheless, some information or studies, that are not expected to change the conclusion on the inclusion into Annex I, are needed as confirmatory data. They should preferably be submitted to the original Rapporteur Member State (France) at the latest 6 months before the date of inclusion of the active substance into Annex I :

- A new 5-batch analysis is required to support each source and to ensure compliance of current production of each source of copper hydroxide to the specifications. This must include the analysis of all relevant and significant impurities using validated methods of analysis. As Nickel has been found in the source in some sources of copper coumpounds used as active substances for PT08, nickel should be searched in these analysis.
  If Nickel is present, but its form unknown, it should not be present above its worst case classification limit of 0.01%. Besides, a method of analysis of Nickel should therefore be provided as well.

- Methods of analysis for the relevant impurities were not provided and must be provided before the product authorization stage.

- Validation data for the methods of analysis copper in soil and water were not provided and must be provided.

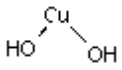
- Further data must be provided to fully validate the analytical method for the determination of the active substance in the biocidal product.

Appendix 1 – Listing of endpoints

Chapter 1: Identity, Physical and Chemical Properties, Details of Uses, Further Information, and Proposed Classification and Labelling

Active substance (ISO Common Name)	Copper hydroxide
Function (*e.g.* fungicide)	Fungicide, insecticide
Rapporteur Member State	France

Identity (Annex IIA, point II.)

Chemical name (IUPAC)	Copper (II) hydroxide
Chemical name (CA)	Copper hydroxide
CAS No	20427-59-2
EC No	243-815-9
Other substance No.	CIPAC code number for copper compounds is 44
Minimum purity of the active substance as manufactured (g/kg or g/l)	62.9 % w/w as copper equivalent to 96.5 % w/w copper (II) hydroxide
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	Lead : max 0.005% Cadmium : max 0.0005% Arsenic : max 0.0004% (see detail in the confidential part of the CAR)
Molecular formula	CuH_2O_2
Molecular mass	97.54 g/mol
Structural formula	

Physical and chemical properties (Annex IIA, point III., unless otherwise indicated)

Melting point (state purity)	No melting point – decomposes before melting (97% $Cu(OH)_2$)
Boiling point (state purity)	No boiling point – decomposes before boiling (97% $Cu(OH)_2$)
Temperature of decomposition	> 200°C
Appearance (state purity)	Light blue odourless powder (97% $Cu(OH)_2$)
Relative density (state purity)	$D^{19}{}_{4\,0}$ = 3.978 (97% $Cu(OH)_2$)
Surface tension	Not available, in view of the limited water solubility
Vapour pressure (in Pa, state temperature)	< 10^{-5} Pa theoretically assessed
Henry's law constant (Pa m^3 mol^{-1})	Not applicable
Solubility in water (g/l or mg/l, state temperature)	pH 8.9, T = 20 °C: 0.0066 mg/l
	pH 8.9, T = 30 °C: 0.0072 mg/l
	Solubility in pure CO_2 free water; pH results from by the active substance itself (Copper hydroxide)
	pH 4.1, T = 20 °C: 8184 mg/l
	pH 9.1, T = 20 °C: 0.0335 mg/l
	Buffered solutions. The solubility is displaced at low pH due to consumption of H^+ during dissociation of the salt
Solubility in organic solvents (in g/l or mg/l, state temperature) (Annex IIIA, point III.1)	In n-heptane, p-xylene, 1,2-dichloroethane, methanol, acetone, ethylacetate:
	< 10 g/l at T = 30°C, respectively
Stability in organic solvents used in biocidal products including relevant breakdown products (IIIA, point III.2)	. Not determined as copper hydroxide will be used only in aqueous formulations
Partition coefficient (log P_{OW}) (state temperature)	Not appropriate, due to the nature of the active substance (inorganic salt). Partition coefficients in water, sediments and soils are used instead.
Hydrolytic stability (DT_{50}) (state pH and temperature) (point VII.7.6.2.1)	Not appropriate, due to the nature of the active substance (inorganic salt)
Dissociation constant (not stated in Annex IIA or IIIA; additional data requirement from TNsG)	Not available: only required if water solubility cannot be measured.
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	Not appropriate, due to the nature of the active substance (inorganic salt)
Photostability (DT_{50}) (aqueous, sunlight, state pH) (point VII.7.6.2.2)	Not appropriate, due to the nature of the active substance (inorganic salt)
Quantum yield of direct phototransformation in water at Σ > 290 nm (point VII.7.6.2.2)	Not appropriate, due to the nature of the active substance (inorganic salt)
Flammability	Not highly flammable
Explosive properties	No explosive groups contained not explosive

Classification and proposed labelling (Annex IIA, point IX.)

	Directive 67/548/EEC	Regulation 1272/2008
With regard to physical/chemical data	Not classified	
With regard to toxicological data	T, Toxic R23, Toxic by inhalation R22, Harmful if swallowed R41, Risk of serious damage to eyes Safety phrases: S25: Avoid contact with eyes S26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice S36/37/39: Wear protective clothing, gloves and eyes/face protection S45: In case of accident or if you feel unwell, seek medical advice immediately (show the label where possible) S57: Use appropriate container to avoid environmental contamination	Acute Tox. 4/H302 – Harmful if swallowed Acute Tox. 3/H331 – Toxic if inhaled Eye Dam. 1/H318 - Causes serious eye damage
With regard to fate and behaviour data	R53, May cause long-term adverse effects in the aquatic environment	Aquatic chronic category 1/H410 - Very toxic to aquatic organisms and may cause long lasting effects in the aquatic environment
With regard to ecotoxicological data	N, Dangerous for the environment R50, Very toxic to aquatic organisms Safety phrase S60: this material and its container must be disposed as hazardous waste S61 : Avoid release to the environment. Refer to special instruction/safety data sheets	Aquatic chronic category 1/H410 - Very toxic to aquatic organisms and may cause long lasting effects in the aquatic environment

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method) (Annex IIA, point 4.1)	Electrogravimetric Method : CIPAC 44/TC/M/3.1 Methods for total copper determination, not specific to copper (II) hydroxide. Purity can be calculated from the total copper content because other copper forms (i.e. metallic and cuprous) are not expected to be present in the technical material
Impurities in technical active substance (principle of method) (Annex IIA, point 4.1)	DIN18121-1(1998), DIN EN 13137:2001 Methods for arsenic and cadmium must be provided

Analytical methods for residues

Soil (principle of method and LOQ) (Annex IIA, point 4.2)	Flame Atomic Absorption (EPA 7210, 220.1) Validation data must be provided
Air (principle of method and LOQ) (Annex IIA, point 4.2)	Not available for lack of volatility and no exposition via the respiratory system when used in wood preservatives
Water (principle of method and LOQ) (Annex IIA, point 4.2)	Furnace Atomic Absorption (EPA 220.2, 7211) Validation data must be provided
Body fluids and tissues (principle of method and LOQ) (Annex IIA, point 4.2)	Not relevant as not toxic
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	Not available for lack of exposure
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	Not available for lack of exposure

Chapter 3: Impact on Human Health

Absorption, distribution, metabolism and excretion in mammals (Annex IIA, point 6.2)

Rate and extent of oral absorption:	It was agreed during the TMIII09 that an oral absorption of 36% for humans and 25% for animals have to be used.
Rate and extent of dermal absorption:	It was agreed during the TMIII09 that a dermal absorption of 5% has to be used for diluted solutions and 100% for the concentrated product.
Distribution:	Once absorbed by oral route, copper is bound to albumin and transcuprein and then rapidly transported to the liver where it is incorporated to ceruloplasmin, a transport protein that circulates in the organism and deliver the copper to other organs. The liver is the main organ involved in copper distribution and plays a crucial role in copper homeostasis by regulating its release. It should be however noted that a minor fraction of the absorbed dose can directly be distributed to peripheral organs. In both humans and animals, copper is tightly regulated at a cellular level, involving metallothionein and metallochaperones. These regulating molecules prevent from the accumulation of potentially toxic, free copper ions within the cell. In addition to the liver, the brain is another organ which contains relatively high concentrations of copper.
Potential for accumulation:	All mammals have metabolic mechanisms that maintain homeostasis (a balance between metabolic requirements and prevention against toxic accumulation). Because of this regulation of body copper, indices of copper status remain stable except under extreme dietary conditions. This stability was demonstrated in a study in which human volunteers received a diet containing total copper in the range 0.8 to 7.5 mg/d. Under these conditions, there were no significant changes in commonly used indices of copper status, including plasma copper, ceruloplasmin, erythrocyte superoxide dismutase and urinary copper.
Rate and extent of excretion:	Biliary excretion is quantitatively the most important route, with a mean copper excretion estimated to be in the order of 1.7 mg Cu/day (24.6 ± 12.8 µg Cu/kg bodyweight). A small amount of copper is also lost in urine and in sweat. Excretion of endogenous copper is influenced by dietary copper intake. When the copper intake is low, turnover is slow and little endogenous copper is excreted and vice versa. Faecal copper losses reflect dietary copper intake with some delay as intake changes and copper balance is achieved. Urinary losses do not contribute to the regulation of copper stores and contribute very little to the overall balance.
Toxicologically significant metabolite	None.

Acute toxicity (Annex IIA, point 6.1)

Rat LD_{50} oral	Males: 878 mg/kg bw

	Females: 657 mg/kg bw Combined (m+f): 763 mg/kg bw
Rat LD_{50} dermal	> 2000 mg/kg
Rat LC_{50} inhalation	$0.205 < LC_{50} < 1.08$ mg/l air
Skin irritation	Slightly irritating but does not require classification.
Eye irritation	Irritating
Skin sensitization (test method used and result)	Not sensitising

Repeated dose toxicity (Annex IIA, point 6.3)

Species/ target / critical effect	The test substance used the following study was copper (II) sulphate. Rat/ liver/ inflammation Rat/ kidney/ cytoplasmic droplets Rat, mouse/ forestomach/ minimal to moderate hyperplasia of the squamous mucosa
Lowest relevant oral NOAEL / LOAEL	16.3 mgCu/kg bw/d
Lowest relevant dermal NOAEL / LOAEL	Not available
Lowest relevant inhalation NOAEL / LOAEL	Not available

Genotoxicity (Annex IIA, point 6.6)	The test substance used in each of the following studies was copper (II) sulphate pentahydrate. 1. Ames test in Salmonella typhimurium - negative in both the presence and absence of S9 mix. 2. Bone marrow micronucleus study in the mouse – negative at a dose of 447 mg/kg bw. 3. *In vivo/in vitro* unscheduled DNA synthesis study in the livers of orally dosed male rats – negative, following treatment with doses of 632.5 or 2000 mg/kg bw. These studies demonstrate that copper is not mutagenic in the in vitro and in vivo test systems used.

Carcinogenicity (Annex IIA, point 6.4)

Species/type of tumour	Available studies of the carcinogenicity of copper compounds in rats and mice have given no indication that copper salts are carcinogenic.
lowest dose with tumours	Not applicable

Reproductive toxicity (Annex IIA, point 6.8)

Species/ Reproduction target / critical effect	The test substance used in the following study was copper (II) sulphate pentahydrate. Rat/Two-generation study/No evidence of effects on the fertility potential of either male or female rats.
Lowest relevant reproductive NOAEL / LOAEL	Copper sulphate cannot be regarded as having adverse effects on fertility in the animals tested. 1500 ppm NOAEL in rat two-generation study = 23.6-43.8 mgCu/kg bw/d (maximal dose tested)
Species/Developmental target / critical effect	Mouse/ Developmental toxicity/ malformations (study with major methodological deficiencies)
Lowest relevant developmental NOAEL / LOAEL	6 mg Cu/kg bw/d (NOAEL maternal toxicity = 6 mg Cu/kg bw/d) **However rat two-generation study indicates that copper sulphate pentahydrate has no teratogenic properties.**

Neurotoxicity / Delayed neurotoxicity (Annex IIIA, point VI.1)

Species/ target/critical effect Lowest relevant developmental NOAEL / LOAEL.	No evidence for neurotoxic potential from other studies.

Other toxicological studies (Annex IIIA, VI/XI)

	None.

Medical data (Annex IIA, point 6.9)

Direct observation, eg clinical cases, poisoning incidents if available; data point 6.12.2.	Acute symptoms resulted in metallic taste, salivation, epigastric pain, nausea, vomiting and diarrhoea. Anatomo-pathological examinations after self-poisoning (ingestion varying between 1 and 100 g of copper dissolved in water) revealed ulcerations of gastro-intestinal mucosa, hepatic damages (dilatation of central vein, cell necrosis and bile thrombi) and kidney lesions (congestion of glomeruli, swelling or necrosis of tubular cells and sometimes haemoglobin casts). Chronic symptoms, occurred in a voluntary intoxication by daily ingestion of 30 mg of copper for 2 years and 60 mg during the third year, were malaise, jaundice, hepatomegaly and splenomegaly. Liver examination revealed micronodular cirrhosis. In the particular case of vineyard sprayers intoxication by the Bordeaux mixture (unknown doses), lung lesions with focal distribution were observed: alveoli filled with desquamated macrophages, granuloma in the alveoli septa and fibro-hyaline nodules.

Summary (Annex IIA, point 6.10)	Value	Study	Safety factor
ADI (if residues in food or feed)	0.15 mgCu/kg bw/day	EFSA(2008)	Not applicable
AEL short and medium term	0.082 mgCu/kg bw/d	90d in rats	MOE ref = 50
AEL long-term	0.041 mgCu/kg bw/d	90d in rats	MOE ref = 100
Drinking water limit	No data reported		
ARfD (acute reference dose)	Not applicable		

Acceptable exposure scenarios (including method of calculation)

Professional users:

Industrial dipping (including mixing and loading, and post-application) Users : trained industrial workers Frequency: 5 cycles/day, 2.5 hours/day, daily (chronic) Dipping model 1	Tier-PPE	Systemic doses (mg as/kg bw)	
		Inhalation exposure	*Dermal exposure*	*Total exposure*
	Tier 1: gloves, minimal clothing, no RPE	8.05 $x10^{-4}$	5.18 $x10^{-1}$	5.18 $x10^{-1}$
	Tier 2 : gloves, protective clothing, no RPE	8.05 $x10^{-4}$	1.18 $x10^{-1}$	1.19 $x10^{-1}$

Vacuum pressure impregnation (including mixing and loading, and post-application) Users : trained industrial workers Frequency: 3 cycles/day , 5 hours/day, daily (chronic) Handling model 1	Tier-PPE	Systemic doses (mg as/kg bw)	
		Inhalation exposure	*Dermal exposure*	*Total exposure*
	Tier 1: gloves, minimal clothing, no RPE	8.15 x 10^{-4}	9.94 x 10^{-2}	1.00 x 10^{-1}
	Tier 2: gloves, protective clothing, no RPE	8.15 x 10^{-4}	*2.17 x 10^{-2}*	*2.25 x 10^{-2}*

Non-professional users	Not relevant		
Indirect exposure as a result of use			
Handling, cutting and sanding treated timbers Users : professionals Frequency: daily (chronic)	Tier-PPE	Systemic doses (mg as/kg bw)	
		Inhalation exposure	*Dermal exposure*	*Total exposure*
	Tier 1: no PPE	2.7 x 10^{-3}	1.4 x 10^{-4}	2.8 x 10^{-3}
	Tier 2: gloves, RPE	2.7 x 10^{-4}	1.4 x 10^{-5}	2.8 x 10^{-4}

Handling, cutting and sanding treated timbers Users : adult consumers Frequency: few events per year (acute)	Tier-PPE	Systemic doses (mg as/kg bw)	
		Inhalation exposure	*Dermal exposure*	*Total exposure*
	Tier 1: no PPE	2.7 x 10^{-3}	1.4 x 10^{-4}	2.8 x 10^{-3}

Children playing on playground structure outdoors

Users : children

Frequency: daily (chronic)

Tier-PPE	Systemic doses (mg as/kg bw)		
	Inhalation exposure	*Dermal exposure*	*Total exposure*
Tier 1: no PPE	-	2.7×10^{-4}	2.7×10^{-4}

Infant playing on playground structure outdoors and mouthing

Users : infants

Frequency: daily (chronic)

Tier-PPE	Systemic doses (mg as/kg bw)		
	Oral exposure	*Dermal exposure*	*Total exposure*
Tier 1: no PPE	3.6×10^{-3}	4.0×10^{-4}	4.0×10^{-3}

Infant chewing a preserved timbe off-cut

Users : infants

Frequency: few events per year (acute)

Tier-PPE	Systemic doses (mg as/kg bw)		
	Oral exposure	*Dermal exposure*	*Total exposure*
Tier 1: no PPE	3.5×10^{-3}	-	3.5×10^{-3}

Chapter 4: Fate and Behaviour in the Environment

Route and rate of degradation in water (Annex IIA, point 7.6, IIIA, point XII.2.1, 2.2)

Hydrolysis of active substance and relevant metabolites (DT_{50}) (state pH and temperature)	Not applicable to metals.
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	Not applicable to metals.
Readily biodegradable (yes/no)	Not applicable to metals.
Biodegradation in seawater	Not applicable to metals.
Non-extractable residues	Not applicable to metals.
Distribution in water / sediment systems (active substance)	The distribution of metals between aqueous phase and soil/sediment/suspended matter should preferentially be described on the basis of measured soil/water, sediment/water and suspended matter/water equilibrium distribution coefficient (TECHNICAL GUIDANCE DOCUMENT on Risk Assessment Part II Appendix VIII, 2003; TECHNICAL GUIDANCE DOCUMENT Annex 4-VIII Environmental risk assessment for metals and metal compounds (RIP 3.2-2). From the literature overview, the following partitioning coefficients have thus been derived for Cu metal and Cu compounds: **Partition coefficient in suspended matter** Kp_{susp} = 30,246 l/kg (log Kp (pm/w) = 4.48) (50^{th} percentile) (Heijerick *et al,* 2005) **Partition coefficient in sediment** Kpsed = 24,409 l/kg (log Kp(sed/w) = 4.39) (50th percentile) (Heijerick *et al.,* 2005)
Distribution in water / sediment systems (metabolites)	Not applicable to metals.

Route and rate of degradation in soil (Annex IIIA, point VII.4, XII.1.1, XII.1.4; Annex VI, para. 85)

Mineralization (aerobic)	Not Relevant for the nature of the active substance which an inorganic metal salt
Laboratory studies (range or median, with number of measurements, with regression coefficient)	DT_{50lab} (20°C, aerobic): Not applicable to metals.
	DT_{90lab} (20°C, aerobic): Not applicable to metals.
	DT_{50lab} (10°C, aerobic): Not applicable to metals.
	DT_{50lab} (20°C, anaerobic): Not applicable to metals.
	Not applicable to metals.
Field studies (state location, range or median with number of measurements)	DT_{50f}: Not applicable to metals.

	DT_{90f}: Not applicable to metals.
Anaerobic degradation	Not applicable to metals.
Soil photolysis	Not applicable to metals.
Non-extractable residues	Not applicable to metals.
Relevant metabolites - name and/or code, % of applied a.i. (range and maximum)	Not applicable to metals.
Soil accumulation and plateau concentration	Although unable to degrade, the affect of ageing on the distribution of copper in soil results in increased immobilisation by long term adsorption and complexation reactions in the soil.

Adsorption/desorption (Annex IIA, point XII.7.7; Annex IIIA, point XII.1.2)

Ka , Kd Ka_{oc} , Kd_{oc} pH dependence (yes / no) (if yes type of dependence)	The distribution of metals between aqueous phase and soil/sediment/suspended matter should preferentially be described on the basis of measured soil/water, sediment/water and suspended matter/water equilibrium distribution coefficient (TECHNICAL GUIDANCE DOCUMENT on Risk Assessment Part II Appendix VIII, 2003; TECHNICAL GUIDANCE DOCUMENT Annex 4-VIII Environmental risk assessment for metals and metal compounds (RIP 3.2-2). From the literature overview, the following partitioning coefficients have thus been derived for Cu metal and Cu compounds: **Partition coefficient in soil** Kd = 2120 l/kg (log K_p = 3.33) (50^{th} percentile) (Sauvé *et al.* 2000)

Fate and behaviour in air (Annex IIIA, point VII.3, VII.5)

Direct photolysis in air	Not relevant for metals
Quantum yield of direct photolysis	Not relevant for metals
Photo-oxidative degradation in air	Not relevant for metals
Volatilization	Not relevant for metals

Monitoring data, if available (Annex VI, para. 44)

Soil (indicate location and type of study)	No data submitted nor required
Surface water (indicate location and type of study)	No data submitted nor required
Ground water (indicate location and type of study)	No data submitted nor required
Air (indicate location and type of study)	No data submitted nor required

Chapter 5: Effects on Non-target Species

Toxicity data for aquatic species (most sensitive species of each group)
(Annex IIA, Point 8.2, Annex IIIA, Point 10.2)

Acute toxicity to aquatic organisms	No acute toxicity data are presented as the toxicity was evaluated using a SSD based on chronic toxicity data.
Chronic toxicity to aquatic organisms in the FRESHWATER COMPARTMENT	**SSD result: HC5-50 = 7.8 µg Cu / l as reasonable worst case** **Freshwater algae and higher plants:** Lowest NOEC used in the SSD = 15.7 µg Cu /L (growth of *Pseudokirchneriella subcapitata*) Highest NOEC used in the SSD = 510.2 µg Cu /L (growth of *Chlorella vulgaris*) **Freshwater Invertebrates:** Lowest NOEC used in the SSD = 4 µg Cu /L (mortality and reproduction of *Ceriodaphnia dubia*) Highest NOEC used in the SSD = 181 µg Cu /L (reproduction of *Daphnia magna*) **Freshwater Fishes:** Lowest NOEC used in the SSD = 2.2 µg Cu /L (growth of *Oncorhynchus mykiss***)** Highest NOEC used in the SSD = 188 µg Cu /L (mortality of *Perca fluviatilis)*
Chronic toxicity to aquatic organisms in the SEDIMENT COMPARTMENT	**SSD result: HC5-50 = 1741 mg Cu/kg OC,** corresponding to **87 mg Cu/kg dry weight for a sediment with 5 % O.C**.(TGD default value) **Sediment organisms:** Lowest NOEC used in the SSD = 18.3 mg Cu /kg d.w. (growth and reproduction of *Tubifex tubifex*) Highest NOEC used in the SSD = 580.9 mg Cu /kg d.w. (survival of *Tubifex tubifex*) High-quality chronic benthic NOECs for six benthic species, representing 62 NOEC values were retained for the PNEC derivation. NOEC values were related to sediment characteristics (e.g., Organic Carbon (OC) and Acid Volatile Sulphides (AVS)), influencing the bioavailability and thus toxicity of copper to benthic organisms. The derivation of the freshwater HC5-50 sediment for copper was therefore based on the OC-normalized dataset, containing only low-AVS sediments. Using the log-normal species sensitivity distribution a freshwater HC5-50 sediment of 1741 mg Cu/kg OC was derived through the statistical extrapolation method.
Chronic toxicity to Sewage microorganisms	The lowest reliable observed **NOEC** value was noted for the inhibition of respiration = **0.23 mg/l**

Effects on earthworms or other soil non-target organisms

Acute toxicity to soil organisms (Annex IIIA, point XIII.3.2)	No acute toxicity data are presented as the toxicity was evaluated using a SSD based on chronic toxicity data.
Chronic toxicity to soil organisms in the TERRESTRIAL COMPARTMENT	**SSD result: HC5-50 = 45.6 mg Cu/kg dry weight was used as reasonable worst case value for Europe in absence of site-specific information on soil properties.** **Terrestrial higher plants:** Lowest NOEC used in the SSD = 18 mg Cu /kg d.w. (*Hordeum vulgare*) Highest NOEC used in the SSD = 698 mg Cu /kg d.w. (*Lycopersicon esculentum)* **Terrestrial Invertebrates:** Lowest NOEC used in the SSD = 8.4 mg Cu /kg d.w. (cocoon production of *Eisenia andrei*) Highest NOEC used in the SSD = 1460 mg Cu /kg d.w. (reproduction of *Falsomia candida)* **Soil micro-organisms:** Lowest NOEC used in the SSD = 30 mg Cu /kg d.w. (glucose respiration) Highest NOEC used in the SSD = 2402 mg Cu /kg d.w. (maize respiration)

Effects on terrestrial vertebrates

Acute toxicity to mammals (Annex IIIA, point XIII.3.3)	No data
Acute toxicity to birds (Annex IIIA, point XIII.1.1)	No data
Dietary toxicity to birds (Annex IIIA, point XIII.1.2)	No data
Reproductive toxicity to birds (Annex IIIA, point XIII.1.3)	No data

Effects on honeybees (Annex IIIA, Point XIII.3.1)

Acute oral toxicity	No data
Acute contact toxicity	No data

Effects on other beneficial arthropods (Annex IIIA, Point XIII.3.1)

Laboratory studies	No data
Semi-field studies	No data
Field studies	No data

Bioconcentration (Annex IIA, Point 7.5)

Bioconcentration factor (BCF)	For the naturally occurring substances such as essential metals as copper, bioaccumulation is complex, and many processes are available to modulate both accumulation and potential toxic impact. Biota regulates their internal concentrations of essential metals through homeostatic control mechanisms (i.e. active regulation, storage). As a result of these processes, at low metal concentrations, organisms accumulate essential metals more actively in order to meet their metabolic requirements than when they are being exposed at higher metal concentrations. As a consequence of homeostatic processes, and unlike many organic substances, the BCF/BAF is not independent of exposure concentrations for metals and it is inversely related to exposure concentrations. Thus, the use of ratios Cbiota/Cwater or Cbiota/Csediments as an overall approach for estimating copper bioconcentration factors is thus not appropriate.
Depuration time(DT_{50}) **(DT_{90})**	Not applicable for metals
Level of metabolites (%) in organisms accounting for > 10 % of residues	Not applicable for metals

Appendix II: List of Intended Uses

Object and/or situation	Member State or Country	Product name	Organisms controlled	Formulation		Application			Applied amount per treatment			Remarks
(a)			(c)	Type (d-f)	Conc. of a.s. (i)	Method Kind (f-h)	Number min–max (k)	Interval between applications (min)	g a.s./l (min–max)	Water l/m^2 (min–max)	g a.s./m^2 (min–max)	(m)
Fungi Use Class (UC) 1, 2, 3, 4-1	All	SPU-01860-F	Wood destroying fungi and soft rotting micro-fungi	Soluble concentrate	1% to 4% in aqueous solution 5% to 15% in aqueous solution	Vacuum pressure treatment Dipping treatment	Single treatment	Not applicable	n.a.	n.a.	n.a.	(1)
Wood destroying insects Use Class (UC) 1, 2, 3, 4-1	All	SPU-01860-F	Wood destroying insects	Soluble concentrate	1% to 4% in aqueous solution 5% to 15% in aqueous solution	Vacuum pressure treatment Dipping treatment	Single treatment	Not applicable	n.a.	n.a.	n.a.	

(1) A target concentration of 0.5 kg Cu/m^3 has been claimed referred to the rate that is necessary if copper is used in combination with co-biocides such as quaternary ammonium compounds contained in SPU-01860-F for example, but according to tests produced in the dossier, a target concentration of 1.29 kg Cu/m^3 would be needed as a substance alone (EN113) if a product is used containing just copper and no co-biocides..

(a) e.g. biting and suckling insects, fungi, molds;
(b) *e.g.* wettable powder (WP), emulsifiable concentrate (EC), granule (GR)
(c) GCPF Codes – GIFAP Technical Monograph No 2, 1989 ISBN 3-8263-3152-4);
(d) All abbreviations used must be explained
(e) g/kg or g/l;
(f) Method, *e.g.* high volume spraying, low volume spraying, spreading, dusting, drench;
(g) Kind, *e.g.* overall, broadcast, aerial spraying, row, bait, crack and crevice equipment used must be indicated;
(h) Indicate the minimum and maximum number of application possible under practical conditions of use;
(i) Remarks may include: Extent of use/economic importance/restrictions

Appendix III: List of studies

Data protection is claimed by the applicant in accordance with Article 12.1(c) (i) and (ii) of Council Directive 98/8/EC for all study reports marked "Yes" in the "Data Protection Claimed" column of the table below. Data protection is claimed under Article 12.1(c) (i) or (ii).These claims are based on information from the applicant. It is assumed that the relevant studies are not already protected in any other Member State of the European Union under existing national rules relating to biocidal products. It was however not possible to confirm the accuracy of this information.

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
A 3.1.3	Walter, D.	2003	Relative Density of SPU-00620 Laboratory: GAB Doc. No.: 20031137/01-PCRD Date: 23.07.2003 GLP: yes; not published	Y	SPU
A 3.3	Walter, D.	2003	Appearance, Colour and Odour of SPU-00620 Laboratory: GAB Doc. No.: 20031137/01-PCAO Date: 23.07.2003 GLP: yes; not published	Y	SPU
A 3.5	Walter, D.	2003	Water solubility of SPU-00620 Laboratory: GAB Doc. No.: 20031137/01-PCSB Date: 30.10.2003 GLP: yes; not published	Y	SPU
A 3.7	Walter, D.	2003	Solubility of SPU-00620 in Organic Solvents Laboratory: GAB Doc. No.: 20031137/01-PSBO Date: 23.07.2003 GLP: yes; not published	Y	SPU
A 3.10	Smeykal, H.	2003	SPU-00620 Thermal stability Laboratory: Siemens-Axiva Doc. No.: 20030459.01 Date: 26.06.2003 GLP: yes; not published	Y	SPU
A 3.13	Walter, D.	2003	Surface tension of SPU-00620 Laboratory: GAB Doc. No.: 20031137/01-PCST Date: 23.07.2003 GLP: yes; not published	Y	SPU
A 4.1	Warncke, U.	2003	Validated method of analysis for the determination of copper in SPU-00620-F Laboratory: Spiess-Urania Chemicals GmbH - Versuchsstation Christinenthal Doc. No.: Wa-15-07-03-00620 Date: 15.07.2003; not published	Y	SPU
A 4.2 /01	Carey, D.	1989	Method Validation Report for Terrestrial Outdoor Field Dissipation Study with Copper-Containing Pesticides Laboratory: Biospherics Doc. No.: URA-97-08740-108 Date: 16.01.1989 GLP: yes; not published	Y	SPU

A 4.2 /02	Burguera, J.L., et al.	1993	In vivo sample uptake and on-line measurements of zinc and copper in whole blood by microwave-assisted mineralization and flow injection AAS Atomic Spectroscopy; 1993; No.4; Vol. 14; 90-94 Doc. No.: 00620B-IIA-42c Date: 00.08.1993; published	N	Public
A 5/01	Sundman, C.E.	1984	Tests with ammoniacal copper and alkyl-ammonium compounds as wood preservatives. IRG/WP 84-3299	N	Public
A 5/02	Rennie, P.M.S., Gray, S.M., Dickinson D.J.	1987	Copper-based water-borne preservatives: copper adsorption in relation to performance against soft rot. IRG/WP 87-3452	N	Public
A 5/03	Cooper, P.A.	1988	Diffusion and interaction of components of water-borne preservatives in the wood cell wall. IRG/WP 88-3474.	N	Public
A 5/04	Waldie, C., Cornfield, J.A.	1992	Investigation of copper fixation in timber by sodium nitrite. IRG/WP 92-3707.	N	Public
A 5/05	Thomason, S.M., Pasek, E.A.	1997	Amine copper reaction with wood components: acidity versus copper adsorption. IRG/WP 97-30161.	N	Public
A 5/06	Zhang, J., Kamdem, D.P.	1999	Interaction of copper amine complexes with wood: influence of copper source, amine ligands and amine to copper molar ratio on copper retention and leaching. IRG/WP 99-30203	N	Public
A 5/07	Roussel, C., Haluk, J.P., Pizzi, A., Thevenon, M.F.	2000	Copper based wood preservatives: anew approach using fixation with resin acids of rosin. IRG/WP 00-30249.	N	Public
A 5/08	Kamdem, D.P., Zhang J.	2000	Contribution of wood components on the absorption of copper amine. IRG/WP 00-30216	N	Public
A 5/09	Jiang, W., Ruddick, J.N.R.	2000	A comparison of the leaching resistance of copper 2 - ethanolamine and copper ethylenediamine treated Scots pine. IRG/WP 00-30233.	N	Public
A 5/10	Ung, Y.T., Cooper, P.A.	2004	Effect of species, retention, and conditioning temperature on copper stabilization and leaching for ACQ-D. IRG/WP 04-30342.	N	Public
A 5/11	Tascioglu, C., Cooper, P.A., Ung Y.T.	2005	Adsorption of ACQ and Cu MEA wood preservatives in red pine IRG/WP 05-30374.	N	Public
A 5/12	Gray, S., Dickinson, D.J.	1987	Copper based water-borne preservatives: the biological performance of wood treated with various formulations. IRG/WP 87-3451.	N	Public
A 5/13	Morris, P.I.	1990	IUFRO rating system compares favourably to weight loss for soil-bed testing. IRG/WP 90-2343.	N	Public
A 5/14	Jin, L., Archer, K., Preston, A.	1991	Surface characteristics of wood treated with various AAC, ACQ, and CCA formulations after weathering. IRG/WP 91-2369.	N	Public
A 5/15	Ohlson, B., Simonson, R.	1992	Lignin-copper, a new wood preservative without arsenic and chromium. IRG/WP 92-3702.	N	Public
A 5/16	Williams, G.R., Brown J.	1993	Natural exposure weathering tests: their role in the assessment of wood preservative efficacy. IRG/WP 93-20006.	N	Public
A 5/17	Preston, A., Archer, K., Jin, L.	1994	Performance of copper-based wood preservatives in above ground and ground contact tests. IRG/WP 94-30057.	N	Public
A 5/18	Conradie, D., Turner, P., Conradie, W.E., Pendelebury, J., Pizzi, T.	1995	Copper linoleate: a new low toxicity wide spectrum, heavy duty wood preservative. IRG/WP 95-30082	N	Public
A 5/19	Hedley, M., Tsunoda, K., Suzuki, K.	1995	Field tests of preservative treated radiata pine in Japan. IRG/WP 95-30083.	N	Public
A 5/20	Nicholas, D.D., Schultz, T.P.	1997	Comparative performance of several ammoniacal copper preservative systems. IRG/WP 97-30151.	N	Public

A 5/21	Häger, B., Bergman, Ö.	1997	Stake test with ammoniacal copper in combination with different agents started in 1962. IRG/WP 97-30130.	N	Public
A 5/22	Molnar, S, Dickinson, D.J., Murphy, R.J.	1997	Microbial ecology of treated lap-joints exposed at Hilo, Hawaii, for 24 months. IRG 97-20107.	N	Public
A 5/23	Drysdale, J.A., Hedley, M.E., Loh, E., Hong, L.T.	2000	Comparative performance of copper azole and copper chrome arsenate treated rubber wood in Australian, Malaysian and New Zealand test sites. IRG/WP 00-30213.	N	Public
A 5/24	Jermer, J., Evans, F.G., Johanson, I.	2001	Experiences with penetration of copper-based wood preservatives. IRG/WP 01-20233.	N	Public
A 5/25	Wakeling, R.	2001	Effect of test site location on in-ground preservative performance after six years. IRG/WP 01-20231.	N	Public
A 5/26	Suttie, E.D., Bravery, A.F., Dearling, T.B.	2002	Alternatives to CCA for ground contact protection of timber: a perspective from the U.K. performance and service life expectations. IRG/WP 02- 30289.	N	Public
A 5/27	Creffield, J., Drysdale, J.A., Chew N.	1996	In-ground evaluation of a copper azole wood preservative (Tanalith E) at a tropical Australian test site. IRG/WP 96-30100.	N	Public
A 5/28	Henningson, B., Norman E .	1980	A marine borer test with waterborne preservatives. IRG/WP 80-452.	N	Public
A 5/29	Humar, M., Petric, M., Pohleven, F., Sentjurc, M.	2000	Changes of EPR spectra of wood impregnated with copper based preservative during exposure to *Antrodia vaillantii*. IRG/WP 00-10355.	N	Public
A 5/30	Pohleven, F., Humar, M., Amartey, S., Benedik, J.	2002	Tolerance of wood decay fungi to commercial copper-based wood preservatives. IRG/WP 02-30291.	N	Public
A 6.1.1	Sterner, W., Chibanguza, G.	1988	Acute Oral Toxicity in Rats with Copper Hydroxide (in Accordance with OECD Principle 401) Laboratory: IBR Doc. No.: URA-97-08740-045 Date: 01.12.1988 GLP: no, not mandatory in year 1988; not published	Y	SPU
A 6.1.2	Sterner, W., Chibanguza, G.	1988	Acute Dermal Toxicity in Rats with Copper Hydroxide (In Accordance with OECD Principle 402) Laboratory: IBR Doc. No.: URA-97-08740-046 Date: 01.12.1988 GLP: no, not mandatory in year 1988; not published	Y	SPU
A 6.1.3	Chevalier, F.	2003	Acute inhalation toxicity study of SPU-00620-F in rats Laboratory: LPT Doc. No.: 17150/03 Date: 18.12.2003 GLP: yes; not published	Y	SPU
A 6.1.4.1	Sterner, W., Chibanguza, G.	1988	Cutaneous Irritation Test with Copper Hydroxide on the Rabbit Laboratory: IBR Doc. No.: URA-97-08740-048 Date: 01.11.1988 GLP: no, not mandatory in year 1988; not published	Y	SPU

A 6.1.4.2	Sterner, W., Chibanguza, G.	1988	Eye Irritation Test with Copper Hydroxide on the Rabbit Laboratory: IBR Doc. No.: URA-97-08740-049 Date: 01.12.1988 GLP: no, not mandatory in year 1988; not published	Y	SPU
A 6.1.5	Bien, E.	1992	Guinea Pig Maximisation Test of Skin Sensitization with URA-08740-F-O-WP Laboratory: IBR Doc. No.: URA-97-08740-050 Date: 00.07.1992 GLP: yes; not published	Y	SPU
A 6.2 /01	Leeming, N.M.	2003	Absorption, distribution, metabolism and excretion of copper in humans and in domestic and laboratory animals Laboratory: EUCuTF Doc. No.: 00620B-IIA-62a Date: 05.11.2003; not published	Y	SPU
A 6.2 /02	Himmelstein, M.W.	2003	Five copper substances - absorption, distribution, and excretion in male rats (Draft) Laboratory: Haskell Doc. No.: 00620B-IIA-62b Date: 18.11.2003 GLP: yes; not published	Y	SPU
A 6.2 /03	Roper, C.S.	2003	The in vitro percutaneous absorption of copper from various formulations through human skin Laboratory: Inveresk Doc. No.: 22829 Date: 27.08.2003 GLP: yes; not published	Y	SPU
A 6.2 /04	Anonymous	1996	Trace elements in human nutrition and health - Chapter 7 World Health Organisation; 1996; 7; 123-143 Doc. No.: 00620B-IIA-62c Date: 00.00.1996; published	N	Public
A 6.2 /05	Anonymous	1998	Copper - Environmental Health Criteria 200 World Health Organisation; 1998; 360p. Doc. No.: 00620B-IIA-62d Date: 00.00.1998; published	N	Public
A 6.2 /06	Mason, K.E.	1979	A conspectus of research on copper metabolism and requirements of man J. Nutrition; 1979; 109; 11; 1979-2066 Doc. No.: 97-08740-041 Date: 00.11.1979; published	N	Public
A 6.2 /07	Österberg, R.	1980	Physiology and Pharmacology of Copper Pharmac. Ther.; 1980; 9; 121-146 Doc. No.: 97-08740-043 Date: 00.00.1980; published	N	Public
A 6.2 /08	Winge, D., Mehra, R.	1990	Host Defense against Copper Toxicosis International Review of Experimental Pathology; 1990; 31; 47-83 Doc. No.: 97-08740-110 Date: 00.00.1990; published	N	Public
A 6.2 /09 **A 7.5.5** /05	Aoyagi, S., Baker, D.H.	1993	Bioavailability of copper in analytical-grade and feed-grade inorganic copper sources when fed to provide copper at levels below the chick's requirement Poultry Sci.; 1993; 72; 1075-1083 Doc. No.: 00620B-IIA-62e Date: 00.00.1993; published	N	Public

A 6.2 /10 **A 7.5.5** /06	Baker, D.H.	1999	Cupric oxide should not be used as a copper supplement for either animals or humans Am. Soc. Nutri. Sci. J. Nutr.; 1999; 129; 2278-2279 Doc. No.: 00620B-IIA-62f Date: 00.00.1999; published	N	Public
A 6.2 /11	Cage, S.	2003	Copper compounds – in vitro dermal penetration study through human skin. Huntingdon Life Sciences Ltd., Huntingdon, UK, Report no.: CSV 004/023929 Date: July 15, 2003 GLP: yes, not published.	Y	SPU
A 6.2 /12	Toner, F., Roper, C.S.	2004	The in vitro percutaneous absorption of copper from various formulations through human skin – dermal delivery. Inveresk Research, Tranent, Scotland Report no.: 23873 Date: June 18, 2004 GLP: yes; not published.	Y	SPU
A 6.3.1	Boyden, R., et al.	1937	Effect of Feeding High Levels of Copper to Albino Rats The Journal of Nutrition; 1938; 4; 15; 397-402 Doc. No.: URA-97-08740-051 Date: 00.00.1938; published	N	Public
A 6.4.1 /01	Hébert, C.D.	1993	NTP Technical Report on Toxicity Studies of Cupric Sulfate Administered in Drinking Water and Feed to F344/N Rats and B6C3F1 Mice NTP Toxicity Rep. Series No.29, NIH Publication 93-3352; 1993 Doc. No.: 00620-2-05-47a Date: 00.07.1993; published	N	Public
A 6.4.1 /02	Hébert, C.D., et al.	1993	Subchronic Toxicity of Cupric Sulfate Administered in Drinking Water and Feed to Rats and Mice Fundam. Appl. Toxicol.; 1993; 21; 461-475 Doc. No.: 00620-2-05-47b Date: 00.00.1993; published	N	Public
A 6.4.1 /03 **A 6.8.1** /05 **A 6.8.2** /02	Anonymous	1982	Joint FAO/WHO Expert Committee on Food Additives: Copper WHO Food Additives SeriesToxicological Evaluation of Certain Food Additives; 1982; 17; 265-296 Doc. No.: URA-97-08740-057 Date: 00.00.1982; published	N	Public
A 6.4.1 /04	Miranda, C., et al.	1981	Dietary Copper Enhances the Hepatoxicity of Senecio jacobaea in Rats Toxicol. Appl. Pharmacol.; 1981; 60; 418-423 Doc. No.: 97-08740-055 Date: 00.00.1981; published	N	Public
A 6.4.1 /05	Ochiai, T., et. al.	1985	Oral Acute and Chronic Feeding Toxicity Tests on Green Patina (Basic Cupric Carbonate) in Rats Shokuhin Eiseigaku Zasshi; 1985; Vol.26; No.6; 605-616 Doc. No.: 00940B-IIA-611b Date: 00.00.1985; published	N	Public
A 6.4.1 /06	Fujita, M., Nakazawa, H.	1985	The influence of chronic exposure to basic cupric carbonate on levels of copper, iron, and zinc in tissues of rats Shokuhin Eiseigaku Zasshi; 1985; 26; 617-623 Doc. No.: 00620B-IIA-641a Date: 00.00.1985; published	N	Public
A 6.4.1 /07	Hall, E., MacKay, E.M.	1931	Does Copper Poisoning Cause Pigmentation and Cirrhosis of the Liver? Am. J. Path.; 1931; 7(4); 327-342 Doc. No.: 97-08740-059 Date: 00.07.1931; published	N	Public

A 6.5 /01	Harrison, J.W.E., et. al.	1954	The Safety and Fate of Potassium Sodium Copper Chlorophyllin and Other Copper Compounds J. Am. Pharm. Ass.; 1954; XLIII; 12; 722-737 Doc. No.: URA-97-08740-067 Date: 00.00.1954; published	N	Public
A 6.5 /02	Haywood, S.	1980	The Effect of Excess Dietary Copper on the Liver and Kidney of the Male Rat J. Comp. Path.; 1980; 90; 217-232 Doc. No.: 97-08740-054 Date: 00.00.1980; published	N	Public
A 6.5 /03	Haywood, S.	1985	Copper Toxicosis and Tolerance in the Rat; I - Changes in Copper Content of the Liver and the Kidney J. Path.; 1985; 145; 149-158 Doc. No.: 97-08740-053 Date: 00.07.1985; published	N	Public
A 6.6.1 /01	Ballantyne, M.	1994	Study to determine the ability of Copper II sulphate pentahydrate to induce mutation in five histidine-requiring strains of Salmonella typhimurium Laboratory: Hazleton Doc. No.: 456/31 Date: 21.06.1994 GLP: yes; not published	Y	SPU
A 6.6.1 /02	Shimizu, H., et al.	1985	The results of microbial mutation test for forty-three industrial chemicals Jpn. J. Ind. Health; 1985; 27; 400-419 Doc. No.: 00620B-IIA-661a Date: 00.00.1985; published	N	Public
A 6.6.4 /01	Riley, S.E.	1994	Copper II Sulphate Pentahydrate: Induction of micronuclei in the bone marrow of treated mice Laboratory: Hazleton Doc. No.: 456/33 Date: 07.07.1994 GLP: yes; not published	Y	SPU
A 6.6.4 /02	Agarwal, K., et al.	1990	Clastogenic effects of copper sulphate on the bone marrow chromosomes of mice in vivo Mut. Res.; 1990; 243; 1-6 Doc. No.: 00620B-IIA-664a Date: 00.00.1990; published	N	Public
A 6.6.4 /03	Ornaghi, F., Giavini, E.	1989	Induction of micronuclei in pre-implantation rat embryos in vivo Mut. Res.; 1989; 225; 71-74 Doc. No.: 00620B-IIA-664b Date: 00.00.1989; published	N	Public
A 6.6.4 /04	Tinwell, H, Ashby, J.	1990	Inactivity of copper sulphate in a mouse bone-marrow micronucleus assay Mut. Res.; 1990; 245; 223-266 Doc. No.: 00620B-IIA-664c Date: 00.00.1990; published	N	Public
A 6.6.5	Ward, P.J.	1994	Copper II sulphate pentahydrate: measurement of DNA synthesis in rat liver using an in vivo / in vitro procedure Laboratory: Hazleton Doc. No.: 456/32 Date: 20.07.1994 GLP: yes; not published	Y	SPU
A 6.6.6	Bhunya, S.P., Pati, P.C.	1987	Genotoxicity of an Inorganic Pesticide, Copper Sulphate in Mouse in vivo Test System Cytologia; 1987; 52; 801-808 Doc. No.: 00620B-IIA-666 Date: 00.00.1987; published	N	Public

A 6.7 /01	Howell, J.S.	1958	The effect of copper acetate on p-dimethylaminoazobenzene carcinogenesis in the rat Br. J. Cancer; 1958; 12; 594-610 Doc. No.: 00620B-IIA-67a Date: 00.00.1958; published	N	Public
A 6.7 /02	Haywood, S., Loughran, M.	1985	Copper toxicosis and tolerance in the rat, II Tolerance - a liver protective adaption Liver; 1985; 5; 267-275 Doc. No.: 00620B-IIA-67b Date: 00.00.1985; published	N	Public
A 6.8.1 /01	Munley, S.M.	2003	Five copper substances - repeated dose toxicity and tolerability study in non-pregnant rabbits Laboratory: Haskell Doc. No.: 00620B-IIA-681a Date: 17.11.2003 GLP: yes; not published	Y	SPU
A 6.8.1 /02	Munley, S.M.	2003	Copper - a 23-day tolerability study in non-pregnant rabbits Laboratory: Haskell Doc. No.: 00620B-IIA-681b Date: 17.11.2003 GLP: yes; not published	Y	SPU
A 6.8.1 /03	Munley, S.M.	2003	Copper hydroxide - pilot developmental toxicity study in rabbits Laboratory: Haskell Doc. No.: 00620B-IIA-681c Date: 17.11.2003 GLP: yes; not published	Y	SPU
A 6.8.1 /04	Munley, S.M.	2003	Copper hydroxide - developmental toxicity study in rabbits Laboratory: Haskell Doc. No.: 00620B-IIA-681d Date: 17.11.2003 GLP: yes; not published	Y	SPU
A 6.8.1 /06	Haddad, D.S., et al.	1991	The effect of copper loading on pregnant rats and their offspring Functional and Developmental Morphology; 1991; 1; 17-22 Doc. No.: 00620B-IIA-681e Date: 00.00.1991; published	N	Public
A 6.8.1 /07	Marois, M., Buvet, M.	1972	Etude de l'action de l'ion cuivre sur la gestation de la ratte et de la lapine (Study on the effect of copper ions on the gestation of the rat and the rabbit) C.R. Seances Soc. Biol. Fil. (Paris); 1972; 166; 1237-1240 Doc. No.: 00620B-IIA-681f Date: 00.00.1972; published	N	Public
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