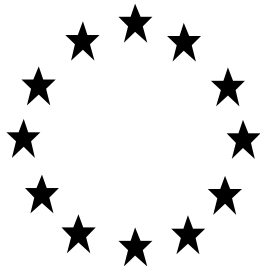
Regulation (EU) No 528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report



Copper, granulated

Product-type 8

(Biocide for use as wood preservative)

December 2015

FRANCE

CONTENTS

1. STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1. Procedure followed

This assessment report has been established as a result of the evaluation of the new active substance granulated copper, (7440-50-8), as product-type 8 (wood preservative), carried out in the context of Directive 98/8/EC concerning the placing of biocidal products on the market[1], with the original view to the possible inclusion of this substance into Annex I or IA to that Directive, then carried out in the context of Regulation (EU) No 528/2012[2], with a view to the possible approval of this active substance.

On 30th of August 2013, France competent authorities received a dossier from the Arch Timber Protection. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation on 6th of March 2014.

The hazard assessment of copper, granulated was conducted in line with the assessment of copper compounds dossiers for PT8 for which the active substances have already been included into the annex I of Directive 98/8/EC. It has to be noted that Arch Timber Protection has a letter of access for the PT8 copper compounds dossiers, which permits to use several agreed end-points for PT8 copper compounds in the assessment of copper, granulated as PT8.

On 3rd of April 2015, the Rapporteur Member State submitted to ECHA and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report.

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 Agency. Revisions agreed upon were presented at the Biocidal Products Committee and its Working Groups meetings and the competent authority report was amended accordingly.

1.2. Purpose of the assessment report

The aim of the assessment report is to support the opinion of the Biocidal Products Committee and a decision on the approval of copper, granulated for product-type 8, and, should it be approved, to facilitate the authorisation of individual biocidal products. In the evaluation of applications for product-authorisation, the provisions of Regulation (EU) No 528/2012 shall be applied, in particular the provisions of Chapter IV, 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 from the Agency web-site shall be taken into account.

[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] Regulation (EU n° 528/2012 of the European Parliament and of the council o 22 May 2012 concerning the making available on the market and use of biocidal products.

However, where conclusions of this assessment report are based on data protected under the provisions of Regulation (EU) No 528/2012, such conclusions may not be used to the benefit of another applicant, unless access to these data for that purpose has been granted to that applicant.

1.3. Applicant

Name: Arch Timber Protection

Address:

Technical Centre
Wheldon Road
Castleford
West Yorkshire WF10 2JT
UK

2. OVERALL SUMMARY AND CONCLUSIONS

2.1. Presentation of the Active Substance

Copper, granulated is being proposed as an alternative precursor for the active substance Cu^{2+} used in industrial wood preservation products (PT08). Previously, basic copper carbonate, copper oxide and copper hydroxide have been evaluated as precursors for the active substance Cu^{2+} for PT 8 and they have been included into Annex I of Directive 98/8/EU in 2012. Final Competent Authority Reports (CAR) are therefore available for these substances.

The supporting documentation for the precursors relies on a core copper dossier developed by the European Copper Institute (ECI) for the purposes of a Voluntary Risk Assessment of copper and copper compounds (EU RAR – EU Risk Assessment Report). It is proposed for the support of copper, granulated as a new precursor of the active substance Cu^{2+} that the core copper dossier can be used in an identical manner. The core copper dossier relies on data on soluble copper compounds (e.g. copper sulfate/copper chloride) and the resulting risk assessment should be considered as conservative approach using read-across from copper sulfate to other less soluble substances e.g copper, granulated, even if it may result in over-estimation of the effects for poorly soluble substances. However, this approach is considered appropriate to reduce the amount of animal testing.

Therefore, for the active substance dossier on copper, granulated, the final CAR endorsed for basic copper carbonate has been used as the basis of this new subsmission, with the following exceptions:

1. General Substance Information
    a. Identification
    b. Purity/impurity
    c. Physico-chemical properties
    d. Classification and labelling
2. Human Health Effects Assessment
    a. Acute toxicity
    b. Irritation and corrosivity
    c. Sensitisation

It is proposed by the Applicant that the copper, granulated is completely solubilised in the solvent of choice, monoethanolamine, and the resulting product is identical to the dummy product previously evaluated in the dossier for basic copper carbonate. Therefore assessments for copper, granulated is identical to those previously performed by the RMS and Member States for basic copper carbonate (PT8). These dossiers are reproduced for completeness in this submission.

Note: The substance copper, granulated is recycled copper in granular form, and is defined as active substance as manufactured according to the REACH definition. The active substance reacts as cupric ion Cu2+.
The active substance has been defined as copper, granulated for the purposes of this submission as a new precursor of the active substance Cu^{2+}. In the CLP guidance, copper massive is defined as a sphere with a diameter > 1 mm and with a corresponding surface area of < 0.67 mm^2/mg (<6.74 cm^2/g).
The particles of the active substance copper, granulated are cylindrical with a size higher than 1 mm for one dimension (the length ranges between 0.9 and 6.0 mm with a mean at 2.1 mm) and with the other size below 1 mm (the width ranges between 0.494 and 0.949 mm with a mean at 0.706 mm) whereas the surface area of the active substance copper, granulated has been found to be 25.6 cm^2/g which is significantly above the limit for massive. Therefore the active substance copper, granulated cannot be defined as massive form.

The active substance copper, granulated cannot also be defined as a powder because the active substance is not classified by inhalation based on the particle size of the active substance. Copper powder can have a much lower particle size than the one of the active substance which will lead to a classification by inhalation. It is an issue to have under the same name different substances with different classification and toxicological properties.

Therefore for the purposes of this submission, the active substance has been defined as copper, granulated and is considered between massive and powder form.

The active substance does not fulfil the criteria of article 3.1(z) of the BPR, therefore it is not a nanomaterial.

The applicant is not currently placing nano forms of copper, granulated on the market. Therefore, the current assessment report does not cover potential nanoforms of this active substance, should such forms exist.

2.1.1. Identity, Physico-Chemical Properties & Methods of Analysis

2.1.1.1. Identity, Physico-Chemical Properties & Methods of Analysis of active substance

Tableau 2.1-1: Identification of copper, granulated

CAS-No.	7440-50-8
EINECS-No.	231-159-6
Other No. (CIPAC, ELINCS)	None
IUPAC Name	Copper
Common name, synonyma	Copper, granulated
Molecular formula	Cu
Structural formula	Cu
Molecular weight (g/mol)	63.55

The active substance as manufactured is copper, granulated which has a purity of > 99.0%. The active substance reacts as cupric ion Cu^{2+}.

The issues related to the setting of the reference specification of active substance copper, granulated are the same as the ones identified and discussed for the other copper compounds PT8. The specification of copper, granulated has been assessed regarding to the batches tested in the toxicological and ecotoxicological studies. The tested batch of copper from the key toxicological study used to perform the human health risk assessment, was considered as the one to use to compare and validate the specification of copper, granulated as submitted by the applicant. This approach is the one which was followed and agreed for the Annex I inclusion of the active substances copper PT 8 dossiers.

Result of the assessment of the reference specifications of granulated Cu are presented in the document Confidential specification_Cu_granulated.

Copper, granulated as manufactured contains four relevant impurities: arsenic, cadmium, nickel and lead.

There is one source which is acceptable. The specifications are covered by the tested batches.

2.1.1.1.1. Physico-chemical properties

Copper, granulatedCopper, granulated is a course granular solid with a cylindrical shape with slight metallic odour. The length ranges between 0.9 and 6.0 mm with a mean at 2.1 mm and the width ranges between 0.494 and 0.949 mm with a mean at 0.706 mm. Its melting point is 1059-1069 °C. It is not required to test for vapour pressure as the melting point is above 300 ºC. Solubility in water is pH dependent (acidic conditions). The solubilisation results of the oxido-reduction reaction of the copper metal into ionic copper. Cu(0) → Cu(I) → Cu (II). At low pH, these reactions are promoted. At pH 6.34-7.56 and at 20 °C the solubility is 1 mg/L.

Further data should be provided at different pH. It does not have any flammable, explosive or oxidising properties.

The active substance is not a nanomaterial.

2.1.1.1.2. Analytical methods for determination and identification

Copper is determined by complexometric titration with EDTA. The method uses anitric acid digestion to dissolve the copper into solution. The method is not specific to copper metal. However this is acceptable as an XRD shows no other form of copper than Copper (0).

Trace metals of toxicological significance can be determined by ICP-MS. Before analysis, the samples are dissolved in an acid nitric mixture. The provided analytical method is validated.

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, limited validation data were accepted.

No method is required for analysis of residues in food or feedstuffs.

2.1.1.2. Identity, physico-chemical properties and methods of analysis of the biocidal product

There is one representative product "Amine Copper solution" (ACQ-C2D) which contains up to 13% ranging between 10 and 13 % of copper in the form of copper, granulated. The content of the substance in a product should not be a range. This should be clarified.

The biocidal product is an intense cobalt blue liquid, with a slight ammonia odour. Its pH is slightly basic since pH = 9.54 at 23 °C. It has a relative density of 1.220. It has neither flammable nor explosive properties. It is a weak oxidising agent.
The product is stable 12 months at ambient temperature and 50 days at 30 °C.
Surface tension, persistent foaming and compatibility with other product will be required at the product authorisation stage.

A validated analytical method must be provided at the product authorization stage for the determination of copper in the product.

2.1.2. Intended Uses and Efficacy

The assessment of the biocidal activity of the active substance demonstrates that it has a sufficient level of efficacy against the target organism(s) and the evaluation of the summary data provided in support of the efficacy of the accompanying product, establishes that the product may be expected to be efficacious.

In addition, in order to facilitate the work of Member States in granting or reviewing authorisations, the intended uses of the substance, as identified during the evaluation process, are listed in Appendix II.

2.1.2.1. Field of uses

Product Type 8 (PT) wood preservative

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

The active substance is restricted to industrial use only, in timber treatment plants operated by professionals.

Copper, granulated is being proposed as an alternative precursor for the active substance Cu^{2+}. As basic copper carbonate has been evaluated as precursor for the active substance and was agreed for Annex I inclusion of Directive 98/8/EC in 2012; cross reference to this dossier has been accepted from an efficacy point of view. Indeed, the copper, granulated is completely solubilized in the solvent monoethanolamine and the resulting product is identical to the representative product previously evaluated in the dossier for basic copper carbonate.

Then the representative biocidal product ACQ-C2D is supplied as water soluble preservative concentrate. It is applied by vacuum pressure for the treatment of timbers of Use Class (UC) 1, 2, 3 and 4.

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

2.1.2.2. Function

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

2.1.2.3. Mode of action

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

Copper acts by prevention of fungal infestation. Upon contact with the fungicide layer, the spores passively take up copper II cations which hinder germination. Copper II cations also act as a feeding and cell poison in insects independent from the kind of application. The threshold concentration is about 0.1 % of elemental copper. Amongst others, the influence of copper II cations in the organism causes unspecific denaturation of proteins and enzymes. For this reason it also acts as a feeding and cell poison in insects.

2.1.2.4. Objects to be protected, target organism

The target species are fungi (wood rotting basidiomycetes and soft rot fungi) and insects. Regarding insects, an efficacy against wood boring beetles and termites has been claimed by Arch Timber Protection. It should be noticed that no claim concerning the efficacy of copper on blue stain and mould, although efficacy against these organisms is well known and documented.

Copper efficacy was examined for the following target organisms:

- For the product ACQ-C2D (WPCTF):

Application mode	**Target organism**	**active substances rate**
vacuum pressure timber impregnation	Fungi: Wood rotting basidiomycetes and soft rot fungi Insects: Wood boring beetles and termites	The typical use of copper for each use class is likely to be : UC 1, 2, 3≥1.9 kg Cu/m^3 sapwood loading UC 4≥ 3.42 kg Cu/m^3 sapwood loading These data are based on the current state of the art concerning the practical uses of copper based products during the last decades, related to the expected life of wooden elements treated with copper based products

Taking into account of the potential influence of the formulation on the efficacy, concentrations proposed above of active substance copper should be considered as an indicator only.

2.1.2.5. Resistance

According to the data submitted in the dossier, no development of resistance from the target fungi has been reported. Nevertheless, based on literature data, there are strains of some species of wood destroying fungi that exhibit tolerance to copper and then it should pay attention to possible occurrence of resistance.

According to the data submitted, no 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.

2.1.3. Classification and Labelling

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

- Active substance

Regulation 1272/2008	
Classification and Hazard statements	Eye Irrit. 2 / H319 - Causes serious eye irritation Aquatic Acute 1/H400 – Very toxic to aquatic life Aquatic chronic 1/H410 - Very toxic to aquatic life with long lasting effects

A CLH report presenting this proposal was sent to ECHA the 8th April 2015.

- Biocidal product: ACQ-C2D (WPCTF)

Regulation 1272/2008	
Classification and Hazard statements	Acute Tox. 4/H302 Harmful if swallowed Acute Tox. 3/H331 Toxic if inhaled Skin Corr. 1B/H314 Causes skin burns and eye damages Aquatic chronic 2/H411 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

Foreword

Copper is a micronutrient. It is **essential** for life and necessary for all living cells. It is used in many enzyme systems, particularly in energy transfer where the property of electron transfer is exploited in photosynthesis and catabolism. It is involved in the reactions and functions of many enzymes (e.g. amine oxidase, ceruloplasmin, cytochrome-c oxidase...) and in addition, copper is involved in angiogenesis, neurohormoneangiogenesis, neuro-hormone release, oxygen transport and regulation of genetic expression. Copper is present in almost all foods, and some products. Most human diets naturally include between 1 and 2 mg/person/day of copper, with some containing up to 4 mg/person/day.

The copper transport mechanisms in the organism form part of the system of

homeostasis: the body is able to maintain a balance of dietary copper intake and excretion that allows normal physiological processes to take place. The relationship between copper concentration and observed effects show a flattened 'U'-shaped dose-response curve. The left side of the 'U' curve represents deficiency, where intake of copper is less than required. This can lead to lethality, especially in children, where copper is essential for growth. Copper deficiency is associated with growth retardation, anemia, skin lesions, impaired immunity, intestinal atrophy, impaired cardiac function, reproductive disturbance, neurological defects and skeletal lesions. Copper is essential for normal physiological function such as cellular respiration, free radical defence, synthesis of melanin, connective tissue, iron metabolism, regulation of gene expression, and normal function of the heart, brain and immune system.

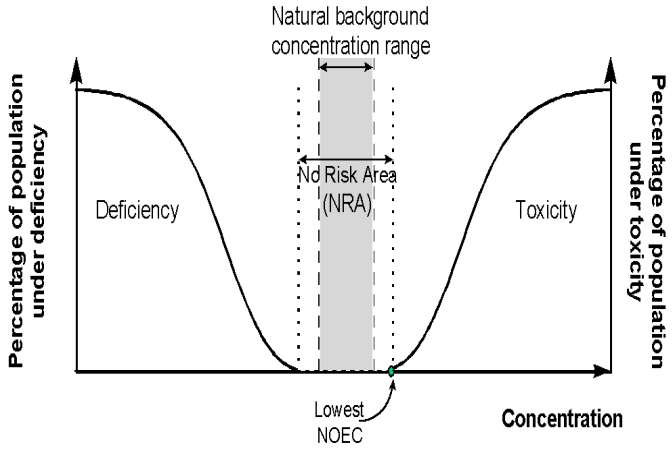


Figure 2.2-1: Dose-response curve for copper (adapted from Ralph and McArdle, 2001).

The central near-horizontal part of the 'U' curve represents homeostasis, where intake and excretion are balanced and copper level is in a normal range. The right-hand part of the 'U' represents toxicity or excess copper disease. Chronic copper toxicity is extremely rare, and the upper limit of homeostasis has never been strictly defined.

The active substance released from copper, granulated is the cupric ion.

Although a full guideline ADME study has not been performed for copper, the knowledge of copper in the human body at the level of the organism, organ, cell and gene is sufficient to meet the requirements of the Regulation. Extensive information is available relating to the toxicokinetics and toxicodynamics of the copper ion within the human body. The cupric ion is an inorganic charged species that cannot exist in an un-solvated, un-associated state and so cannot be prepared in a pure form. Submission of toxicology data for Cu^{2+} is therefore not possible or relevant. Under these circumstances, information relating to copper sulfate pentahydrate is provided instead and where data for the copper sulfate pentahydrate is not available, information has been supplied with other forms of copper which have been demonstrated to all produce cupric ion in a bioequivalence study.

2.2.1.1.1. Metabolism

Absorption

- **Oral administration**

The proportion absorbed in a clinical study over 90 days varied between 56 % for subjects

receiving 0.8 mg Cu/day, 36 % for individuals receiving 1.7 mg Cu/day and 12% for individuals receiving 7.5 mg Cu/day.

To determine the systemic NOAEL, as stated in the Technical Meetings (TM) III08, and consistencely with the EU RAR[4], the percentage of the administered copper sulfate pentahydrate retained to be available for absorption following administration in the diet for rats is 25 % whereas 36 % will be used as the oral absorption value in humans.

- **Dermal administration**

For the active substance, in order to harmonize BPR dossier and EU RAR, the dermal delivery of copper compound concentrate and in solution retained at TMIII08 was 5 %.

- **Inhalation administration**

No animal or human studies were available to supply an inhalation absorption level. Thus, the default absorption value of 100 % is used in the 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.

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.

2.2.1.1.2. Acute toxicity

No acute toxicity was realised with copper, granulated. The acute toxicity of biocidal copper, granulated is based on coated copper flake studies.

A study proposed under REACH dossier by applicants shows that when the particle size and surface area are taken into account, the toxicity can differ by different release rate of cupric ion.

[4] Voluntary risk assessment reports (VRAR) submitted to ECHA based on industry initiative to follow the risk assessment procedures of Existing Substance Regulation (EEC) No 793/93 June 2008.

The surface of coated copper flake was measured as 2.9 m^2/g whereas a typical powder was measured as 0.024 m^2/g. A much higher reactivity and solubility of coated copper flake than copper, granulated can therefore be anticipated (more close to powder criteria). Relative bioaccessibility in gastric fluids of 0.1 and 1% were noted for copper massive and copper powder, respectively, compared to 42-71% for coated copper flake and 100% for copper sulphate.

Evidence for the absence of concerns related to "acute oral toxicity" of copper in granulate and massive forms can be obtained from the toxicity data, expressed as "biosoluble" copper for respectively copper flakes, and $CuSO_4$. The biosoluble effects levels are calculated as the LD_{50} (mg substance/kg bw) x % Cu x % biosoluble.

Acute toxicity of copper compounds, expressed as external doses of substance and calculated as internal dose, using the biosolubility data.

Source Material Tested	Administered LD_{50} (mg substance/kg bw)	Cu Biosolubility (%)	LD_{50} as biosoluble Cu (mg Cu/kg bw)
Cu flakes; 98% Cu	300 – 500 (5 µm)	42 – 71 (8.5 µm)	231 (121 – 341) (5 µm)
$CuSO_4$; 25.4% Cu	481	100	123
CuCl; 63.78% Cu	336	67 – 94	144 - 201

Finally, in comparing the submitted data on the particle size and surface area of copper, granulated with the copper massive and powder data, this confirms that the copper, granulated would not be classified by the oral route.

Oral:

A linear relationship was observed between the surface area and the copper biosolubility in gastric fluids. Linear extrapolation demonstrates that a relative Cu biosolubility of 6 to <17% is needed to be outside of the criteria for an oral classification entry. Indeed, considering the limit maximum of 2000 mg/kg/d to not classify an active substance, a release between 6 and 17% are necessary to obtain the range of LD_{50} as biosoluble Cu of 123-341 mg Cu/kg bw, which lead to a classification. The relative biosolubilities of copper powder is 1% , further confirming that for copper granulates, there is no need for an acute oral classification entry.

Based on the results of the acute oral toxicity study, coated copper flake is classified as Acute Tox 4 – H302 according to the classification criteria as given in CLP regulation (LD_{50} = 300-500 mg/kg bw for males and females). Comparing the submitted data on the particle size and surface area of copper, granulated with the copper massive and powder data above, this indicates that the copper, granulated would also not be classified by the oral route.

Inhalation:

There is no acute inhalation toxicity study available. Indeed, copper, granulated is not available as inhalable particles compared to coated copper flake which is classified Acute Tox 3. For coated copper flake, the particle size is small with a high surface area meaning that the substance can enter into respiratory tract and induces local but also systemic toxicity.

In conclusion, the classification of the coated copper flake cannot be extrapolated to copper,

granulated; no classification is guaranteed for copper, granulated.

Dermal:

Coated copper flake is not classified by dermal route. In this context, considering all the data mentioned above and that none of the assessed copper compounds is classified for skin, no toxicity for copper, granulated is suspected.

2.2.1.1.3. Skin and eye irritation

Coated copper flake is not classified as skin irritant but classified as eye irritant. Considering the local effects, this classification for coated copper flakes is considered as a worst case for copper, granulated.
Consequently, the same classification is proposed for copper, granulated: No classified for skin irritation and eye irritant category 2, H319.

2.2.1.1.4. Skin sensitization

Coated copper flake is not hazardous or classified as a skin sensitising.
Considering the relative high potential bio-solubility of coated copper flakes compared to copper, granulated and copper massive materials, it can be concluded that copper, granulated and massive forms (including copper, granulated), do not need to be classified for skin sensitisation.

For systemic effect after repeated exposure, the most toxic form of any copper salt is the Cu^{2+} ion and the copper compound which releases more Cu^{2+} is the most soluble salt: copper sulphate. In this context, to avoid assay in animals, it was decided at TM III 08 to extrapolate data from copper sulphate to the other copper compounds when no data is available.
For several compounds, toxicity of anion could be suspected. In this case, a specific assessment could be realized. However, for copper, granulated, there is none anion. Therefore, use the data of copper sulphate is conservative.
This read across between copper compounds and copper sulphate for repeated toxicity and CMR endpoints was adopted by TM for previous PT8 and PT2 copper dossiers. This approach was also presented in the CLH report for copper compounds.

2.2.1.1.5. Oral repeated toxicity

With regard to oral repeated dose toxicity, the 90-day dietary study was considered to be the pivotal study for Cu^{2+} presented as copper sulphate pentahydrate and should be considerated also as the key study for copper, granulated risk assessment. Based on kidney damages, consisting in an increase of cytoplasmic protein droplets, a NOAEL of 1000 ppm in rats (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). The NOAEL of 16.3 mg/kg bw/d was used for the risk characterisation.

Mice equally displayed forestomach lesions when exposed through diet to copper sulphate

for 92 days but this occurred at a much higher dose (4000 ppm, corresponding to 187 and 267 mgCu/kg bw/day in males and females, respectively). No other damage was observed in mice.

Subchronic and chronic studies in the dog can be waived, as the dog is an unsuitable animal model for studying copper toxicity in relation to man. Indeed, dogs have a different form of albumin compared to rats and humans, and cannot excrete copper in the bile as readily as most other species. The dog is not a good animal model for human risk assessment of copper.

2.2.1.1.6. Dermal repeated toxicity

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 and the weak rate of dermal penetration, a toxic effect is not expected.

2.2.1.1.7. Inhalation repeated toxicity

There were no inhalation repeated dose toxicity studies. No exposure of copper, granulated by this route is expected. During use of product, the inhalation exposure will be by exposure to ion Cu^{2+}. Indeed, in the representative product, all copper, granulated is dissolved into $Cu2^{+}$ before used.

2.2.1.1.8. Genotoxicity

- *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.
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, nor DNA damage in a rat hepatocyte UDS assay.
Equivocal results of additional *in vivo* genotoxicity studies from the public domain [redacted] are observed, but these studies do not meet the higher reliability criteria (1 or 2) under the regulation. Copper is therefore considered as non genotoxic

2.2.1.1.9. Chronic toxicity and 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, based on the available data, human data and due to the lack of genotoxicity there is no need to conduct new carcinogenicity studies.

2.2.1.1.10. Reproductive toxicity

Developmental toxicity

A developmental study in mice was submitted but suffers from major methodological deficiencies including no information on maternal toxicity and is neither adequate for classification and labelling nor for risk assessment.

A two generation study is also available. This study also gives valuable information on the teratogenicity potential of copper in the rat, notably, investigation of F1 and F2 litters showed no test substance related effects on the following parameters:

- pups survival, sex ratio, and survival indices during the lactation period, body weights and clinical observations during lactation,
- macroscopic examination of pups that died during the lactation period, of weanlings with external abnormalities or clinical signs and of randomly selected weanlings,
- microscopic observations of any gross findings and of liver and brain from randomly selected high-dose and control weanlings.

It is considered inappropriate to consider copper and copper compounds as potential teratogenic compounds due to the complex role of copper in regulating normal foetus development in humans at levels considered higher than would be expected to occur through the normal production and use of any copper compound.

Fertility

According to the two-generation oral reproduction study in rats administered with copper sulphate pentahydrate, 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, granulated (by read across) should not be classified as reprotoxic compounds.

2.2.1.1.11. Neurotoxicity

From a neurotoxicological point of view, copper has been suspected to be involved in the pathogenesis of the Alzheimer's disease and other prion-mediated encephalopathies. Although no valid neurotoxicity study was submitted, no evidence of a neurotoxic potential of copper is suspected from the available studies in animals up to now. No further study was therefore deemed necessary.

2.2.1.2. Effects assessment

AEL DERIVATION

The key health effect to consider in the risk characterization is kidney and forestomach damages observed in the 90-day dietary study, which determined a NOAEL of 1000 ppm (16.3 and 17.3 mgCu/kg bw/day in male and female respectively) in rats. This NOAEL is considered to be the most appropriate in the risk characterization for short-term and chronic exposures (carcinogenicity studies considered unnecessary).

To determine the systemic NOAEL, as stated in TMIII08, consistencely with the EU RAR, the percentage of the administered copper sulphate pentahydrate retained to be available for absorption following administration in the diet for rats is 25 %. Therefore, the systemic NOAEL, based on the NOAEL of 16.3 mgCu/Kg bw/d and the oral absorption of 25% for animals is:

$$NOAELsystemic = NOAEL * 0.25 = 4.1 mgCu \cdot kg^{-1} bw/d$$

To derive the AEL from the NOAEL, the NOAEL is first converted to a systemic NOAEL then it is divided by the assessment factors taking into account uncertainties and extrapolations. The assessment factors were discussed during the TM IV08 and TMI09 for TP 8 copper substances. The same assessment factors wil be used in this coated copper flake dossier..

- Acute-term AEL

The acute-term AEL is the NOAEL (16.3 mg Cu/kg bw/day) times 25%, the absorption factor, divided by the 50-fold safety factor, corresponding to the MOE_{ref} (5 for inter-species variation and 10 for intra-species variation). **An acute-term AEL of 0.082 mg Cu /kg/d** is proposed.

- Medium-term AEL

The medium-term AEL is the NOAEL (16.3 mg Cu/kg bw/day) times 25%, the absorption factor, divided by the 50-fold safety factor, corresponding to the MOE_{ref} (5 for inter-species variation and 10 for intra-species variation). **A medium-term AEL of 0.082 mg Cu /kg/d** is proposed.

- Long-term AEL

The long-term AEL is the NOAEL (16.3 mg Cu/kg bw/day) times 25%, the absorption factor, divided by the 100-fold safety factor, corresponding to the MOE_{ref} (5 for inter-species variation, 10 for intra-species variation and 2 for the duration of exposure from sub-chronic to chronic). **A long-term AEL of 0.041 mg Cu /kg/d** is proposed.

2.2.1.3. Exposure assessment

The representative product is a preventive, industrially applied wood preservative.

It is applied to timber in its diluted ready to use concentration in closed system industrial timber impregnation plant using vacuum pressure treatment cycles. These plants are

automatic in operation and the process begins once the door to the treatment vessel has been closed and locked.

After the treatment process is complete, the timber is held for a post-treatment conditioning period at the treatment plant before being moved into storage for stock or placed into the supply and distribution chains.

The treated timber can then be used either by professional or non-professional persons for a variety of end use applications.

The product "Amine Copper solution" chosen for exposure assessment is considered to be a representative product covering all copper/amine products on the EU market.

Copper concentration is typically 13% w/w in concentrate, which is diluted before impregnation to up to 0.57% w/v copper solution.

The concentration of the solution and the loading into the sapwood depend on the use classes. Hereafter are typical applied concentrations and loadings. The copper loadings are consistent with the efficient doses determined in Document IIIB 5.10.

For a 9.5% Copper solution	Use Classes 1, 2 & 3	Use Class 4
Solution strength	3.33%	6%
Cu concentration in solution	0.317%	0.57%
Solution uptake (in sapwood)	600 L /m^3	600 L /m^3
Cu loading into sapwood	1.9 kg/m^3	3.42 kg/m^3

For a 13% copper solution	Use Classes 1, 2 & 3	Use Class 4
Solution strength	2.44%	4.38 %
Cu concentration in solution	0.317%	0.57%
Solution uptake	600 L /m^3	600 L /m^3
Cu loading into wood	1.9 kg/m^3	3.42 kg/m^3

Therefore, 2 assessments is presented for primary exposure. For secondary exposure, as a worst case approach, only the highest dose is used.

The absorption coefficients used in the assessment exposure are presented in the following table.

	Inhalation route	Oral route	Dermal route
Rate of absorption	100 %	36 % for humans 25% for animals	Concentrated product: 100% Diluted solutions: 5 %

A dermal absorption value of 100% is proposed for concentrate product, considering the corrosive property of product.

2.2.1.3.1. Primary exposure

In this context, 3 phases of potential exposure of industrial users (professional) exist :

- Mixing and loading phase
- Application phase
- Post- application phase.

However, the exposure during the mixing and loading operations is negligible in case of automated transfer/pumping dilution. The exposure during connecting lines would be very low or accidental. Moreover, the product is classified as corrosive. In this context, all the measures to avoid dermal contact will be taking at the industrial level.

The exposure during application is estimated by handling model1, available in TNsG on human exposure part 2 of 2002 and user guidance, considering three treatment cycles of 3 hours each daily.

The exposure during post-application (including maintenance, recycling and disposal) is considered as included in the indicative values from the model.

In tier 1, gloves (default value of model) and no coverall are considered.

In tier 2, coverall is added and the clothing penetration is reduced from 100% to 20% for used of coated coverall.

Values used for the exposure assessment of industrial professional during vacuum pressure treatment.

Parameter	Value		Reference
Concentration of Cu	0.317% w/w	0.57% w/w	
Task duration	3 cycles of 180 min or 540 min		TNsG, 2002
Body weight	60 kg		HEEG opinion: default human factor values for use in exposure assessments for biocidal products, endorsed at TM II 2013
Respiration rate	1.25 m3/hour		HEEG opinion: default human factor values for use in exposure assessments for biocidal products, endorsed at TM II 2013
Dermal absorption	5%		Active substance data
Inhalation absorption	100%		Default value
Inhalation exposure	1.9 mg/m3		Handling model 1 of TNsG 2002 part 2 – page 160 and user guidance page 26 considering the product as water based.
Potential body exposure	8570 mg/cycle		
Actual hand exposure (inside gloves)	1080 mg/cycle		
PPE penetration factors			
Tier IIa: gloves and coated coverall	Gloves: see actual exposure Coated coverall: 10%		HEEG opinion: default protection factors for protective clothing and gloves agreed in TMI 2010

The exposures are represented in the following table:

Task	PPE	Concentration of Cu in solution of treatment	Inhalation systemic exposure mg Cu/kg/d	Dermal systemic exposure mg Cu/kg/d	Total systemic exposure mg Cu/kg/d

Treatment by industrial of wood by vacuum pressure	Tier I: gloves (included in the model)	0.317%	1.13 E-03	8.0 E-02	8.0 E-02
		0.57%	2.03 E-03	1.4 E-01	1.4 E-01
	Tier IIa: gloves and coated coverall	0.317%	1.13 E-03	1.54 E-02	1.65 E-02
		0.57%	2.03 E-03	2.76 E-02	2.96 E-02

Intended uses are restricted to professional application, so non-professional primary exposure are not expected.

2.2.1.3.2. Secondary exposure

The secondary human exposure assessment considers the potential for the exposure of a person in which they may come into contact with copper treated timber. The scenarios used in this assessment are those contained in the TNsG on Human Exposure part 2 and User guidance. The following scenarios have been identified as being relevant for assessing the potential exposure of humans to amine copper treated timbers during and after their use:

- Adults (consumers) - Acute Handling, cutting and sanding treated timbers
- Infants - Acute Chewing preserved timber off-cuts
- Adults (workers) - Chronic Handling, cutting and sanding treated timbers
- Children - Chronic Playing on preserved timber playground equipment
- Infants – Chronic Playing on preserved timber playground equipment and mouth contacts with the treated timber surface

Because there are no volatilised copper residues from amine copper treated wood, exposure by inhalation is considered as negligible.

The scenario of children who lies down near a swimming pool is not assessed in this document. However, if this use is required at the product authorization step, a specific assessment should be realized.

In order to calculate the dermal exposure due to a transfer from wood surface to skin, it is necessary to know the concentration of copper at the surface of wood pieces which can be dislodged to skin by repeated contacts. Copper surface concentration was estimated following 2 methodologies, called Tier 1 and 2.

1) Tier 1

Tier 1 is based on the conservative assumption that all copper in the 1-cm outer layer is in the surface. Considering the copper loadings of 3.42 kg /m^3, for HC 4 class, this leads to a surface concentration 3.42 mg/cm^2. HC 4 class will cover the exposure by HC 1, 2, 3 wood (considering the copper loadings of 1.9 kg/m^3).

Then the default values proposed in TNsG, for notably release and transfer, will be used.

2) Tier 2

When a refinement is necessary an tier 2 is proposed. A dislodgeable surface concentration value of **2 µg Cu/cm^2** value is used and is a figure considered representative of handling treated timber around 48 hours plus after treatment, and for timber that is in the supply chain up until the time that it has been installed in service.

This figure was chosen in a conservative approach on the basis of 3 references.

The results of the exposure assessment are reported in following tables:

Scenario	Total exposure
	Systemic dose mg Cu as / kg bw/d
Acute exposure- Sanding treated timbers	4.5 E-03
Acute exposure- Infant chewing preserved timber off-cuts Tier 1	1.97 E-01
Acute exposure- Infant chewing preserved timber off-cuts Tier 2	3.46 E-03
Chronic exposure- Sanding treated timbers	4.1 E-02
Chronic exposure- Playing on playground structure outdoors	9.89 E-03
Chronic exposure- Playing on playground structure outdoors and mouthing Tier 1	6.18
Chronic exposure- Playing on playground structureoutdoors and mouthing Tier 2	4.00 E-03

2.2.1.4. Risk characterization

The human health risk characterisation is performed using the following AELs.

	mg Cu /kg/d
Acute-term AEL	0.082
Medium-term AEL	0.082
Long-term AEL	0.041

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).

2.2.1.4.1. Risk characterisation for primary exposure scenarios

Industrial professional users

The %AELs are reported in the table below.

Summary of Risk assessment for industrial professional users during short-term exposure.

Task : Handling of wood and equipment during vacuum-pressure impregnation (including mixing and loading, and post-application)					
Users :	Industrial workers				
Tier - PPE	**Hazard Class**	**Exposure path**	**Systemic dose mgCu/kg bw/d**	**Acute Toxicity**	
				AELlong-term (mgCu/kg bw)	**Expo as % AEL**
Tier 1 : gloves, minimal clothing, no RPE	HC 1, 2 or 3	Inhalation and dermal exposure	8.0 E-02	0.041	189.3
	HC 4	Inhalation and dermal exposure	1.4 E-01	0.041	340.3
Tier 2a : gloves, coated coverall, no RPE	HC 1, 2 or 3	Inhalation and dermal exposure	1.65 E-02	0.041	40.2
	HC 4	Inhalation and dermal exposure	2.96 E-02	0.041	72.3

NOAEL systemic = 4.1 mgCu/kg bw/d

For wood of class 1, 2, 3 and 4, the AEL is superior to 100% when only gloves are worn. The risk becomes acceptable when a coverall and gloves are worn.

The risks for industrial users under these conditions (with gloves and coated coverall) are then acceptable.

Non-professional users

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

2.2.1.4.2. Risk characterisation for secondary (indirect) exposure scenarios

The %AELs were calculated for secondary exposure scenarios and reported in the tables below.

Summary of Risk assessment for secondary exposure / Use Class HC 4 (Copper loading: 3.42 kg/m^3), considering a worst case

Scenario	Exposure path	Total exposure (mgCu/kg bw/d)	AEL (mgCu/kg bw/d)	Expo as % AEL
Acute exposure- Sanding treated timbers	Inhalation and dermal	4.5 E-03	0.082	5.5
Acute exposure- Infant chewing preserved timber off-cuts - Tier 1	Oral	1.97 E-01	0.082	240.2
Acute exposure- Infant chewing preserved timber off-cuts - Tier 2	Oral	3.46 E-03	0.082	4.2
Chronic exposure- Sanding treated timbers	Inhalation and dermal	4.1 E-02	0.041	98.2
Chronic exposure- Playing on playground structure outdoors	Dermal	9.89 E-03	0.041	23.5
Chronic exposure- Playing on playground structure outdoors and mouthing - Tier 1	Oral and dermal	6.18	0.041	14706
Chronic exposure- Playing on playground structure outdoors and mouthing - Tier 2	Oral and dermal	4.00 E-03	0.041	9.5

The % of AEL on the "Infant playing on playground structure outdoors and mouthing" (Tier 1) is very largely >100. However, it is considered that the exposure value is based on an unrealistic estimate of the dislodgeable copper. By using the more realistic tier 2, it can be seen that the % of AEL is acceptable.

The % of AEL on the "Infant chewing preserved timber off-cuts" (Tier 1) is also above 100 %. However, it is considered that the model in the TNsG Human Exposure is unrealistic in that it is unlikely that an infant could chew a piece of timber 4cm x 4 cm x 1 cm and certainly would not be able to generate enough saliva to extract wood preservative from the inside the block of treated wood. It is proposed instead that the infant can remove the dislodgeable residues of copper from the surface of the wood and ingest this material. Treated wood is very hard and is highly likely to be distasteful for the infants. The infant would probably also expel unpleasant tasting materials from its mouth. By taking into account these elements in the more realistic Tier 2, it can be seen that the % AEL < 100, risk is then considered as acceptable.

For all other *scenarii*, % of AEL values are acceptable in Tier 1, the risks for professionals and consumers under the conditions specified above are then acceptable.

Secondary exposure via food contamination

As stated in the toxicological foreword, the case of copper is rather particular since this element is naturally present in the environment and also at stake and essential for many metabolic functions and reactions for both plants and animals. Copper is also used as fungicide in plants for phytopharmaceutical purposes and for veterinary purposes[5]. Copper is authorized as a feed additive under EU Reg. 479/2006[6] in nutrition of livestock with range content of 15 to 170 mg/kg in the complete feedingstuffs. According to Directive 2002/46/EC[7], copper is also used as a food supplement. Additionally, copper is already significantly involved for phytopharmaceutical purposes under EU Reg. 396/2005 with rather significant rates (in order of kg/ha/year) covered by MRLs under the EU regulation Reg. (EC) N°149/2008[8] (in range of 2 to 1000 mg/kg). Furthermore, inasmuch no direct interaction of treated wood with food is supported in context of this application.
However, at the product authorisation stage, if use of the product results in transfert of residues to food, , a dietary risk assessment (DRA) will be required.

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

Application by vacuum impregnation of copper, granulated as an approx. 0.317 % aqueous solution (elemental copper) in preventive wood protection of classes 1, 2, 3 or an approx. 0.57 % aqueous solution (elemental copper) in preventive wood protection of class 4 leads to unacceptable risk for professional facility workers if only gloves are worn. However, risk becomes acceptable if gloves and coated coverall are worn.

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

[5] The European Agency for the Evaluation of Medicinal Products (EMEA), Veterinary Medicines Evaluation Unit, EMEA/MRL/431/98-Final, May 1998, Committee for Veterinary Medicinal Products – Copper Chloride, Copper Gluconate, Copper Heptanoate, Copper Oxide, Copper Methionate, Copper Sulphate and Dicopper Oxyde – summary report, p.1-4 : http://www.ema.europa.eu/docs/en_GB/document_library/Maximum_Residue_Limits_-_Report/2009/11/WC500013010.pdf

[6] COMMISSION REGULATION (EC) No 479/2006 of 23 March 2006 as regards the authorization of certain additives belonging to the group compounds of trace elements, OJ L 86 24/03/2006, p. 4-7 : http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32006R0479&qid=1399886943661&from=EN

[7] DIRECTIVE 2002/46/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 10 June 2002 on the approximation of the laws of the Member States relating to food supplements, OJ L 183, 12.7.2002, p. 1-16 http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:02002L0046-20111205&qid=1399993783567&from=EN

[8] Commission Regulation (EC) No 149/2008 of 29 January 2008 amending Regulation (EC) No 396/2005 of the European Parliament and of the Council by establishing Annexes II, III and IV setting maximum residue levels for products covered by Annex I thereto (Text with EEA relevance), OJ L 58, 01/03/2008, p. 1–398 : http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32008R0149&qid=1399895764828&from=EN

2.2.2. Environmental 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, granulated is the cupric ion (Cu^{2+}), which may be released to the environment at a low rate. This section is extracted from the CAR of Copper carbonate PT8 included in the annex I of Directive 98/8/EC dated on 9/02/2012.

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 as an inorganic moiety 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) (50^{th} percentile)

Partition coefficient in sediment

Kpsed = 24 409 L/kg (log Kp(sed/w) = 4.39) (50^{th} percentile)

Partition coefficient in soil

Kpsoil = 2 120 L/kg (log Kp (soil/w) = 3.33) (50^{th} 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. Effects 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) and during the review of Copper compounds used as biocidal active substance for PT8.

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 unprotective for 10% of the EU surface waters. It was considered as a reasonable worst case for Europe in a generic context during the previous discussions on copper compound dossiers at the EU level.

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 reference value for the risk characterisation.

The AF=1 has been chosen due to the uncertainty 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 choice of the AF of 1 has been challenged during the WG-IV 2015 and it was stated, with a slight majority of MSs, that the AF of 1 was kept to derive the PNECwater. However, it was also concluded that the conditions for using an AF of 1 in general should be re-discussed in the frame of the revision of Vol. IV Part B. And therefore, this AF should be re-discussed at the renewal stage of the first copper substances (in PT8) in case the revision of the guidance or new data available show the need of a revised AF.

The HC5-50 of 7.8 µg Cu/l, with an AF=1, was used as a reference value for risk assessment 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 has been chosen due to the uncertainty 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.

As for the PNECwater derivation, the choice of the AF of 1 has been challenged during the WG-IV 2015 and it was stated, that the AF of 1 was kept to derive the PNECsediment. Therefore, this AF should be re-discussed at the renewal stage of the first copper substances (in PT8) in case the revision of the guidance or new data available show the need of a revised AF.

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)

2.2.2.2.3. 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. More explanations are given in the environmental exposure assessment chapter.

As for the PNECwater derivation, the choice of the AF of 1 has been challenged during the WG-IV 2015 and it was stated, that the AF of 1 was kept to derive the PNECsoil. Therefore, this AF should be re-discussed at the renewal stage of the first copper substances (in PT8) in case the revision of the guidance or new data available show the need of a revised AF.

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.

2.2.2.2.4. 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 (AF=1) of 0.23 mg/l expressed as dissolved copper and carried forward as $PNEC_{STP}$ to the risk characterisation.

2.2.2.2.5. Summary of PNECS

Compartment	PNEC	Unit
STP	0.23	[$mg.L^{-1}$]
Freshwater	7.8	[$\mu g.L^{-1}$]
Sediment	87 18.9	[$mg.kg_{dwt}^{-1}$] [$mg.kg_{wwt}^{-1}$]
Soil	45.6 40.35	[$mg.kg_{dwt}^{-1}$] [$mg.kg_{wwt}^{-1}$]

2.2.2.3. PBT and POP assessment

Copper, granulated as inorganic metal is excluded from the PBT assessment taking into account the Annex XIII of Reach regulation 1272/2008.

The POP criteria is not relevant as copper, granulated is an inorganic compound.

2.2.2.4. Exposure assessment

The concentrations of copper in the environment were estimated following the recommendations given in the currently available guidance documents. The wood life stages considered for the exposure assessment were: industrial wood treatment, storage of treated wood and wood in-service for Use Class 3 and Use Class 4. 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.

As cooper is a natural endogenous compound, the releases linked to its use as wood preservative have been added to the background environmental concentrations. In a first step, the predicted added concentrations of copper were calculated, in line with the equation

given by the ESD[9]. 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. They show that, after 18 months ageing, the NOEC values increased for plants and invertebrates corresponding to a decrease of the copper toxicity threshold. For micro-organisms, the NOEC values also increased but this is probably linked to an adaptation phenomenon to copper. The 18 months ageing tests were however not long enough to show a total removal of copper 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. Possible underlying mechanisms were detailed by the applicant and this decrease in copper toxicity with ageing has been taken into account, but for the exposure assessment and not for the hazard assessment. Since this factor was determined over a period of 18 months, it can be applied for PEC calculations over the same amount of time or higher (*i.e.* TIME 2 of the ESD 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. This strategy was validated at TMIII08.

Intended uses

The intended use of the representative biocidal product is an industrial treatment of wood by vacuum pressure impregnation for the Use Classes 1 to 4.

Leaching rates evaluation

The emissions to the environment for the stages of storage and wood in-service were calculated on the basis of leaching test results. Nevertheless, none of the studies submitted by the applicant for the determination of the leaching rates completely complies with the current requirements for this type of test. As a first Tier, calculations were also made

[9] OECD Revised Emission Scenario Document for wood preservatives' (ESD), 2013.

assuming a worst case assumption of 100% copper leaching from treated wood over the service life of wood treated by vacuum pressure impregnation (20 years).

2.2.2.5. Risk characterization

2.2.2.5.1. Aquatic compartment (including sediment)

Vacuum pressure impregnation

SCENARIO			PEC/HC_{5-50} Natural background		PEC/ HC_{5-50} Regional background	
			Surface water	**Sediment**	**Surface water**	**Sediment**
vacuum pressure application	Application	-	**2.00**	**5.36**	**2.26**	**5.90**
vacuum pressure application	Storage	-	**1.68**	**4.48**	**1.94**	**5.02**
Service life of treated wood	Noise barrier (Use Class 3)	Time 1	0.18	0.44	0.44	0.97
		Time 2[1]	0.11	0.24	0.37	0.78
	Bridge over a pond (Use Class 3)[2]	Time 1	0.13	**4.23**	0.39	**4.77**
		Time 2[1]	0.12	**6.56**	0.38	**7.10**
	Jetty in a lake (Use Class 4b)[2]	Time 1	0.12	**1.14**	0.38	**1.68**
		Time 2[1]	0.12	**2.72**	0.38	**3.25**
	Sheet piling (Use Class 4b)[2]	Time 1	**61.06**	**332.32**	**61.32**	**332.86**
		Time 2[1]	**1.04**	**5.29**	**1.30**	**5.83**

[1] Time 2 considering leaching data

[2] For surface water, removal processes were taken into account (adsorption onto suspended matter and sediment, and time weighted average concentrations)

Estimated risks from **industrial treatment by vacuum pressure impregnation** indicate unacceptable risks to surface water and sediment when results are expressed as total concentration, either considering a natural or 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 unacceptable risks to the aquatic environment 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 the **wood-in-service phase,** the relevant scenarios tested for Use Classes 3 and 4b indicate acceptable risks for surface water and sediment when releases from wood

treated by vacuum pressure impregnation are directed to a sewage treatment plant (Noise barrier scenario – Use Class 3) but show unacceptable risks when the treated wood is located above or in a water body (Bridge over a pond scenario – Use Class 3, Jetty in a lake and Sheet pilling scenario – Use Class 4b) even when removal processes are considered (adsorption onto suspended matter and sediment and time-weighted averaging of concentrations). Since unacceptable risks are identified where direct loses to water are foreseen, there should be a labelling for Use Class 3 against the use of treated wood where direct losses to water are possible. The uses in Class 4b should not be allowed.

2.2.2.5.2. Sewage treatment plant organism

SCENARIO			PEC/PNEC
vacuum pressure application	Application	-	0.93
Service life of treated wood	Noise barrier (Use Class 3)	Time 1	0.04
		Time 2	2.30E-04

Considering the representative product, PEC/PNEC ratios indicate acceptable risks to sewage treatment plant either from industrial treatments, or from wood-in-service releases (Noise barrier scenario).

2.2.2.5.3. Atmosphere

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

2.2.2.5.4. Terrestrial compartment

<u>vacuum pressure impregnation</u>

			PEC/PNEC Natural background	PEC/PNEC Regional background
vacuum pressure application	Application	-	0.81	0.95
vacuum pressure application	Storage	-	**64.81**	**64.95**
Service life of treated wood	Noise barrier – Direct releases (Use Class 3)	Time 1	0.35	0.62
		Time 2[1]	0.20	0.34
	Noise barrier – Indirect releases via the STP (Use Class 3)	Time 1	0.31	0.59
		Time 2[1]	0.13	0.27
	House (Use Class 3)	Time 1	0.50	0.77
		Time 2[1]	0.32	0.45
	Transmission pole (Use Class 4a)	Time 1	0.38	0.65
		Time 2[1]	0.35	0.48
	Fense post (Use Class 4a)	Time 1	0.30	0.58
		Time 2[1]	0.21	0.34

[1] Time 2 considering leaching data

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

The outdoor **storage** of treated wood on bare soil 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).

Concerning the Use Classes 3 and 4a, the PEC/PNEC ratios calculated for **wood in service** treated by industrial vacuum pressure impregnation are below 1 for all the corresponding scenarios (House, Noise barrier, Fence post and Transmission pole) considering a natural or a regional background concentration and a Tier 2 approach with more realistic leaching rates from studies. The wood treated by vacuum pressure impregnation can be allowed for a use in Class 3 and 4a.

2.2.2.5.5. Ground water

Considering the representative product, copper is strongly absorbed and immobile in soil. Therefore, no copper is expected to reach groundwater. Copper as wood preservative is not

expected to pose a risk for groundwater contamination following the use of the representative product.

2.2.2.5.6. Secondary poisoning

Copper is an essential micronutrient, needed for optimal growth and development of micro-organisms, plants, animals and humans. Copper acts as an active cofactor in over 20 enzymes and proteins. To ensure appropriate copper tissue levels without causing toxicity from copper excess, internal copper levels are homeostatically regulated by all living organisms. Homeostatic regulation of copper allows organisms, within certain limits, to maintain their total body copper level and to maintain physiologically required levels of copper in their various tissues, both at low and high copper intakes.

In the aquatic environment, homeostatic regulation of invertebrates and fish resulted in an inverse relationship between copper BCFs and concentrations in the water. The importance of such homeostasis regulation was recognised in the regulatory framework of aquatic hazard classification (OECD, 2001). Similarly, in terrestrial plants, copper BCFs were inversely related to copper levels in soils.

The molecular mechanism of copper homeostasis is related to 2 key elements: P-type ATPases that can pump copper across biological membranes in either direction and copper chaperones, important for the intracellular copper homeostasis. This cellular copper homeostasis mechanism is considered as being universal as the sequences of copper chaperones are highly conserved between species.

Besides these active regulation mechanisms, some groups of organisms have developed additional internal regulation mechanism (molecular binding and sequestration) as a strategy to cope against copper excess.

In higher organisms, dietary copper exposure studies in mammals and humans have shown that the intestinal adsorption / biliary excretion of copper is regulated with varying dietary intakes. Research indeed demonstrated that copper adsorption in humans can vary between 11 and 75 %, depending on the dietary intake. Similarly, mammals and birds, can rely on intestinal adsorption and biliary excretion to maintain internal copper levels with large variation in dietary intakes.

Based on the above information, bioaccumulation and biomagnification phenomenons are considered as not applicable for copper.

2.2.3. Assessment of endocrine disruptor properties

The active substance is not considered to have endocrine disrupting properties.

2.3. Overall conclusions

The outcome of the assessment for copper, granulated in product-type 8 is specified in the BPC opinion following discussions at the 13rd meeting of the Biocidal Products Committee (BPC). The BPC opinion is available from the ECHA web-site.

SCENARIO		Human primary exposure		Human secondary exposure		Aquatic compartment	STP	Terrestrial compartment	Ground water	Air	Secondary poisoning
		Industrial professional	**Non professional**	**Worker**	**Consumer**						
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 4a					NR	NR	Acceptable	NR	NR	NR
	Class 4b					**Not acceptable**	NR	NR	NR	NR	NR

Overall conclusions: Vacuum pressure impregnation process does not lead to unacceptable risk for uses in class 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. A use in class 3 with direct realease to water or in class 4b should not be allowed unless additional data or appropriate mitigation measures lead to an acceptable risk

NR: Non relevant
* Considering the wearing of PPE

2.4. Requirement for further information related to the product

Further data on products containing copper, granulated shall be required as detailed below:

- a dermal absorption study on the product ;
- A clarification about the active substance content in the product (a range is not acceptable), a validated analytical method for the determination of copper in the product, the surface tension, the persistent foaming of the product and compatibility with other product must be provided at the product authorization stage.

2.5. List of endpoints

The most important endpoints, as identified during the evaluation process, are listed in Appendix I.

Appendix I: List 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
Function (*e.g.* fungicide)	Fungicide/Insecticide

Rapporteur Member State	France.

Identity (Annex IIA, point II.)

Chemical name (IUPAC)	Copper
Chemical name (CA)	Copper
CAS No	7440-50-8
EC No	231-159-6
Other substance No.	CIPAC n°44
Minimum purity of the active substance as manufactured (g/kg or g/l)	990 g/kg as copper in form of granulated copper
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	Lead : <0.008g/kg Cadmium : <0.001g/kg Arsenic : <0.005g/kg Nickel : <0.01g/kg
Molecular formula	Cu
Molecular mass	63.55
Structural formula	Cu

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

Melting point (state purity)	1059 – 1069 °C Purity: 99.7%
Boiling point (state purity)	Not required for substances that melt at temperatures in excess of 360°C.
Temperature of decomposition	Thermally stable up to 1000°C.
Appearance (state purity)	Course, granular red brown solid with a cylindrical shape (the length ranges between 0.9 and 6.0 mm with a mean at 2.1mm and the width ranges between 0.494 and 0.949mm with a mean at 0.706mm). Purity>99.0%
Relative density (state purity)	8.78 Purity: 99.7%
Surface tension	Not applicable for substances with a water solubility of < 1 mg l^{-1}
Vapour pressure (in Pa, state temperature)	It is not required to test for vapour pressure as the melting point is above 300ºC.
Henry's law constant (Pa m^3 mol^{-1})	Cannot be determined.
Solubility in water (g/l or mg/l, state temperature)	pH 6.34-7.56, 20ºC Samples shaken 14-16 days Average concentration=1.0mgl^{-1}
Solubility in organic solvents (in g/l or mg/l, state temperature) (Annex IIIA, point III.1)	Soluble in aqueous monoethanolamine but is practically insoluble in organic solvents.
Stability in organic solvents used in biocidal products including relevant breakdown products (IIIA, point III.2)	Not required. The active substance as manufactured does not include any organic solvents. If biocidal products are formulated with organic solvents, the compatibility between copper, granulated and solvents and the stability of the products will be studied in document III B
Partition coefficient (log P_{OW}) (state temperature)	Not relevant for the ecotoxicological risk assessement, due to the specific absorption mechanism of copper.
Hydrolytic stability (DT_{50}) (state pH and temperature) (point VII.7.6.2.1)	pH_____: pH_____: pH_____: Not applicable for metal compounds.
Dissociation constant (not stated in	Not relevant, metallic copper cannot

Annex IIA or IIIA; additional data requirement from TNsG)	dissociate in water, due to its structure. Copper, granulated is slightly soluble in water and the solubilisation results of oxido-reduction reaction of the copper metal into ionic copper. Any addition of acid would result in reaction with the copper
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	Determination of UV spectra is not applicable to metals
Photostability (DT_{50}) (aqueous, sunlight, state pH) (point VII.7.6.2.2)	Not applicable.
Quantum yield of direct phototransformation in water at Σ > 290 nm (point VII.7.6.2.2)	Not applicable.
Flammability	Not flammable.
Explosive properties	Not explosive

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

According to GHS

with regard to physical/chemical data	
with regard to toxicological data	
with regard to fate and behaviour data	Eye Irrit. 2 / H319 - Causes serious eye irritation Aquatic Chronic 1 H410: Very toxic to aquatic life with long lasting effects
with regard to ecotoxicological data	Aquatic Acute 1 (M-Factor acute 1). H400: Very toxic to aquatic life.

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method) (Annex IIA, point 4.1)	Titration with EDTA. The method uses nitric acid digestion to dissolve the copper into solution. The method is not specific to copper metal. However this is acceptable as an XRD shows no other form of copper than Copper (0).
Impurities in technical active substance (principle of method) (Annex IIA, point 4.1)	Trace metals of toxicological significance can be determined by ICP-MS. Before analysis, the samples are dissolved in an acid nitric mixture. The provided analytical method is validated.

Analytical methods for residues

Soil (principle of method and LOQ)	Flame Atomic Absorption (EPA 7210, 220.1)

(Annex IIA, point 4.2)	Residues of copper may be determined in soils using ICP-AES methods (e.g. AOAC official method 990.8). The estimated instrumental limit of detection (LOD) is 6 µg Cu/l. (LOQ not determined). Another suitable method is AAS (e.g. US EPA method 7210), with an LOQ of 0.2 mg/L. For both methods of analysis, the sample must first be digested.
Air (principle of method and LOQ) (Annex IIA, point 4.2)	Residues of copper may be determined in air using Flame-AAS or ICP-AES methods (e.g. NIOSH methods 7029 or 7300 respectively). The estimated instrumental limits of determination (LOD) are 0.05 and 0.07 µg Cu/filter (LOQ not determined).
Water (principle of method and LOQ) (Annex IIA, point 4.2)	Furnace Atomic Absorption (EPA 220.2, 7211) In water, trace elements may be determined by Inductively Coupled Plasma – Mass Spectroscopy (ICP-MS) (e.g. US EPA method 220.7). The LOD for this method was estimated at 3 µg Cu/l and the LOQ was determined at 20 µg Cu/l. Other suitable methods include AAS with direct aspiration (LOD 20 µg/l, LOQ 200 µg/l) (e.g. US EPA method 220.1) and AAS with graphite furnace (LOD 1 µg/l, LOQ 5 µg/l) (e.g. US EPA method 220.2). For all three methods of analysis, the sample must first be digested.
Body fluids and tissues (principle of method and LOQ) (Annex IIA, point 4.2)	ICP-AES may also be used for analysing elements in body fluids and tissues following acid digestion of the sample. LOQs are 10 µg/100 g blood, 2 µg/g tissue (e.g. NIOSH method 8005) and 0.25 µ/sample of urine (NIOSH method 8310).
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	Not applicable
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	Not applicable

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 TMIII08 that a dermal absorption of 5% has to be used for copper compound.
Rate and extent of Inhalative absorption:	100%
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	Not classified
Rat LD_{50} dermal	> 2000 mg/kg bw, not classified
Rat LC_{50} inhalation	No data. However, at the product authorization, if an application by spraying is realised, this point should be assessed. Moreover, the product is often applied in solution and not in form of copper, granulated, and the properties are not the same. Remark: a classification for this endpoint was proposed for coated copper flake.
Skin irritation	Not classified as irritating
Eye irritation	Classified as eye irritant cat 2: H319
Skin sensitization (test method used and result)	Not classified as a skin sensitiser

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/mg kg/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, although not fully reliable, 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	NOAEL= 106 mg Cu/kg/d No information on maternal toxicity **However rat two-generation study with copper sulphate pentahydrate does not raise any particular teratogenic concern**.

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 acute and medium term	0.082 mg/kg bw/d	90d in rats	MOE ref = 50
AEL long-term	0.041 mg/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	
Non-professional users	
Indirect exposure as a result of use	../.. Dietary risk assessment : concerning secondary exposure via food contamination, available knowledge about the natural occurrence of copper, physiological needs, physico-chemical properties and regulations already in force constitute appreciable information to consider as not relevant its influence for the consumer. Furthermore, inasmuch no direct interaction of treated wood with food is supported in context of this application. However, at the product authorisation stage, if use of the product induces contact with food and/or feed, a dietary risk assessment (DRA) will be required.

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 Kpsusp = 30,246 l/kg (log Kp (pm/w) = 4.48) (50th 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.
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 Kp = 3.33) (50th percentile)

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 from 139 individual NOEC/EC10 values: 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 from 62 individual NOEC values: 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*)
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 from 252 individual chronic NOEC/EC10 values: 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

Chapter 6: Other End Points
None required

Appendix II: List of Intended Uses

Object and/or situation (a)	Member State or Country	Product name	Organisms controlled (c)	Formulation		Application			Applied amount per treatment			Remarks: (m)
				Type (d-f)	Conc. of as (i)	method kind (f-h)	number min max (k)	interval between applications (min)	g as/L min max	water L/m^2 min max	g as/m^2 min max	
Fungi and insects Use Class (UC) 1, 2, 3, 4	**All**	ACQ-C2D	Fungi and insects	SL (Soluble concentrate)	13 %	vacuum/ pressure impregnation	one	Not applicable	See remarks	See remarks	See remarks	(1)

(1) Typical concentration of product in working solution:
3.33 % for use classes 1, 2 and 3 with Cu loadings of 1.9 kg/m^3.
6 % for use class 4 with Cu loadings of 3.42 kg/m^3.
The concentrate product may contain above 9.5%w/w copper, as long as the product is suitably diluted to give the stated copper concentrations in the treatment solution.

(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 60 of Regulation (EU) No 528/2012.

Section No / Reference No[10]	Author(s)[11]	Year	Title[12] Source (where different from company) Company Report No. GLP (where relevant) (Un)Published	Data Protection Claimed (Yes/ No)	Owner
A3.1.1	Jussi Liipo, Maija-Leena Metsärinta, Päivi Kinnunen, Kirsi Virta, Elina Wiik, Matti Santala, and Säde Harle	2010	Characterization of copper powder, Outotec Research Oy, Report No. 10113-ORC-T, unpublished	Yes	European Copper Institute
A3.1.3	Jussi Liipo, Maija-Leena Metsärinta, Päivi Kinnunen, Kirsi Virta, Elina Wiik, Matti Santala, and Säde Harle	2010	Characterization of copper powder, Outotec Research Oy, Report No. 10113-ORC-T, unpublished	Yes	European Copper Institute

[10] ***Section Number/Reference Number*** should refer to the section number in Doc III-A or III-B. If the study is non-key, and hence not summarised in Doc III but mentioned in Doc II, it should be included in the reference list alongside related references and its location in Doc II indicated in brackets. (If there is a need to include a cross-reference to PPP references then an additional column can be inserted).

[11] ***Author's Name*** should include the author's surname before initial (s) to enable the column to be sorted alphabetically. If the Human Rights Charter prevents author's surnames on unpublished references being included in non-confidential documents, then it will be necessary to consider including 'Unpublished [number/year & letter] ' in Doc II, and both ' Unpublished [number/year & letter]' and the 'Authors Name' in the reference list'. This may necessitate the need for an additional column to state whether a reference is unpublished which can then be sorted.

[12] ***Title, Source (where different from company), Company, Report No., GLP (where relevant), (Un)Published*** should contain information relevant to each item (ideally on separate lines within the table cell for clarity). If useful, the name of the electronic file containing the specific study/reference could be added in brackets.

A3.3.1	Hughes, K	2013	Particulate copper metal analysis (surface area and weight distribution), Arch Timber Protection. Report No. TSR 13 01, unpublished	Yes	Arch Timber Protection
A3.5	Jussi Liipo, Maija-Leena Metsärinta, Päivi Kinnunen, Kirsi Virta, Elina Wiik, Matti Santala, and Säde Harle	2010	Characterization of copper powder, Outotec Research Oy, Report No. 10113-ORC-T, unpublished	Yes	European Copper Institute
A3.7	Hughes, K (a)	2013	Dissolution of Copper Granules, Report No. TSR 13 02, unpublished	Yes	Arch Timber Protection
A3.7	Hughes, K (b)	2013	Analysis of solids isolated from a copper amine solution. Arch Timber Protection. Report No. TSR 13 03, unpublished	Yes	Arch Timber Protection
A 4.1	Anonymous	2003	Determination of iron, lead and zinc in copper carbonate. Not GLP, unpublished.	Yes	Adchem (Australia) Pty. Limited
A 4.1	Anonymous	2004 a	Determination of Copper in Copper Oxide and Basic Copper Carbonate. Not GLP, unpublished.	Yes	Alchema Limited
A 4.1	Anonymous	2004 b	Determination of lead and cadmium in copper oxide and copper carbonate using atomic absorption spectroscopy. Not GLP, unpublished.	Yes	Alchema Limited
A 4.1	CIPAC	-	CIPAC method for total copper 44/TC/M/3.2. Volumetric thiosulphate method. CIPAC E, Page 44. Not GLP, published.	No	Public domain

A 4.1	CIPAC	-	CIPAC method for total copper 44/TC/M/3.1. Electrolytic method (Referee method). CIPAC E, Page 42. Not GLP, published.	No	Public domain
A 4.1	Credland, D.R.	2000	Analysis of contaminated land for toxic and heavy metals by inductively coupled plasma atomic emission spectroscopy. ASUS metod 577, Version 1. Not GLP, unpublished.	Yes	Alchema Limited
A 4.1	O'Connor, B.J. and Mullee, D.M.	2001	Copper Carbonate (Wet Dense): Preliminary Analysis. Safepharm Laboratories Limited, Project ID: 453/021. GLP, Unpublished.	Yes	William Blythe Limited
A 4.2	AOAC	1993	AOAC Official Method 990.08,. Metals in Solid Wastes; Inductively Coupled Plasma Atomic Emission Method. AOAC Official Methods of Analysis; Metals and Other Elements, Chapter 9, page 31. Not GLP, published.	No	Public domain
A 4.2	EPA	1983	Methods for Chemical Analysis of Water and Wastes. Method 220.2 (Copper. Atomic Absorption, furnace technique). Washington, DC; U.S. Environmental Protection Agency. Not GLP, published.	No	Public domain
A 4.2	EPA	1983	Inductively Coupled Plasma – Atomic Emission Spectrometric Method for Trace Element Analysis of Water and Wastes – Method 200.7. Washington, DC; U.S. Environmental Protection Agency. Not GLP, published.	No	Public domain

A 4.2	EPA	1986	Test Methods for Evaluating Solid Waste, Physical/Chemical Methods (SW-846). Method 7210 (Copper. Atomic Absorption, direct aspiration). Washington, DC; U.S. Environmental Protection Agency. Not GLP, published. And appended: EPA, 1986. Test Methods for Evaluating Solid Waste, Physical/Chemical Methods (SW-846). Method 3050B (Acid digestion of sediments, sludges and soils). Washington, DC; U.S. Environmental Protection Agency. (published).	No	Public domain
A 4.2	EPA	1986	Methods for Chemical Analysis of Water and Wastes. Method 220.1 (Copper. Atomic Absorption, direct aspiration). Washington, DC; U.S. Environmental Protection Agency. Not GLP, published.	No	Public domain
A 4.2	NIOSH	1987	Method 8005. NIOSH Manual of Analytical Methods, Fourth Edition, 8/15/94. Not GLP, published.	No	Public domain
A 4.2	NIOSH	1987	Method 8310. NIOSH Manual of Analytical Methods, Fourth Edition, 8/15/94. Not GLP, published.	No	Public domain
A 4.2	NIOSH	N/A	Method 7029. NIOSH Manual of Analytical Methods, Fourth Edition, 8/15/94. No GLP, published.	No	Public domain
A 5	Cockcroft, R.	1981	Wood Destroying Basidomyctest Vol. 1. IRG 81/1121	No	Public domain

A 5	Connell M, Cornfield J A and Williams G R	1993	A New Timber Preservative. Rec of the Annual Convention of the British Wood Preserving and Damp-proofing Association pp 28-36	No	Public domain
A 5	Eaton, R.A. & Hale, M.D.C.	1993	Wood: Decay Pests and Protection'. Chapman and Hall	No	Public domain
A 5	Fox R F , Pasek E A , Patel J	2000	Laboratory Termite testing of Copper/Boron / Tebuconazole . International Research Group on Wood Preservation. Document No. IRG/WP 00-20192	No	Public domain
A 5	Greaves H	1977	Potential toxicants for controlling soft rot in hardwoods 1. Laboratory screening tests using a filter paper technique Material und Organismen 12 Bd 1997 Heft	No	Public domain
A 5	Pohleven, F., Miha, H., Sam, A & Jaka, B.	2002	Tolerance of wood decay fungi to commercial copper based wood preservatives. IRG Document No. 02-30291.	No	Public domain
A 5	Preston A, Walcheski P, Archer K, Zahora A and Jin L	2000	The Ground Proximity Decay Test Method, International Research Group on Wood Preservation Doc No. 00-20205	No	Public domain
A 5	Price E.A.S and Watson, R.W.	1962	Review of water-borne preservatives Rec. of 12th Annual Convention of the British Wood Preserving and Damp-proofing Association, London	No	Public domain
A 5	Thornton J D	1977	Potential toxicants for controlling soft rot in hardwoods II Laboratory tests using sawdust Material und Organismen 12 Bd 1997 Heft 3	No	Public domain

A 6.1.1(1)	[redacted]	2001	Copper powder: Acute oral toxicity in the rat – Acute toxic class method. [redacted] SPL Project Number: 1451/001. (unpublished)	Yes	Eckart
A 6.1.2(1)	[redacted]	2001	Acute dermal toxicity (limit test) in the rat. [redacted] SPL Project Number: 1451/002 (unpublished).	Yes	Eckart
A 6.1.4(1)	[redacted]	2002	Copper Powder - Acute dermal irritation in the rabbit. [redacted] SPL Project Number: 1451/004. (unpublished).	Yes	Eckart
A 6.1.4(2)	[redacted]	2001	Copper powder: acute eye irritation in the rabbit. [redacted] SPL Project Number: 1451/005. (unpublished).	Yes	Eckart
A 6.1.5	[redacted]	2001	Copper powder: skin sensitisation in the guinea pig – Magnusson and Kligman Maximisation Method. [redacted] SPL Project Number: 1451/006 (unpublished).	Yes	Eckart
A 6.12.2	Chuttani HK, Gupta PS, Gulati S, Gupta DN.	1965	Acute Copper Sulfate Poisoning. Am J Med, 39: 849-854; Not GLP; published	No	Public domain
A 6.12.2	O'Donohue JW, Reid MA, Varghese A, Portmann B, Williams R	1993	Micronodular cirrhosis and acute liver failure due to chronic copper self-intoxication. Eur. J. Gastroenterol. 5:561-562; Not GLP; published	No	Public domain

A 6.12.2	O'Connor, J.M., Bonham, M.P., Turley, E., McKeown, A., McKelvey-Martin, V.J., Gilmore, W.S. and Strain, J.J.	2003	Copper supplementation has no effect on markers of DNA damage and liver function in healthy adults (FOODCUE Project). Ann Nutr Metab, 47: 201-206. Not GLP, Published	No	Public domain
A 6.12.2	Pimentel JC, Marques F	1969	Vineyard sprayer's lung - A new occupational disease. Thorax, 24, 678-688; Not GLP; published	No	Public domain
A 6.12.2	Pimentel JC, Menezes AP.	1977	Liver disease in vineyard sprayers. Gastroenterology 72:275-283; Not GLP; published	No	Public domain
A 6.12.2	Pimentel JC, Menezes AP.	1975	Liver granulomas containing copper in vineyard sprayer's lung - A new Etiology of Hepatic Granulomatosis. Am. Rev. Respir. Dis. 111:189-195; Not GLP; published	No	Public domain
A 6.12.2	Pratt, W.B., Omdahl, J.L. and Sorenson, R.J.,	1985	Lack of Effects of Copper Gluconate Supplementation. The American Journal of Clinical Nutrition, 42: 681 – 682. Not GLP, Published	No	Public domain
A 6.12.2	Rock, E., Mazur, A., O'Connor, J.M., Bonham, M.P., Rayssiguier, Y. & Strain, J.J	2000	The Effect of Copper Supplementation on Red Blood Cell Oxidizability and Plasma Antioxidants in Middle-Aged Healthy Volunteers. Free Radical Biology and Medicine. 28 (3); 324-329. Not GLP, Published	No	Public domain
A 6.12.2	Tanner MS, Portmann B, Mowat AP, Williams R, Pandit AN, Mills CF, Bremner I.	1979	Increased hepatic copper concentration in Indian Childhood Cirrhosis. Lancet 1:1203-5; Not GLP; published	No	Public domain

A 6.12.2	Turley, E., McKeown, A., Bonham, M.P., O'Connor, J.M, Chopra, M., Harvey, L.J., Majsak-Newman, G., Fairweather-Tait, S.J., Bugel, S., Sandstrom, B. Rock, E., Mazur, A., Tayssiguier, Y. & Strain, J.J.	2000	Copper supplementation in Humans Does Not Affect the Susceptibility of Low Density Lipoprotein to In Vitro Induced Oxidation (Foodcue Project). Free Radical Biology & Medicine, 29: (11); 1129-1134. Not GLP, Published	No	Public domain
A 6.12.4	Plamenac P, Santic Z, Nikulin A, Serdarevic H.	1985	Cytologic changes of the respiratory tract in vineyard spraying workers. Eur J Respir Dis, 67: 50-55; Not GLP; published	No	Public domain
A 6.12.4	Scheinberg IH, Sternlieb I.	1994	Is non-Indian childhood cirrhosis caused by excess dietary copper? Lancet, 344: 1002-1004; Not GLP; published	No	Public domain
A 6.12.4	Tanner MS, Kantarjian AH, Bhave SA, Pandit AN.	1983	Early introduction of copper-contaminated animal milk feeds as a possible cause of Indian Childhood Cirrhosis. Lancet 2: 992-995; Not GLP; published	No	Public domain
A 6.12.5	International Programme on Chemical Safety	1990	Poisons Information Monograph (PIM G002): Copper and copper salts; Not GLP; Published	No	Public domain
A 6.12.7	International Programme on Chemical Safety	1990	Poisons Information Monograph (PIM G002): Copper and copper salts; Not GLP; Published	No	Public domain
A 6.12.8	International Programme on Chemical Safety	1990	Poisons Information Monograph (PIM G002): Copper and copper salts; Not GLP; Published	No	Public domain

A 6.2	Allen, M.M., Barber, R.S., Braude, R. and Mitchell, K.G.	1961	Further studies on various aspects of the use of high-copper supplements for growing pigs. Brit. J. Nutr., 15: 507 – 522, Not GLP Published	No	Public domain
A 6.2	Amaravadi, R., Glerum, D.M. and Tzagoloff, A.	1997	Isolation of a cDNA encoding the human homolog of COX17, a yeast gene essential for mitochondrial copper recruitment. Hum Genet. 99: 329-333. Not GLP, Published.	No	Public domain
A 6.2	Aoyagi, S. and 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 Science. 72: 1075-1083. Not GLP, Published	No	Public domain
A 6.2	Baker, D.H., Odle, J., Funk, M.A. and Wieland, T.M.	1991	Research Note: Bioavailability of Copper in Cupric Oxide, Cuprous Oxide, and in a Copper-Lysine Complex. Poultry Science. 70: 177-179. Not GLP, Published	No	Public domain
A 6.2	Buescher, R.G., Griffin, S.A. and Bell, M.C.	1961	Copper Availability to Swine from Cu64 Labelled Inorganic Compounds. Journal of Animal Science, 20: 529-531. Not GLP, Published	No	Public domain
A 6.2	Bunch, R.J., Speer, V.C., Hays, V.W. and McCall, J.T.	1963	Effects of High Levels of Copper and Chlortetracycline on Performance of Pigs. J. Animal Sci. 22: 56-60. Not GLP, Published	No	Public domain
A 6.2	Bunch, R.J., Speer, V.C., Hays, V.W., Hawbaker, J.H. and Catron, D.V.	1961	Effects of copper Sulfate, Copper oxide and Chlortetracycline on Baby Pig Performance. J. Animal Sci. 20: 723-726. Not GLP, Published	No	Public domain
A 6.2	Campbell, C.H., Brown, R. and Linder, M.C.	1981	Circulating Ceruloplasmin is an Important Source of Copper for Normal and Malignant Animal Cells. Biochim. Biophys. Acta. 678: 27-38. Not GLP, Published.	No	Public domain

A 6.2	Cromwell, G.L., Stahly, T.S. and Monegue, H.J.	1989	Effects of Source and Level of Copper on Performance and Liver Copper Stores in Weanling Pigs. J. Animal Sci. 67: 2996-3002. Not GLP, Published	No	Public domain
A 6.2	Culotta, V.C., Klomp, J.S., Casareno, R.L.B., Krems, B. And Gitlin, J.D	1997	The Copper Chaperone for Superoxide Dismutase. The Journal of Biological chemistry. 272 (38): 23469 – 23472. Not GLP, Published	No	Public domain
A 6.2	Darwish, H.M., Cheney, J.C., Schmitt, R.C. and Ettinger, M.J.	1984	Mobilisation of copper (II) from plasma components and mechanism of hepatic copper transport. Am. J. Physiol., 246 (9):G72-G79. Not GLP, Published.	No	Public domain
A 6.2	Gunshin, H., Mackenzie, B, Berger, U.V., Gunshin, Y., Romero, M.F., Boron, W.F., Nussberger, S., Gollan, J.L. & Hediger, M.A.	1997	Cloning and Characterisation of a Mammalian Proton-Coupled Metal-Ion transporter. Nature. 388:482-488. Not GLP, Published.	No	Public domain
A 6.2	Kegley, E.B. and Spears, J.W.	1994	Bioavailability of feed-grade copper sources (oxide, sulfate, or lysine) in growing cattle. J. Animal Sci. 72: 2728-2734. Not GLP, Published	No	Public domain
A 6.2	Klomp, L.W.J., Lin, S.J., Yuan, D.S., Klausner, R.D., Culotta, V.C. and Gitlin, J.D.	1997	Identification and Functional Expression of HAH1, a Novel Human Gene Involved in Copper Homeostasis. The Journal of Biological Chemistry 272(14): 9221-9226. Not GLP, Published.	No	Public domain
A 6.2	Lee S.H., Lancey R., Montaser A., Madani N., Linder M.C.	1993	Ceruloplasmin and copper transport during the latter part of gestation in the rat. Proc Soc Exp Biol Med 203: 428-39. Not GLP, Published.	No	Public domain

A 6.2	Linder M.C., Weiss K.C. and Hai, V.M.	1987	Structure and function of transcuprein in transport of copper by mammalian blood plasma. In: Hurley L.C., Keen C.L., Lonnerdal, B. and Rucker, R.B. (eds). Trace Elements in Man and Animals (TEMA-6). New York: Plenum, 141–144. Not GLP, Published.	No	Public domain
A 6.2	McArdle, H.J., Gross S.M., Danks D.M. & Wedd, A.G.	1990	Role of Albumin's Copper Binding Site in Copper Uptake by Mouse Hepatocytes. Am. J. Physiol. 258 (Gastrointest. Liver Physiol. 21): 988-991. Not GLP, Published.	No	Public domain
A 6.2	McArdle, H.J., Gross, S.M. and Danks, D.M.	1988	Uptake of Copper by Mouse Hepatocytes. Journal of Cellular Physiology, 136: 373-378. Not GLP, Published.	No	Public domain
A 6.2	Norvell, M.J., Gable, D.A. and Thomas, M.C.,	1975	Effects of feeding high levels of various copper salts to broiler chickens. In Trace Substances in Environmentsl Health – 9, (Hemphill, D.D., Ed). University of Missouri, Columbia, MO. Not GLP, Published	No	Public domain
A 6.2	Pirot, F., Millet, J., Kalia, Y.N. & Humbert, P	1996	In vitro Study of Percutaneous Absorption, Cutaneous Bioavailability and Bioequivalence of Zinc and Copper from Five Topical Formulations. Skin Pharmacol. 9: 259-269. Not GLP, Published.	No	Public domain
A 6.2	Pirot, F., Panisset, F., Agache, P. & Humbert, P.	1996	Simultaneous Absorption of Copper and Zinc through Human Skin in vitro. Skin Pharmacol. 9: 43-52. Not GLP, Published.	No	Public domain

A 6.2	Rojas, L.X., McDowell, L.R., Cousins, R.J., Martin, F.G., Wilkinson, N.S., Johnson, A.B. and Velasquez, J.B.	1996	Interaction of different organic and inorganic zinc and copper sources fed to rats. J. Trace Elements Med. Biol. 10: 139-144. Not GLP, Published	No	Public domain
A 6.2	Scott, K.C. & Turnlund, J.R.,	1994	Compartment Model of Copper Metabolism in Adult Men. J. Nutr. Biochem. 5: 342-350. Not GLP, Published.	No	Public domain
A 6.2	Turnlund, J.R., Keen, C.L. and Smith, R.G.	1990	Copper status and urinary and salivary copper in young men at three levels of dietary copper. Am. J. Clin. Nutr. 51: 658-64.Not GlP, Published.	No	Public domain
A 6.2	Turnlund, J.R., Ketes, W.R., Peiffer, G.L. and Scott, K.C	1998	Copper absorption, excretion and retention by young men consuming low dietary copper determined using the stable isotope 65Cu. Am. J. Clin. Nutr., 67: 1219 – 1225. Not GLP, Published	No	Public domain
A 6.2	Turnlund, J.R., Keyes, W.R., Anderson, H.L. and Acord, L.L.	1989	Copper absorption and retention in young men at three levels of dietary copper by use of the stable isotope 65Cu. Am. J. Clin. Nutr. 49:870-878.Not GLP, Published.	No	Public domain
A 6.2	Turnlund, J.R., Wada, L., King, J.C., Keyes, W.R. and Lorra, L.A	1988	Copper Absorption in Young Men Fed Adequate and Low Zinc Diets. Biological and Trace Element Research, 17: 31 – 41. Not GLP, Published	No	Public domain

A 6.2	van Berge Henegouwen, G.P., Tangedahl, T.N., Hofmann, A.F., Northfield, T.C. La Russo, N.F. and McCall, J.T.,	1977	Biliary Secretion of Copper in Healthy Man. Quantitation by an intestinal perfusion technique. Gastroenterology, 72:1228-1231. Not Published.	No	Public domain
A 6.2	Van den Berg, G.J., Van Wouwe, J.P and Beynen, A.C.,	1990	Ascorbic Acid Supplementation and Copper Status in Rats. Biological Trace Element Research, 23: 165-172. Not GLP, Published	No	Public domain
A 6.2	Walker, R.W.	1982	The Result of a Copper Bracelet Clinical Trial and Subsequent Studies. P 469 – 478. In: J. R. J. Sorenson (ed) Inflammatory Diseases and Copper: The Metabolic and Therapeutic Roles of Copper and Other Essential Metalloelements in Humans; Humana Press; Clifton N.J., USA. Not GLP, Published.	No	Public domain
A 6.2	Weiss K.C. & Linder M.C.	1985	Copper transport in rats involving a new plasma protein. Am. J. Physiol. 249: E77-88. Not GLP, Published.	No	Public domain
A 6.2	Whitaker, P. & McArdle, H.J.	1997	Iron Inhibits Copper Uptake by Rat Hepatocytes by Down-Regulating the Plasma Membrane NADH Oxidase. In. Fisher, P.W., L'Abbe, M.R., Cockell, K.A. et al. (Eds). Trace Elements in Man and Animals. (TEMA9). NRC Research Press, Ottowa, pp 237-239	No	Public domain
A 6.2	Wirth, W.L. and Linder, M.M.	1985	Distribution of Copper Among Components of Human Serum. JNCI. 75: 277-284. Not GLP, Published.	No	Public domain

A 6.2	Xin, Z., Waterman, D.F., Hemken, R.W., Harmon, R.J. and Jackson, J.A	1991	Effects of copper sources and dietary cation-anion balance on copper availability and acid-base status in dietary calves. J. Dairy Sci. 74: 3167-3173. Not GLP, Published	No	Public domain
A 6.2	Zhou, B. & Gitschier, J.	1997	hCTR1; A Human Gene for Copper Uptake Identified by Complementation in Yeast. Proc. Natl. Acad. Sci USA. 94:7481-7486. Not GLP, Published.	No	Public domain
A 6.4.1	Hébert, C.D.,	1993	NTP Technical Report on toxicity studies of cupric sulphate (CAS No. 7758-99-8) administered in drinking water and feed to F344/N rats and B6C3F1 mice. National Toxicology Program, Toxicity Report Series No. 29, United States Department of Health and Human Services (NIH Publication 93-3352). GLP, Published	No	Public domain
A 6.4.1	Hébert, C.D.,	1993	NTP Technical Report on toxicity studies of cupric sulphate (CAS No. 7758-99-8) administered in drinking water and feed to F344/N rats and B6C3F1 mice. National Toxicology Program, Toxicity Report Series No. 29, United States Department of Health and Human Services (NIH Publication 93-3352). GLP, Published	No	Public domain
A 6.5	Burki, H.R. and Okita, G.T.	1969	Effect of oral copper sulfate on 7,12-dimethylbenz(α)anthracene carcinogenesis in mice. Br. J. Cancer Sep; 23(3): 591-596. Not GLP, Published.	No	Public domain

A 6.5	Carlton, W.W. and Price, P.S.	1973	Dietary Copper and the Induction of Neoplasms in the Rat by Acetylaminofluorene and Dimethylnitrosamine. Fd Cosmet. Toxicol. 11: 827-840 (published).	No	Public domain
A 6.5	De Vries, D.J., Sewell, R.B. and Beart P.M.	1986	Effects of Copper on Dopaminergic Function in the Rat Corpus Striatum. Experimental Neurology, 91: 546-558. Not GLP, Published	No	Public domain
A 6.5	Hall, E.M. and Butt, E.M	1928	Experimental Pigment Cirrhosis Due to Copper Poisoning. It's Relation to Hemochromatosis. Archives of Pathology, 6: 1-25. Not GLP, Published	No	Public domain
A 6.5	Hall, E.M. and Mackay, E.M.	1931	Experimental Hepatic Pigmentation and Cirrhosis. I. Does Copper Poisoning Produce Pigmentation and Cirrhosis of the Liver? The American Journal of Pathology, 7: 327-342. Not GLP, Published	No	Public domain
A 6.5	Harrison, J.W.E., Levin, S.E. and Trabin, B.	1954	The Safety and Fate of Potassium Sodium Copper Chlorophyllin and Other Copper Compounds. Journal of the American Pharmaceutical Association, 43(12): 722-737. Not GLP, Published.	No	Public domain
A 6.5	Haywood, S.	1980	The Effect of Excess Dietary Copper on the Liver and Kidney of the Male Rat. Journal of Comparative Pathology, 90: 217-232. Not GLP, Published	No	Public domain
A 6.5	Haywood, S.	1985	Copper Toxicosis and Tolerance in the Rat. I – Changes in Copper Content of the Liver and Kidney. Journal of Pathology, 145: 149-158. Not GLP, Published	No	Public domain

A 6.5	Haywood, S. and Comerford, B.	1980	The Effect of Excess Dietary Copper on Plasma Enzyme Activity and on the Copper Content of the Blood of the Male Rat. Journal of Comparative Pathology, 90: 233-238. Not GLP, Published	No	Public domain
A 6.5	Haywood, S. and Loughran, M.	1985	Copper Toxicosis and Tolerance in the Rat. II. Tolerance – a Liver Protective Adaptation. Liver, 5: 267-275. Not GLP, Published	No	Public domain
A 6.5	Haywood, S. and Loughran, M.	1985	Copper Toxicosis and Tolerance in the Rat. II. Tolerance – a Liver Protective Adaptation. Liver, 5: 267-275. Not GLP, Published	No	Public domain
A 6.5	Liu, C.-C.F. and Medeiros, D.M.	1986	Excess Diet Copper Increases Systolic Blood Pressure in Rats. Biological Trace Element Research, 9: 15-24. Not GLP, Published	No	Public domain
A 6.5	Tachibana, K.	1952	Pathological Transition and Functional Vicissitude of Liver During Formation of Cirrhosis by Copper. The Nagoya Journal of Medical Science, 15: 108-114. Not GLP, Published	No	Public domain
A 6.5	Wiederanders, M.D. and Wasdahl, W.W.	1968	Acute and Chronic Copper Poisoning in the Rat. The Journal-Lancet, Minneap, 88: 286-291. Not GLP, Published	No	Public domain
A 6.6.1	Ballantyne, M.	1994	Study to Determine the Ability of Copper II Sulphate Pentahydrate to Induce Mutation in Five Histadine-Requiring Strains of Salmonella typhimurim. Hazleton Europe. Report No. 456/31. GLP, Unpublished	Yes	WPCTF
A 6.6.4	Agarwal, K., Sharma, A. and Talukder, G.,	1990	Clastogenic effects of copper sulphate on the bone marrow chromosomes of mice in vivo. Mutation Research, 243:1-6. Not GLP, Published	No	Public domain

A 6.6.4	Bhunya, S.P. & Pati, P.C.	1987	Genotoxicity of an Inorganic Pesticide, Copper Sulpahte in Mouse in vivo Test System. Cytologia. 52: 801-808. Not GLP, Published.	No	Public domain
A 6.6.4	[redacted]	1994	Copper II Sulphate Pentahydrate: Induction of Micronuclei in the Bone Marrow of Treated Mice. [redacted] Report No. 456/33.GLP, Unpublished	Yes	WPCTF
A 6.6.4	Tinwell, H. & Ashby, J.	1990	Inactivity of Copper Sulphate in a Bone-Marrow Micronucleus Assay. Mutat. Res. 245: 223-226. Not GLP, Published.	No	Public domain
A 6.6.4	[redacted]	1994	Copper II Sulphate Pentahydrate: Measurement of Unscheduled DNA Synthesis in Rat Liver Using an in vivo/in vitro Procedure. [redacted] Report No. 456/32. GLP, Unpublished	Yes	WPCTF
A 6.7	Burki, H.R. and Okita, G.T.	1969	Effect of oral copper sulfate on 7,12-dimethylbenz(α)anthracene carcinogenesis in mice. Br. J. Cancer Sep; 23(3): 591-596. Not GLP, Published	No	Public domain
A 6.7	Carlton, W.W. and Price, P.S.,	1973	Dietary Copper and the Induction of Neoplasms in the Rat by Acetylaminofluorene and Dimethylnitrosamine. Fd Cosmet. Toxicol. 11: 827-840. Not GLP, Published.	No	Public domain
A 6.7	Harrison, J.W.E., Levin, S.E. and Trabin, B.,	1954	The Safety and Fate of Potassium Sodium Copper Chlorophyllin and Other Copper Compounds. Journal of the American Pharmaceutical Association, 43(12): 722-737. Not GLP, Published	No	Public domain

A 6.8.1	Aulerich, R.J., Ringer, R.K., Bleavins, M.R. and Napolitano, A.	1982	Effects of Supplemental Dietary Copper on Growth, Reproductive Performance and Kit Survival of Standard Dark Mink and the Acute Toxicity of Copper to Mink, 55(2): 337 – 343. Not GLP, Published	No	Public domain
A 6.8.1	Barash, A., Shoham (Schwartz), Z., Borenstein, R. and Nebel, L.	1990	Development of Human Embryos in the Presence of a Copper Intrauterine Device. Gynecol. Obstet. Invest., 29:203-206. Not GLP, Published	No	Public domain
A 6.8.1	Barlow, S.M., Knight, A.F. and House, I.	1981	Intrauterine exposure to copper IUDs and prenatal development in the rat. J. Rep. Fert. , 62: 123 – 130	No	Public domain
A 6.8.1	Chang, C.C. And Tatum, H.J.	1973	Absence of teratogenicity of intrauterine copper wire in rats, hamsters and rabbits. Contraception, 7(5): 413 – 434	No	Public domain
A 6.8.1	DiCarlo, F.J	1980	Syndromes of Cardiovascular Malformations Induced by Copper Citrate in Hamsters. Teratology 21: 89-101. Not GLP, Published	No	Public domain
A 6.8.1	Ferm, V.H. and Hanlon, D.P.	1974	Toxicity of Copper Salts in Hamster Embryonic Development. Biology of Reproduction, 11: 97-101. Not GLP, Published	No	Public domain
A 6.8.1	Haddad, D.S., Al-Alousi, L.A. and Kantarjian, A.H.	1991	The Effect of Copper Loading on Pregnant Rats and Their Offspring. Functional and Developmental Morphology 1(3): 17-22. Not GLP, Published	No	Public domain
A 6.8.1	Kasama, T. and Tanaka, H	1988	Effects of copper administration on fetal and neonatal mice. J. Nutr. Sci. Vitaminol., 34: 595-605. Not GLP, Published	No	Public domain

A 6.8.1	Lecyk, M.	1980	Toxicity of CuSO4 in mice embryonic development. Zoologica Poloniae, 28(2): 101-105. Not GLP, Published	No	Public domain
A 6.8.2	Aulerich, R.J., Ringer, R.K., Bleavins, M.R. and Napolitano, A.	1982	Effects of Supplemental Dietary Copper on Growth, Reproductive Performance and Kit Survival of Standard Dark Mink and the Acute Toxicity of Copper to Mink, 55(2): 337 – 343. Not GLP, Published	No	Public domain
A 6.8.2	Chang, C.C. And Tatum, H.J.	1973	Absence of teratogenicity of intrauterine copper wire in rats, hamsters and rabbits. Contraception, 7(5): 413 – 434	No	Public domain
A 6.8.2	Cromwell, G.L., Monegue, H.J. and Stahly, T.S.	1993	Long-term effects of feeding a high copper diet to sows during gestation and lactation. J. Anim. Sci. 71: 2996-3002. Not GLP, Published	No	Public domain
A 6.8.2	Hébert, C.D.,	1993	NTP Technical Report on toxicity studies of cupric sulphate (CAS No. 7758-99-8) administered in drinking water and feed to F344/N rats and B6C3F1 mice. National Toxicology Program, Toxicity Report Series No. 29, United States Department of Health and Human Services (NIH Publication 93-3352). GLP, Published	No	Public domain
A 6.8.2	Hébert, C.D.,	1993	NTP Technical Report on toxicity studies of cupric sulphate (CAS No. 7758-99-8) administered in drinking water and feed to F344/N rats and B6C3F1 mice. National Toxicology Program, Toxicity Report Series No. 29, United States Department of Health and Human Services (NIH Publication 93-3352). GLP, Published	No	Public domain

A 6.8.2	Lecyk, M.	1980	Toxicity of CuSO4 in mice embryonic development. Zoologica Poloniae, 28(2): 101-105. Not GLP, Published	No	Public domain
A 6.8.2	Llewellyn, G.C., Floyd, E.A., Hoke, G.D., Weekley, L.B. and Kimbrough, T.D.	1985	Influence of dietary aflatoxin, zinc and copper on bone size, organ weight, and body weight in hamsters and rats. Bull. Environ. Contam. Toxicol., 35: 149-156. Not GLP, Published	No	Public domain
A 6.8.2	[redacted]	2005	Copper Sulfate Pentahydrate: Multigeneration Reproduction Study in Rats. [redacted] Project I.D.: DuPont-14226; GLP; Unpublished	Yes	ECI
A 6.9	Murthy, R.C., Lal, S., Saxena, D.K., Shukla, G.S., Mohd Ali, M and Chandra, S.V.	-	Effect of Manganese and Copper Interaction on Behaviour and Biogenic Amines in Rats Fed a 10% Casein Diet. Chem. Biol. Interactions, 37: 299 – 308. Not GLP, Published	No	Public domain
A 7.4.1.1	Buhl, P.C., & Steven, J.H.	1990	Comparative toxicity of inorganic contaminants released by placer mining to early life stages of salmonids. Ecotoxicol. Environ. Saf. Vol. 20, 325-342. Not GLP, Published	No	Public domain
A 7.4.1.1	Howarth, R. S. & Sprague, J. B.	1978	Copper lethality to rainbow trout in waters of various hardness and pH. Water Res. Vol. 12, 455-462. Not GLP, Published	No	Public domain
A 7.4.1.2	Baird, D. J. et al.	1991	A comparative study of genotype sensitivity to acute toxic stress using clones of Daphnia magna. Ecotoxicol Envrion. Saf. Vol. 21, 257-265. Not GLP, Published	No	Public domain

A 7.4.1.2	Dave, G.	1984	Effects of copper on growth, reproduction, survival and haemoglobin in Daphnia magna. Comp. Biochem. Physiol. Vol. 78C (2) 439-443. Not GLP, Published	No	Public domain
A 7.4.1.2	Le Blanc, G. A.	1982	Laboratory investigation into the development of resistance of Daphnia magna to environmental pollutants. Environ. Poll. Vol. A27, 309-322. Not GLP, Published	No	Public domain
A 7.4.1.2	Oikari, A. et al.	1992	Acute toxicities of chemicals to Daphnia magna in humic waters. Sci. Total. Environ. Vol. 117/118, 367-377. Not GLP, Published	No	Public domain
A 7.4.1.3	De Schamphelaere KAC, Janssen CR	2005	A unified bioavailability model for predicting copper toxicity to freshwater green micro-algae; University of Gent; Draft report – not yet published; not GLP; Unpublished	No	Public domain
A 7.4.1.3	Garvey, J.E. et al.*	1991	Toxicity of Copper to the Green Alga Chlamydomonas reinhardtii (Chlorophyceae) as Affected by Humic Substances of Terrestrial and Freshwater Origin. Aquatic Toxicology. Vol. 19, 89-96. Not GLP, Published	No	Public domain
A 7.4.1.3	Ghent University.*	2002	Chronic algae testing of copper with Chlamydomonas reinhardtii and Chlorella vulgaris. Unpublished data	No	Public domain
A 7.4.1.3	Heijerick D., Bossuyt B. and Janssen C.	2001	EURO-ECOLE Assessment of the Bioavailability and Potential Ecological Effects of Copper in European Surface Waters - Subproject 4:Evaluation and improvement of the ecological relevance of laboratory generated toxicity data; no report number; not GLP; Unpublished	No	ECI

A 7.4.1.3	Heijerick*	2002	Heijerick DG, Bossuyt BTA, Indeherberg M, Mingazinni M, Janssen CR, 2002. Effects of varying physico-chemistry of European surface waters on the copper toxicity to the green algae Pseudokirchneriella subcapitata. Not GLP, Not Published (submitted).	No	Public domain
A 7.4.1.3	Nyholm, N. *	1990	Expression of results from growth inhibition toxicity tests with algae. Arch. Environ Contam. Toxicol. Vol 19 (4) 518- 522. Not GLP, Published	No	Public domain
A 7.4.1.3	Schafer, H. et al.*	1994	Biotests using unicellular algae and ciliates for predicting long-term effects of toxicant. Ecotoxicol. Enviorn. Safe. Vol. 27, 64-81. Not GLP, Published	No	Public domain
A 7.4.1.3	Teisseire, H. et al.*	1998	Toxic Responses and Catalase Activity of Lemna minor Exposed to Folpet, Copper and their Combination. Ecotoxicol. Environ. Saf. 40, 194-200. Not GLP, Published	No	Public domain
A 7.4.1.4	Cha, D.K., Allen, H.E. & Song, J.S.	-	Effect of Copper on Nitrifying and Heterotrophic Populations in Activated Sludge. Department of Civil and Environmental Engineering, University of Delaware, USA. Not GLP, Unpublished	Yes	
A 7.4.1.4	Codina, J.C., Muñoz, M.A., Cazorla, F.M., Perez-Garcia, A., Moriñigo, M.A. & De Vicente, A.	1998	The Inhibition of Methanogenic Activity from Anaerobic Domestic Sludges as a Simple Toxicity Bioassay. Water Research. 32 (4) 1338-1342. Not GLP, Published	No	Public domain
A 7.4.1.4	Madoni, P., Davole, D., Gorbim G. & Vescovi, L.	1996	Toxic Effect of Heavy Metals on the Activated Sludge Protozoan Community. Water Research. 30 (1) 135-141. Not GLP, Published	No	Public domain

A 7.4.1.4	Madoni, P., Davoli, D. & Guglielmi, L.	1999	Response of Sour and Aur to Heavy Metal Contamination in Activated Sludge. Water Research. 33 (10): 2459-2464. Not GLP, Published	No	Public domain
A 7.4.2	Ahsanulla, M. & Williams, A.R.	1991	Sublethal Effects and Bioaccumulation of Cadmium, Chromium, Copper and Zinc in the Marine Amphipod, Allorchestes compressa. Mar. Biol. Not GLP, Published.	No	Public domain
A 7.4.2	Amiard, J.C., Amiard-Triquet, C. & Metayer, C.	1985	Experimental Study of Bioaccumulation, Toxicity and Regulation of Some Trace Metals in Various Estuarine and Coastal Organisms. Symp. Biologica. Hung. 29; 313-323 (published).	No	Public domain
A 7.4.2	Benoit, D.A.	1975	Chronic Effects of Copper on Survival, Growth and Reproduction of the Bluegill (Lepomis macrochirus). Trans. Am. Fish. Soc. 104 (2). 353-358. Not GLP, Published.	No	Public domain
A 7.4.2	Borgmann, U., Norwood, W.P. & Clarke, C.	1993	Accumulation, Regulation and Toxicity of Copper, Zinc, Lead and Mercury in Hyalella azteca. Hydrobiologica. 259: 79-89. Not GLP, Published.	No	Public domain
A 7.4.2	Brown, B. E	1977	Uptake of Copper and Lead by a Metal Tolerant Isopod Asellus meridianus. Freshwater Biol. 7: 235-244. Not GLP, Published.	No	Public domain
A 7.4.2	Brungs, W. A. Leonard, E.N., McKim, J.M.	1973	Acute and Long Term Accumulation of Copper by the Brown Bullhead, Ictalurus nebulosus. J. Fish Res. Board. Can. 30: 583-586. Not GLP, Published.	No	Public domain
A 7.4.2	Calabrese, A., MacInnes, Nelson, D.A, Greig, R.A. & Yevich, P.P.	1984	Effects of Long-Term Exposure to Silver or Copper on Growth, Bioaccumulation and Histopathology in the Blue Mussel, Mytilus edulis. Mar. Environ. Res. 11: 253-274. Not GLP, Published.	No	Public domain

A 7.4.2	Canterford, G.S., Buchanan, A.S. & Ducker, S.C.	1978	Accumulation of Heavy Metals by the Marine Diatom Ditylum brightwelli (West) Grunow. Aust. J. Freshwater Res. 29: 613-22. Not GLP, Published	No	Public domain
A 7.4.2	Djangmah, J.S. & Grove, D.J.	1970	Blood and Hepatopancreas Copper in Crangon vulgaris (Fabricius). Comparative Biochemistry and Physiology (published).	No	Public domain
A 7.4.2	Engel, D.W. & Brouwer, M.	1985	Cadmium and Copper Metallothioneins in the American Lobster, Homarus americanus. Environ. Health. Perspect. 66; 87-92 (published).	No	Public domain
A 7.4.2	George, S.G., Pirie, B.J.S., Cheyne, A.R., Coombs, T.L. & Grant, P.T.	1978	Detoxication of Metals by Marine Bivalves. An Ultrastrutural Study of the Compartmentation of Copper and Zinc in the Oyster Ostrea edulis. Marine Biology, 45; 147-156 (published).	No	Public domain
A 7.4.2	Graney, R.L, Cherry, D.S. & Carins Jr., J.	1993	Heavy Metal Indicator Potential of the Asiatic Clam (Corbicula fluminea) in Artificial Stream Systems. Hydrobiological. 102: 81-88. Not GLP, Published.	No	Public domain
A 7.4.2	Kaland, T. Andersen, T. & Hylland, K.	1993	Accumulation and Subcellular Distribution of Metals in the Marine Gastropod Nassarius reticulatus. p37-53. In: R. Dallinger and P.S. Rainbow (eds). Ecotoxicology of Metals in Invertebrates Proceedings of the 1st SETAC European Conference. Lewis Publications; Boca Raton, Fl. USA 461, pp (published).	No	Public domain
A 7.4.2	Kraak, M. H. S., Lavy, D., Peeters, W. H. M. & Davids, C.	1992	Chronic Ecotoxicity of Copper and Cadmium to the Zebra Mussel Dreissena polymorpha. Arch. Envrion. Contam. Toxicol. 23: 363-369. Not GLP, Published.	No	Public domain

A 7.4.2	McLusky, D.S. & Phillips, C. N. K.	1975	Some Effects of Copper on the Polychaete Phyllodoce maculata. Estuarine & Coastal Mar. Sci. 3: 103-108. Not GLP, Published.	No	Public domain
A 7.4.2	Mersch, J., Morhain, E. & Mouvet, C.	1993	Laboratory Accumulation and Depuration of Copper and Cadmium in the Freshwater Mussel Dreissena polymorpha and the Aquatic Moss Rhynchostegium riparioides. Chemosphere. 27 (8): 1475-1485. Not GLP, Published.	No	Public domain
A 7.4.2	Millanovich, F.P., Spies, R., Guram, M.S. & Sykes, E.E.	1976	Uptake of Copper by the Polychaete Cirriformia spirabrancha in the Presence of Dissolved Yellow Organic Matter of Natural Origin. Estuarine and Coastal Mar. Sci. 4: 585-588. Not GLP, Published.	No	Public domain
A 7.4.2	Pesch, C.E. & Morgan, D	1978	Influence of Sediment in Copper Toxicity Tests with the Polychaete Neanthes arenaceodentata. Water Research. 12: 747-751. Not GLP, Published	No	Public domain
A 7.4.2	Phillips, D. J. H.	1976	The Common Mussel Mytilus edulis as an Indicator of Pollution by Zinc, Cadmium, Lead and Copper. I. Effects of Environmental Variables on Uptake of Metals. Mar. Biol. 38: 59-69. Not GLP, Published.	No	Public domain
A 7.4.2	Rainbow, P.S.	1985	Accumulation of Zn, Cu and Cd by Crabs and Barnacles. Estuarine, Coastal Shelf Science. 21; 669-686 (published).	No	Public domain
A 7.4.2	Rainbow, P.S. & White, S. L.	1989	Comparative Strategies of Heavy Metal Accumulation by Crustaceans: Zinc, Copper and Cadmium in a Decapod and Amphipod and a Barnacle. Hydrobiologia 174; 245-262 (published).	No	Public domain

A 7.4.2	Rainbow, P.S. & White, S. L.	1989	Comparative Strategies of Heavy Metal Accumulation by Crustaceans: Zinc, Copper and Cadmium in a Decapod and Amphipod and a Barnacle. Hydrobiologia 174; 245-262 (published).	No	Public domain
A 7.4.2	Rainbow, P.S. & White, S. L.	1989	Comparative Strategies of Heavy Metal Accumulation by Crustaceans: Zinc, Copper and Cadmium in a Decapod and Amphipod and a Barnacle. Hydrobiologia 174; 245-262 (published).	No	Public domain
A 7.4.2	Rainbow, P.S., Scott, A.G., Wiggins, E.S. & Jackson, R.W.	1980	Effect of Chelating Agents on the Accumulation of Cadmium by the Barnacle Semibalanus balanoides, and Complexation of Soluble Cd, Zn and Cu. Marine Ecology. 2; 143-152 (published).	No	Public domain
A 7.4.2	Riley, J.P. & Roth, I.	1971	The Distribution of Trace Elements in Some Species of Phytoplankton Grown in Culture. J. Mar. Biol. Ass. UK. 51: 63-72. Not GLP, Published	No	Public domain
A 7.4.2	Roesijadi, G	1980	Influence of Copper on the Clam Protothaca staminea: effects on Gills and Occurrence of Copper Binding Proteins. Biol. Bull. 158: 233-247. Not GLP, Published.	No	Public domain
A 7.4.2	Shuster, C. N. & B.H. Pringle	1969	Trace Metal Accumulation by the American Eastern Oyster, Crassostrea virginica. Proc. Nat. Shellfish. Ass. 59: 91-103. Not GLP, Published.	No	Public domain
A 7.4.2	Shuster, C.N and Pringle, B.H.	1969	Effects of Trace Metals on Estuarine Molluscs. Proceedings of the 1st Mid-Atlantic Industrial Waste Conference. November 13-15, 197. Not GLP, Published	No	Public domain

A 7.4.2	Solbe, J.F. de L.G. & Cooper, V.A.	1976	Studies on the Toxicity of Copper Sulphate to Stone Loach Neomacheilus Barbatulus (L.) in Hard Water. Wat. Res. 10: 523-527. Not GLP, Published.	No	Public domain
A 7.4.2	Timmermans, K. R. & Walker, P.A.	1989	The Fate of Trace Metals During Metamorphosis of Chrionomids (Diptera, Chironomidae). Environmental Pollution. 62; 73-85 (published).	No	Public domain
A 7.4.2	White, S.L. & Rainbow, P.S.	1982	Regulation and Accumulation of Copper, Zinc and Cadmium by the Shrimp Palaemon elegans. Marine Ecology Progress Series. 8; 95-101 (published).	No	Public domain
A 7.4.2	Winner , R.W.	1984	The Toxicity and Bioaccumulation of Cadmium and Copper as Affected by Humic Acid. Aquatic Toxicology. 5: 267-274. Not GLP, Published.	No	Public domain
A 7.4.2	Young, J.S., Buschbom, R.L., Gurtisen, J.M. & Joyce, S.P.	1979	Effects of Copper on the Sabellid Polychaete, Eudistylia vancouveri: I Concentration Limits for Copper Accumulation. Archives of Environmental Contamination and Toxicology. 8: 97-106. Not GLP. Published	No	Public domain
A 7.4.2	Zaroogian, G.E. & Johnston, M.	1983	Copper Accumulation in the Bay Scallop, Argopecten irradians. Arch. Environ. Contam. Toxicol. 12: 127-133. Not GLP, Published.	No	Public domain
A 7.4.3.1	Collvin, L.*	1984	The effect of copper on growth, food consumption and food conversion of perch Perca fluviatilis L. offered maximal food rations. Aquatic Toxicology (Amsterdam) 6: 105-113. Not GLP, Published	No	Public domain

A 7.4.3.1	Scudder, B. C., J. L. Carter and H. V. Leland*	1988	Effects of copper on development of the fathead minnow, Pimephales promelas Rafinesque. Aquatic Toxicology (Amsterdam) 12: 107-124. Not GLP, Published	No	Public domain
A 7.4.3.1	Solbe, J. F. d. L. G. and V. A. Cooper*	1976	Studies on the toxicity of copper sulphate to stone loach Noemacheilus barbatulus (L.) in hard water. Water Research 10: 523-527. Not GLP, Published	No	Public domain
A 7.4.3.1/ 7.4.3.2	Job, K.M., A.M. Askew and R.B. Foster.*	1995	Development of a water-effect-ratio for copper, cadmium and lead for the Great Works River in Maine using Ceriodaphnia dubia and Salvelinus fontinalis. Bulletin of Environmental Contamination and Toxicology. 54: 29-35. Not GLP, Published	No	Public domain
A 7.4.3.1/ 7.4.3.2	Mount, D. I.*	1968	Chronic toxicity of copper to fathead minnows (Pimephales promelas Rafinesque). Water Research 2: 215-223. Not GLP, Published	No	Public domain
A 7.4.3.1/ 7.4.3.2	Spehar, R. L. and J. T. Fiandt*	1985	Acute and chronic effects of water quality criteria based metal mixtures on three aquatic species. Project Summary EPA/6000/S3-85/074. U. S. Environmental Protection Agency, Environmental Research Laboratory, Duluth, Minnesota. Not GLP, Published	No	Public domain
A 7.4.3.1/ 7.4.3.2	Mount, D. I. and C. E. Stephan.*	1969	Chronic toxicity of copper to the fathead minnow (Pimephales promelas) in soft water. Journal of the Fisheries Research Board of Canada 26: 2449-2457. Not GLP, Published	No	Public domain

A 7.4.3.1/ 7.4.3.2	Mudge, J. E., N. T. E., G. S. Jeane, W. Davis and J. L. Hickam*	1993	Effect of varying environmental conditions on the toxicity of copper to salmon. pp. 19-33. In: J. W. Gorsuch, F. J. Dwyer, C. G. Ingersoll and T. W. L. Point (eds.). Environmental Toxicology and Risk Assessment: 2nd Volume, ASTM STP 1216. American Society for Testing Materials, Philadelphia, Pennsylvania. Not GLP, Published	No	Public domain
A 7.4.3.1/ 7.4.3.2	McKim, J. M. and D. A. Benoit.*	1971	Effects of long-term exposures to copper on survival, growth, and reproduction of brook trout (Salvelinus fontinalis). Journal of the Fisheries Research Board of Canada 28: 655-662. Not GLP, Published	No	Public domain
A 7.4.3.1/ 7.4.3.2	Horning, W. B. and T. W. Neiheisel*	1979	Chronic effect of copper on the bluntnose minnow, Pimephales notatus (Rafinesque). Archives of Environmental Contamination and Toxicology 8: 545-552. Not GLP, Published	No	Public domain
A 7.4.3.1/ 7.4.3.2	Sauter, S., K. S. Buxton, K. J. Macek and S. R. Petrocelli*	1976	Effects of exposure to heavy metals on selected freshwater fish. Toxicity of copper, cadmium, chromium and lead to eggs and fry of seven fish species. Ecological Reseach Series EPA-600/3-76-105. U.S. Environmental Protection Agency, Environmental Research Laboratory, Duluth, Minnesota. Not GLP, Published	No	Public domain
A 7.4.3.2	Belanger, S. E. and D. S. Cherry.*	1990	Interacting effects of pH acclimation, pH, and heavy metals on acute and chronic toxicity to Ceriodaphnia dubia (Cladocera). Journal of Crustacean Biology 10(2): 225-235. Not GLP, Published	No	Public domain

A 7.4.3.2	Brungs, W. A., J. R. Geckler and M. Gast.*	1976	Acute and chronic toxicity of copper to the fathead minnow in a surface water of variable quality. Water Research 10: 37-43. Not GLP, Published.	No	Public domain
A 7.4.3.2	Collvin, L*	1985	The effects of copper on maximum respiration rate and growth rate of perch, Perca fluviatilis L. Water Research 18(2): 139-144. Not GLP, Published	No	Public domain
A 7.4.3.2	Marr, J. C. A., J. Lipton, D. Cacela, J. A. Hansen, H. L. Bergman, J. S. Meyer and C. Hogstrand.*	1996	Relationship between copper exposure duration, tissue copper concentration, and rainbow trout growth. Aquatic Toxicology 36: 17-30. Not GLP, Published	No	Public domain
A 7.4.3.2	Pickering, Q., W. Brungs and M. Gast.*	1977	Effect of exposure time and copper concentration on reproduction of the fathead minnow (Pimephales promelas). Water Research 11(12): 1079-1083. Not GLP, Published	No	Public domain
A 7.4.3.2	Seim, W. K., L. R. Curtis, S. W. Glenn and G. A. Chapman.*	1984	Growth and survival of developing steelhead trout (Salmo gairdneri) continuously or intermittently exposed to copper. Canadian Journal of Fisheries and Aquatic Sciences 41(3): 433-438. Not GLP, Published	No	Public domain
A 7.4.3.4	Arthur, J. W. and E. N. Leonard.*	1970	Effects of copper on Gammarus pseudolimnaeus, Physa integra, and Campeloma decisum in soft water. Journal of the Fisheries Research Board of Canada 27(7): 1277-1283. Not GLP, Published	No	Public domain

A 7.4.3.4	Belanger, S. E., J. L. Farris and D. S. Cherry*	1989	Effects of diet, water hardness, and population source on acute and chronic copper toxicity to Ceriodaphnia dubia. Archives of Environmental Contamination and Toxicology 18: 601-611. Not GLP, published	No	Public domain
A 7.4.3.4	Cerda, B and Olive, J.H.	1993	Effects of Diet on Seven-Day Ceriodaphnia dubia Toxicity Tests; Ohio J. Sci. 93 (3): 44-47, 1993; no report number; not GLP; Published	No	Public domain
A 7.4.3.4	Deaver, E. and J. H. Rodgers, Jr.*	1996	Measuring bioavailable copper using anodic stripping voltammetry. Environmental Toxicology and Chemistry 15(11): 1925-1930. Not GLP, Unpublished	No	Public domain
A 7.4.3.4	Hatakeyama, S. and M. Yasuno.*	1981	A method for assessing chronic effects of toxic substances on the midge, Paratanytarsus parthenogeneticus-effects of copper. Archives of Environmental Contamination and Toxicology 10: 705-713. Not GLP, Published	No	Public domain
A 7.4.3.4	Heijerick D., Bossuyt B. and Janssen C.	2001	EURO-ECOLE Assessment of the Bioavailability and Potential Ecological Effects of Copper in European Surface Waters - Subproject 4:Evaluation and improvement of the ecological relevance of laboratory generated toxicity data; no report number; not GLP; Unpublished	No	ECI
A 7.4.3.4	Heijerick DG, Bossuyt BTA, Indeherberg M, Mingazinni M, Janssen CR,*	2002	Effects of varying physico-chemistry of European surface waters on the copper toxicity to the green algae Pseudokirchneriella subcapitata. Not GLP, Not Published (submitted).	No	Public domain

A 7.4.3.4	Jop, K.M., A.M. Askew and R.B. Foster.*	1995	Development of a water-effect-ratio for copper, cadmium and lead for the Great Works River in Maine using Ceriodaphnia dubia and Salvelinus fontinalis. Bulletin of Environmental Contamination and Toxicology. 54: 29-35. Not GLP, Published	No	Public domain
A 7.4.3.4	Maund S.J., E.J. Taylor and D. Pascoe.*	1992	Population responses of the freshwater amphipod crustacean Gammarus pulex to copper. Freshwater Biology 28: 29-36. Not GLP, Published	No	Public domain
A 7.4.3.4	Nebeker, A. V., A. Stinchfield, C. Savonen and G. A. Chapman	1986	1986; Effects of copper, nickel and zinc on three species of Oregon freshwater snails; Environmental Toxicology and Chemistry 5(9): 807-811; not GLP; Published	No	Public domain
A 7.4.3.4	Nebeker, A. V., C. Savonen, R. J. Baker and J. K. McCrady.*	1984	Effects of copper, nickel and zinc on the life cycle of the caddisfly Clistoronia magnifica (Limnephilidae). Environmental Toxicology and Chemistry 3: 645-649. Not GLP, Published	No	Public domain
A 7.4.3.4	Spehar, R. L. and J. T. Fiandt*	1985	Acute and chronic effects of water quality criteria based metal mixtures on three aquatic species. Project Summary EPA/6000/S3-85/074. U. S. Environmental Protection Agency, Environmental Research Laboratory, Duluth, Minnesota. Not GLP, Published	No	Public domain
A 7.4.3.4	Taylor E.J., S.J. Maund and D. Pascoe.*	1991	Evaluation of a chronic toxicity test using growth of the insect Chironomus riparius Meigen. In: Bioindicators and Environmental Management. Eds. D.W. Jeffrey and B. Madden. Academic Press, United Kingdom, pp. 343-352. Not GLP, Published	No	Public domain

A 7.4.3.4	Van Leeuwen, C. J., J. L. Buchner and H. Van Dijk.*	1988	Intermittent flow system for population toxicity studies demonstrated with Daphnia and copper. Bulletin of Environmental Contamination and Toxicology 40(4): 496-502. Not GLP, Published	No	Public domain
A 7.4.3.4	Winner, R. W.*	1985	Bioaccumulation and toxicity of copper as affected by interactions between humic acid and water hardness. Water Research 19(4): 449-455. Not GLP, Published	No	Public domain
A 7.4.3.5	Belanger, S.E., Farris, J.L., Cherry, D.S., & Cairns, Jr., J.	1990	Validation of Corbicula fluminea Growth Reductions Induced by Copper in Artificial Streams and River Systems. Can. J. Fish. Aquat. Sci. 47: 904-914. Not GLP, Published	No	Public domain
A 7.4.3.5	Borgmann, U., Cover, R. & Loveridge, C.	1980	Effects of Metals on the Biomass Production Kinetics of Freshwater Copepods. Can. J. Fish. Aquat. Sci. 37: 567-575. Not GLP, Published.	No	Public domain
A 7.4.3.5	Clements, W.H., Cherry, D.S. & Cairns Jr., J.	1988	Structural Alterations in Aquatic Insect Communities Exposed to Copper in Laboratory Streams. Environ. Toxicol. Chem. 7: 715-722. Not GLP, Published	No	Public domain
A 7.4.3.5	Clements, W.H., Cherry, D.S. & Cairns, Jr., J.	1989 b	The Influence of Copper Exposure on Predator-Prey Interactions in Aquatic Insect Communities. Freshwater Biology. 21: 483-488. Not GLP, Published.	No	Public domain
A 7.4.3.5	Clements, W.H., Farris, J.L., Cherry, D.S. & Cairns Jr., J.	1989 a	The Influence of Water Quality on Macroinvertebrate Community Responses to Copper in Outdoor Experimental Streams. Aquatic Toxicol. 14: 249-262. Not GLP, Published	No	Public domain

A 7.4.3.5	Girling, A.E., Pascoe, S., Janssen, C.R., Peither, A. Wenzel, A., Schafer, H., Neumeier, B., Mitchell, G.C., Taylor, E.J., Maund, S.J., Lay, J.P., Juttner, I., Crossland, N.O., Stephenson, & Persoone, G.	2000	Development of Methods for Evaluating Toxicity in Freshwater Ecosystems. Ecotoxicol. Environ. Safe. 45, 148-176. Not GLP, Published	No	Public domain
A 7.4.3.5	Hart, B.T., Currey, N.A. & Jones, M.J.	1992	Biogeochemistry and Effects of Copper, Manganese and Zinc Added to Enclosures in Island Billabong, Magela Creek, Northern Australia. Hydrobiologica. 230: 93-134. Not GLP, Published	No	Public domain
A 7.4.3.5	Havens, K. E	1994 b	Structural and Functional Responses of Freshwater Plankton Community to Acute Copper Stress. Environmental Pollution. 86 (3); 259-266. Not GLP, Published	No	Public domain
A 7.4.3.5	Havens, K.E.	1994 a	An Experimental Comparison of the Effects of Two Chemical Stressor on a Freshwater Zooplankton Assemblage. Environmental Pollution. 84: 245-251. Not GLP, Published	No	Public domain
A 7.4.3.5	Hedtke, S. F.	1984	Structure and Function of Copper-Stressed Aquatic Microcosms. Aquatic Toxicology. 5: 227-244. Not GLP, Published	No	Public domain
A 7.4.3.5	Leland, H.V. & Carter, J.L	1985	Effects of Copper on Production of Periphyton, Nitrogen Fixation and Processing of Leaf Litter Sierra Nevada California, Stream. Freshwater Biology. 15: 155-173. Not GLP, Published	No	Public domain

A 7.4.3.5	Leland, H.V. & Carter, J.L.	1984	Effects of copper on Species Composition of Periphyton in a Sierra Nevada, California, Stream. Freshwater Biology. 14: 281-296. Not GLP, Published	No	Public domain
A 7.4.3.5	Leland, H.V. & Kent, E.	1981	Effects of Copper on Microfaunal Species Composition in a Sierra Nevada, California Stream. Verh. Internat. Verein. Liminol. 21: 819-829. Not GLP, Published	No	Public domain
A 7.4.3.5	Leland, H.V., Fend, S.V., Dudley, T.L. & Carter, J.L.	1989	Effects of Copper on Species Composition of Benthic Insects in a Sierra Nevada, California Stream. Freshwater Biology. 21: 163-179. Not GLP, Published	No	Public domain
A 7.4.3.5	Moore, M.V. & Winner, R.W	1989	Relative Sensitivity of Cerodaphnia dubia Laboratory Tests and Pond Communities of Zooplankton and Benthos to Chronic Copper Stress. Aquatic Toxicology. 15: 311-330. Not GLP, Published	No	Public domain
A 7.4.3.5	Schäfers, C.	2003	Community Level Study with Copper in Aquatic Microcosms. Fraunhofer Institute for Molecular Biology and Applied Ecology (IME). Fraunhofer Study Number EECU 01. Not GLP, Unpublished	Yes	European Copper Institute
A 7.4.3.5	Taub, F.B., Kindig, A.C., Meador, J.P. & Swartzman, G.L.	1991	Effects of 'Seasonal Succession' and Grazing on Copper Toxicity in Aquatic Microcosms. Verh. Internat. Verein. Limnol. 24: 2205-2214.	No	Public domain
A 7.4.3.5	Winner, R.W. & Owen, H.A.	1991	Seasonal Variability in the Sensitivity of Freshwater Phytoplankton Communities to a Chronic Copper Stress. Aquatic. Toxicol. 19: 73-88. Not GLP, Published.	No	Public domain

A 7.4.3.5	Winner, R.W., Owen, H.A. & Moore, M.V.	1990	Seasonal Variability in the Sensitivity of Freshwater Lentic Communities to a Chronic Copper Stress. Aquatic Toxicology. 17: 75-92. Not GLP, Published	No	Public domain
A 7.4.3.5	Winner, R.W., Van Dyke, J.S., Caris, N. & Farrel, M.P.	1975	Response of the Macroinvertebrate Fauna to a Copper Gradient in an Experimentally Polluted Stream. Verh. Internat. Verein. Liminol. 19: 2121-2127. Not GLP, Published	No	Public domain
A 7.4.3.6	Milani D., T.B. Reynoldson, U. Borgmann and J. Kolasa.	2003	The relative sensitivity of four benthic invertebrates to metals in spiked sediment exposures and application to contaminated field sediment. Env. Tox and Chem, 22, 4, 845-854; not GLP; Published.	No	Public domain
A 7.4.3.6	Vecchi M., T.B. Reynoldson, A. Pasteris and D. Bonomi.	1999	Toxicity of Copper Spiked Sediments to Tubifex tubifex: Comparison of the 28-day reproductive bioassay with an early life stage bioassay. Env. Tox and Chem, 18, 6, 1173-1179; not GLP; Published	No	Public domain
A 7.5.1.1	Arshad, M. & Frankenberger, W.T.*	1991	Effects of Soil Properties and Trace Elements on Ethylene Production in Soils. Soil Science. 151, 5: 377-386. Not GLP, Published	No	Public domain
A 7.5.1.1	Arshad, M. & Frankenberger, W.T.*	1991	Effects of Soil Properties and Trace Elements on Ethylene Production in Soils. Soil Science. 151, 5: 377-386. Not GLP, Published	No	Public domain
A 7.5.1.1	Bogomolov, D.M., Chen, S.K., Parmalee, R.W, Subler, S. & Edwards, C.A.*	1996	An Ecosystem Approach to Soil Toxicity Testing: A Study of Copper Contamination in Laboratory Soil Microcosms. Applied Soil Ecology. 4: 95-105. Not GLP, Published	No	Public domain

A 7.5.1.1	Bogomolov, D.M., Chen, S.K., Parmalee, R.W, Subler, S. & Edwards, C.A.*	1996	An Ecosystem Approach to Soil Toxicity Testing: A Study of Copper Contamination in Laboratory Soil Microcosms. Applied Soil Ecology. 4: 95-105. Not GLP, Published	No	Public domain
A 7.5.1.1	Bollag, J-M, Barabasz, W.*	1979	Effect of Heavy Metals on the Denitrification Process in Soil. J. Environ. Qual. 8: (2); 196-201. Not GLP, Published	No	Public domain
A 7.5.1.1	Bollag, J-M, Barabasz, W.*	1979	Effect of Heavy Metals on the Denitrification Process in Soil. J. Environ. Qual. 8: (2); 196-201. Not GLP, Published	No	Public domain
A 7.5.1.1	Chang, F-H. & Broadbent, F.E*	1981	Influence of Trace Metals on Carbon Dioxide Evolution from a Yolo Soil. Soil Science. 132: 6; 416-421. Not GLP, Published.	No	Public domain
A 7.5.1.1	Chang, F-H. & Broadbent, F.E*	1981	Influence of Trace Metals on Carbon Dioxide Evolution from a Yolo Soil. Soil Science. 132: 6; 416-421. Not GLP, Published.	No	Public domain
A 7.5.1.1	Chang, F-H. & Broadbent, F.E*	1982	Influence of Trace Metals on Some Soil Nitrogen Transformations. J. Environ. Qual. 11: 1; 1-4. Not GLP, Published.	No	Public domain
A 7.5.1.1	Chang, F-H. & Broadbent, F.E*	1982	Influence of Trace Metals on Some Soil Nitrogen Transformations. J. Environ. Qual. 11: 1; 1-4. Not GLP, Published.	No	Public domain
A 7.5.1.1	Doelman, P. & Haanstra, L*	1984	Short Term and Long Term Effects of Cadmium, Chromium, Copper, Nickel, Lead and Zinc on Soil Microbial Respiration in Relation to Abiotic Soil Factors. Plant and Soil. 79; 317-327. Not GLP, Published.	No	Public domain

A 7.5.1.1	Doelman, P. & Haanstra, L*	1984	Short Term and Long Term Effects of Cadmium, Chromium, Copper, Nickel, Lead and Zinc on Soil Microbial Respiration in Relation to Abiotic Soil Factors. Plant and Soil. 79; 317-327. Not GLP, Published.	No	Public domain
A 7.5.1.1	Doelman, P. & Haanstra, L*	1986	Short and Long Term Effects of Heavy Metals on Urease Activity in Soils. Biol. Fertil. Soils. 2; 213-218. Not GLP, Published.	No	Public domain
A 7.5.1.1	Doelman, P. & Haanstra, L*	1986	Short and Long Term Effects of Heavy Metals on Urease Activity in Soils. Biol. Fertil. Soils. 2; 213-218. Not GLP, Published.	No	Public domain
A 7.5.1.1	Doelman, P. & Haanstra, L.*	1989	Short and Long Term Effects of Heavy Metals on Phosphatase Activity in Soils: An Ecological Dose-Response Model Approach. Biol. Fertil. Soils. 8; 235-241.Not GLP, Published.	No	Public domain
A 7.5.1.1	Doelman, P. & Haanstra, L.*	1989	Short and Long Term Effects of Heavy Metals on Phosphatase Activity in Soils: An Ecological Dose-Response Model Approach. Biol. Fertil. Soils. 8; 235-241.Not GLP, Published.	No	Public domain
A 7.5.1.1	Frostegård, A, Tunlid, A. & Bååth, E.*	1993	Phospholipid Fatty Acid Composition, Biomass and Activity of Microbial Communities from Two Different Soil Types Experimentally Exposed to Different Heavy Metals. App. Environ. Microbiol. 59 (11): 3605-3617. Not GLP, Published	No	Public domain

A 7.5.1.1	Frostegård, A, Tunlid, A. & Bååth, E.*	1993	Phospholipid Fatty Acid Composition, Biomass and Activity of Microbial Communities from Two Different Soil Types Experimentally Exposed to Different Heavy Metals. App. Environ. Microbiol. 59 (11): 3605-3617. Not GLP, Published	No	Public domain
A 7.5.1.1	Haanstra, L. & Doelman, P.*	1984	Glutamic Acid Decomposition as a Sensitive Measure of Heavy Metal Pollution in Soil. Soil Biol. Biochem. 16; 595-600. Not GLP, Published.	No	Public domain
A 7.5.1.1	Haanstra, L. & Doelman, P.*	1984	Glutamic Acid Decomposition as a Sensitive Measure of Heavy Metal Pollution in Soil. Soil Biol. Biochem. 16; 595-600. Not GLP, Published.	No	Public domain
A 7.5.1.1	Haanstra, L. & Doelman, P.*	1991	An Ecological Dose-Response Model Approach to Short and Long Term Effects of Heavy Metals on Arylsulphatase Activity in Soil. Biol. Fert. Soils. 11; 18-23. Not GLP, Published.	No	Public domain
A 7.5.1.1	Haanstra, L. & Doelman, P.*	1991	An Ecological Dose-Response Model Approach to Short and Long Term Effects of Heavy Metals on Arylsulphatase Activity in Soil. Biol. Fert. Soils. 11; 18-23. Not GLP, Published.	No	Public domain
A 7.5.1.1	Hemida, S.K., Omar, S.A. & Abdel-Mallek, A.Y.*	1995	Microbial Populations and Enzyme Activity in Soil Treated with Heavy Metals. Water, Air. Soil Poll. 95: 13-22. Not GLP, Published.	No	Public domain
A 7.5.1.1	Hemida, S.K., Omar, S.A. & Abdel-Mallek, A.Y.*	1995	Microbial Populations and Enzyme Activity in Soil Treated with Heavy Metals. Water, Air. Soil Poll. 95: 13-22. Not GLP, Published.	No	Public domain

A 7.5.1.1	Khan, M. and Scullion, J.	2002	Effects of metal (Cd, Cu, Ni, Pb or Zn) enrichment of sewage-sludge on soil micro-organisms and their activities. Applied Soil Ecology, 20, 145-155; not GLP; Published	No	Public domain
A 7.5.1.1	Maliszewska, W., Dec, S., Wierzbicka, H. & Wozniakowska, A.*	1985	The Influence of Various Heavy Metal Compounds on the Development and Activity of Soil Micro-Organisms. Environ. Poll. (Series A). 37; 195-215. Not GLP, Published	No	Public domain
A 7.5.1.1	Maliszewska, W., Dec, S., Wierzbicka, H. & Wozniakowska, A.*	1985	The Influence of Various Heavy Metal Compounds on the Development and Activity of Soil Micro-Organisms. Environ. Poll. (Series A). 37; 195-215. Not GLP, Published	No	Public domain
A 7.5.1.1	Premi, P.R. & Cornfield, A.H.*	1969	Effects of Addition of Copper, Manganese, Zinc and Chromium Compounds on Ammonification and Nitrification During Incubation of Soil. Plant and Soil. 31: (2); 345-352. Not GLP, Published.	No	Public domain
A 7.5.1.1	Premi, P.R. & Cornfield, A.H.*	1969	Effects of Addition of Copper, Manganese, Zinc and Chromium Compounds on Ammonification and Nitrification During Incubation of Soil. Plant and Soil. 31: (2); 345-352. Not GLP, Published.	No	Public domain
A 7.5.1.1	Quraishi, M.S.I & Cornfield, A.H.*	1973	Incubation Study of Nitrogen Mineralisation and Nitrification in Relation to Soil pH and Level of Copper (II) Addition. Environ. Poll. 4; 159-163. Not GLP, Published.	No	Public domain
A 7.5.1.1	Quraishi, M.S.I & Cornfield, A.H.*	1973	Incubation Study of Nitrogen Mineralisation and Nitrification in Relation to Soil pH and Level of Copper (II) Addition. Environ. Poll. 4; 159-163. Not GLP, Published.	No	Public domain

A 7.5.1.1	Saviozzi, A., Levi-Minzi, R., Cardelli, R. & Riffaldi, R*	1997	The Influence of Heavy Metals on Carbon Dioxide Evolution from A Typic Xerochrept Soil. Water, Air Soil Poll. 93: 409-417 (published).	No	Public domain
A 7.5.1.1	Saviozzi, A., Levi-Minzi, R., Cardelli, R. & Riffaldi, R*	1997	The Influence of Heavy Metals on Carbon Dioxide Evolution from A Typic Xerochrept Soil. Water, Air Soil Poll. 93: 409-417 (published).	No	Public domain
A 7.5.1.1	Skujins, J., Nohrstedt, H-O., Odén, S.*	1986	Development of a Sensitive Biological Method for the Determination of a Low-Level Toxic Contamination in Soils. Swedish J. Agric. Res. 16; 113-118.Not GLP, Published	No	Public domain
A 7.5.1.1	Skujins, J., Nohrstedt, H-O., Odén, S.*	1986	Development of a Sensitive Biological Method for the Determination of a Low-Level Toxic Contamination in Soils. Swedish J. Agric. Res. 16; 113-118.Not GLP, Published	No	Public domain
A 7.5.1.1	Speir, T.W., Kettles, H.A., Percival, H.J. & Parshotam, A*	1999	Is Soil Acidification the Cause of Biochemical Response when Soils are Amended with Heavy Metal Salts? Soil Biology and Biochemistry. 31: 1953-1961. Not GLP, Published	No	Public domain
A 7.5.1.1	Speir, T.W., Kettles, H.A., Percival, H.J. & Parshotam, A*	1999	Is Soil Acidification the Cause of Biochemical Response when Soils are Amended with Heavy Metal Salts? Soil Biology and Biochemistry. 31: 1953-1961. Not GLP, Published	No	Public domain
A 7.5.1.2/ 7.5.6	van Gestel, C.A.M., van Dis, W.A., Dirven-van Breeman, E.M., Sparenburg, P.M. & Baerselman, R.*	1991	Influence of Cadmium, Copper and Pentachlorophenol on Growth and Sexual Development of Eisenia andrei (Oligochaeta; Annelida). Biology and Fertility of Soils. 12; 117-121. Not GLP, Published.	No	Public domain

A 7.5.1.2/ 7.5.6	van Gestel, C.A.M., van Dis, W.A., Dirven-van Breeman, E.M., Sparenburg, P.M. & Baerselman, R.*	1991	Influence of Cadmium, Copper and Pentachlorophenol on Growth and Sexual Development of Eisenia andrei (Oligochaeta; Annelida). Biology and Fertility of Soils. 12; 117-121. Not GLP, Published.	No	Public domain
A 7.5.1.2/ 7.5.6/ 7.5.2.1	Spurgeon, D.J. & Hopkin, S.P.*	1995	Extrapolation of the Laboratory-Based OECD Earthworm Toxicity Test to Metal-Contaminated Field Sites. Ecotoxicity. 4; 190-205	No	Public domain
A 7.5.1.2/ 7.5.6/ 7.5.2.1	Spurgeon, D.J. & Hopkin, S.P.*	1995	Extrapolation of the Laboratory-Based OECD Earthworm Toxicity Test to Metal-Contaminated Field Sites. Ecotoxicity. 4; 190-205	No	Public domain
A 7.5.1.2/ 7.5.6	Svendsen, C. & Weeks, J.M*	1997 a	Relevance and Applicability of a Simple Earthworm Biomarker of Copper Exposure. I. Links to Ecological Effects in a Laboratory Study with Eisenia andrei. Ecotoxicology and Environmental Safety. 36; 72-79	No	Public domain
A 7.5.1.2/ 7.5.6	Svendsen, C. & Weeks, J.M*	1997 a	Relevance and Applicability of a Simple Earthworm Biomarker of Copper Exposure. I. Links to Ecological Effects in a Laboratory Study with Eisenia andrei. Ecotoxicology and Environmental Safety. 36; 72-79	No	Public domain
A 7.5.1.2/ 7.5.2.1	Martin, N.A.,*	1986	Toxicity of Pesticides to Allolobophora caliginosa (Oligochaeta: Lumbricidae). New Zealand Journal of Agricultural Research. 29; 699-706. Not GLP, Published.	No	Public domain

A 7.5.1.2/ 7.5.2.1	Martin, N.A.,*	1986	Toxicity of Pesticides to Allolobophora caliginosa (Oligochaeta: Lumbricidae). New Zealand Journal of Agricultural Research. 29; 699-706. Not GLP, Published.	No	Public domain
A 7.5.2.1	Herbert IN, Svendsen C, Hankard PK and Spurgeon DJ	2004	Comparison of instantaneous rate of population increase and critical-effect estimates in Folsomia candida exposed to four toxicants. Ecotox. Environ. Safety 57:175-183; not GLP; Published	No	Public domain
A 7.5.2.1	Kammenga, J.E., Van Koert, P.H.G., Riksen, J.A.G., Korthals, G.W. & Bakker, J.*	1996	A Toxicity Test in Artificial Soil based on the Life History Strategy of the Nematode Plectus acuminatus. Environmental Toxicology and Chemistry. 15; 722-727. Not GLP, Published.	No	Public domain
A 7.5.2.1	Kammenga, J.E., Van Koert, P.H.G., Riksen, J.A.G., Korthals, G.W. & Bakker, J.*	1996	A Toxicity Test in Artificial Soil based on the Life History Strategy of the Nematode Plectus acuminatus. Environmental Toxicology and Chemistry. 15; 722-727. Not GLP, Published.	No	Public domain
A 7.5.2.1	Lock, K., Janssen, C.R.	2001	Test designs to assess the influence of Soil Characteristics on the Toxicity of Copper and Lead to the Oligochaete Enchytraeus albidus; Ecotoxicology, 10, 137-144; not GLP; Published	No	Public domain
A 7.5.2.1	Ma, W-C.,*	1988	Toxicity of Copper to Lumbricid Earthworms in Sandy Agricultural Soils Amended with Cu-Enriched Organic Waste Materials. Ecological Bulletins. 39; 53-56. Not GLP, Published.	No	Public domain
A 7.5.2.1	Ma, W-C.,*	1988	Toxicity of Copper to Lumbricid Earthworms in Sandy Agricultural Soils Amended with Cu-Enriched Organic Waste Materials. Ecological Bulletins. 39; 53-56. Not GLP, Published.	No	Public domain

A 7.5.2.1	Pedersen, M. B., van Gestel, C.A.M.	2001	Toxicity of copper to the collembolan Folsomia fimetaria in relation to the age of soil contamination; Ecotoxicology and Environmental Safety, 49, 54-59; not GLP; Published	No	Public domain
A 7.5.2.1	Pedersen, M. B., van Gestel, C.A.M., Elmegaard, N.	2000	Effects of copper on reproduction of two collembolan species exposed through soil, food and water. Environmental Toxicology and Chemistry, 19, 10, 2579-2588; not GLP; Published	No	Public domain
A 7.5.2.1	Rundgren S. & Van Gestel, C.A.M.	1988	Comparison of Species Sensitivity. In: Handbook of Soil Invertebrate Toxicity Tests. pp 41-55 Ed. H. Lokke and C.A.M. Van Gestel. J. Wiley and Sons Ltd, Chichester, UK; not GLP; Published.	No	Public domain
A 7.5.2.1	Sandifer, R.D & Hopkin, S.P.	1997	Effects of Temperature on the Relative Toxicities of Cd, Cu, Pb and Zn to Folsomia candida (Collembola). Ecotoxicology and Environmental Safety. 37; 125-130; not GLP; Published	No	Public domain
A 7.5.2.1	Spurgeon DJ, Svendsen C, Kille P, Morgan AJ, Weeks JM.	2004	Responses of earthworms (Lumbricus rubellus) to copper and cadmium as determined by measurement of juvenile traits in a specifically designed test system. Ecotoxicol Environ Saf. 57 (1), 54-64; not GLP; Published	No	Public domain
A 7.5.2.1	van Dis, W.A., Van Gestel, C.A.M., and Sparenburg, P.M.	1988	Ontwikkeling van een toets ter bepaling van sublethale effecten van chemische stoffen op regenwormen; RIVM expert report 718480002; not GLP; Published	No	Public domain

A 7.5.2.1	Van Gestel, C.A.M. & Doornekamp, A. *	1998	Tests of the Oribatid mite Playnothrus peltifer. In Handbook of Soil Invertebrate Toxicity Tests. Ed. H. Lokke and C.A.M. Van Gestel. J. Wiley and Sons Ltd, Chichester, UK. Not GLP, Published.	No	Public domain
A 7.5.2.1	Van Gestel, C.A.M. & Doornekamp, A. *	1998	Tests of the Oribatid mite Playnothrus peltifer. In Handbook of Soil Invertebrate Toxicity Tests. Ed. H. Lokke and C.A.M. Van Gestel. J. Wiley and Sons Ltd, Chichester, UK. Not GLP, Published.	No	Public domain
A 7.5.2.1	van Gestel, C.A.M., Van Dis, W.A., Breemen, E.M. & Sparenburg, P.M.	1989	Development of a Standardised Reproduction Toxicity Test with the Earthworm Species Eisenia fetida andrei Using Copper, Pentachlorophenol and 2, 4-Dichloroaniline. Ecotoxicol. Environ. Safety. 18: 305-312; not GLP; Published.	No	Public domain
A 7.5.2.1	Van Gestel, C.A.M., Van Dis, W.A., Breemen, E.M. & Sparenburg, P.M.*	1989	Development of a Standardised Reproduction Toxicity Test with the Earthworm Species Eisenia fetida andrei Using Copper, Pentachlorophenol and 2, 4-Dichloroaniline. Ecotoxicol. Environ. Safety. 18: 305-312. Not GLP, Published.	No	Public domain
A 7.5.2.1	Van Gestel, C.A.M., Van Dis, W.A., Breemen, E.M. & Sparenburg, P.M.*	1989	Development of a Standardised Reproduction Toxicity Test with the Earthworm Species Eisenia fetida andrei Using Copper, Pentachlorophenol and 2, 4-Dichloroaniline. Ecotoxicol. Environ. Safety. 18: 305-312. Not GLP, Published.	No	Public domain

A 7.5.2.2	Ali, N. A., Ater, M., Sunahara, G., Robidoux, P.Y.	2004	Phytotoxicity and bioaccumulation of copper and chromium using barley (Hordeum vulgare L.) in spiked artificial and natural forest soils. Ecotoxicology and Environmental Safety Volume 57, Issue 3 , March 2004, Pages 363-374; not GLP; Published	No	Public domain
A 7.5.2.2	Alva, A.K., Graham, J.H. & Tucker, D.P.H.*	1993	Role of Calcium in Amelioration of Copper Phytotoxicity for Citrus. Soil Science. 155; 3; 211-218. Not GLP, Published.	No	Public domain
A 7.5.2.2	Belanger, A., Levesque, M.P. & Mathur, S.P.*	1987	The Influence of Variation in Soil Copper on the Yeild and Nutrition of Radishes Grown in Microplots on Two Peat Soils. International Peat Journal. 2; 65-73.Not GLP, Published.	No	Public domain
A 7.5.2.2	Belanger, A., Levesque, M.P., Mathur, S.P.	1987	The influence of variation in soil copper on the yield and nutrition of radishes grown in microplots on two peat soils. International Peat Journal, 2, 65-73; not GLP; Published	No	Public domain
A 7.5.2.2	Brun LA, Le Corff J, Maillet J.	2003	Effects of elevated soil copper on phenology, growth and reproduction of five ruderal plant species. Environ Pollut. 2003;122(3):361-8; not GLP; Published	No	Public domain
A 7.5.2.2	Chhibba, I. M. Nayyar, V.K. & Takkar, P.N.*	1994	Upper Critical Level of Copper in Wheat (Triticum aestivum) Raised on Typic Ustipsamment Soil. Indian Journal of Agricultural Sciences. 64 (5); 285-289 Not GLP, Published.	No	Public domain

A 7.5.2.2	de Haan, S., Rethfeld, H. & van Driel, W.	1985	Acceptable Levels of Heavy Metals (Cd, Cr, Cu, Ni, Pb, Zn) in Soils, Depending on their Clay and Human Content and Cation-Exchange Capacity. Instituut Voor Bodemvruchtbaarheid Haren-Gr. Report No. 0434-6793 (published).	No	Public domain
A 7.5.2.2	de Haan, S., Rethfeld, H. & van Driel, W.*	1985	Acceptable Levels of Heavy Metals (Cd, Cr, Cu, Ni, Pb, Zn) in Soils, Depending on their Clay and Human Content and Cation-Exchange Capacity. Instituut Voor Bodemvruchtbaarheid Haren-Gr. Report No. 0434-6793. Not GLP, Published	No	Public domain
A 7.5.2.2	Jarvis, S.C.	1978	Copper Uptake and Accumulation by Perennial Ryegrass Grown in Soil and Solution Culture. J. Sci. Fd. Agric. 29:12-18 (published).	No	Public domain
A 7.5.2.2	Jarvis, S.C.*	1978	Copper Uptake and Accumulation by Perennial Ryegrass Growth in Soil and Solution Culture. J. Sci. Food. Agric. 29: 12-18. Not GLP, Published.	No	Public domain
A 7.5.2.2	Kalyanaraman, S.B. & Sivagurunathan, P.*	1993	Effect of Cadmium, Copper and Zinc on the Growth of Blackgram. Journal of Plant Nutrition. 16 (10), 2029-2042. Not GLP, Published.	No	Public domain
A 7.5.2.2	Kjær, C. & Elmegaard. N.	1996	Effects of Copper Sulphate on Black Bindweed (Polygonum convolvulus L.) Ectoxicology and Environmental Safety. 33; 110-117 (published).	No	Public domain
A 7.5.2.2	Kjær, C. & Elmegaard. N.*	1996	Effects of Copper Sulphate on Black Bindweed (Polygonum convolvulus L.) Ectoxicology and Environmental Safety. 33; 110-117. Not GLP, Published	No	Public domain

A 7.5.2.2	Korthals, G.W., Alexiev, A.D., Lexmond, T.M., Kammenga, J.E. & Bongers, T.*	1996 a	Long Term Effects of Copper and pH on the Nematode Community in an Agrosystem. Environ. Toxicol. Chem. 15 (6): 979-985. Not GLP, Published.	No	Public domain
A 7.5.2.2	Lexmond, T. M.*	1980	The Effect of Soil pH on Copper Toxicity to Forage Maize Grown Under Field Conditions. Neth. J. Agric. Sci. 28: 164-183. Not GLP, Published.	No	Public domain
A 7.5.2.2	Lexmond, T.M.	1980	The effect of soil pH on copper toxicity to forage maize grown under field conditions. Neth. J. Agric. Science 28, 164-183; not GLP; Published	No	Public domain
A 7.5.2.2	McBride, M.B.*	2001	Cupric Ion Activity in Peat Soil as a Toxicity Indicator for Maize. Journal of Environmental Quality. 30; 78-84. Not GLP, Published	No	Public domain
A 7.5.2.2	Pedersen, M. B., Kjær, C. Elmegaard, N.	2000	Toxicity and Bioaccumulation of Copper to Black Bindweed (Fallopia convolvulus) in Relation to Bioavailability and the Age of Soil Contamination. Archives of Environmental Contamination and Toxicology. 39; 431-439 (published).	No	Public domain
A 7.5.2.2	Pedersen, M. B., Kjær, C. Elmegaard, N.*	2000	Toxicity and Bioaccumulation of Copper to Black Bindweed (Fallopia convolvulus) in Relation to Bioavailability and the Age of Soil Contamination. Archives of Environmental Contamination and Toxicology. 39; 431-439. Not GLP, Published.	No	Public domain
A 7.5.2.2	Rhoads, F.M., Barnett, R.D. & Olson, S.M.*	1992	Copper Toxicity and Phosphorus Concentration in 'Florida 502' Oats. Soil Crop Science Society Florida Proceedings. 51; 18-20. Not GLP, Published.	No	Public domain

A 7.5.2.2	Rhoads, F.M., Barnett, R.D., Olson, S.M	1992	Copper toxicity and phosphorous concentration in "Florida 502" oats. Soil and Crop Science of Florida, 51:18-20; not GLP; Published	No	Public domain
A 7.5.2.2	Roth, J.A., Wallihan, E.F. & Sharpless, R.G*	1971	Uptake by Oats and Soybeans of Copper and Nickel Added to a Peat Soil. Soil Science. 112; 5; 338-342. Not GLP, Published	No	Public domain
A 7.5.2/ 7.5.2.1	Sandifer, R.D. & Hopkin, S. P.*	1996	Effects of pH on the Toxicity of Cadmium, Copper, Lead and Zinc to Folsomia candida Willem, 1902 (Collembola) in a Standard Laboratory Test System. Chemosphere. 33: 12; 2475-2486. Not GLP, Published.	No	Public domain
A 7.5.2/ 7.5.2.1	Sandifer, R.D. & Hopkin, S. P.*	1996	Effects of pH on the Toxicity of Cadmium, Copper, Lead and Zinc to Folsomia candida Willem, 1902 (Collembola) in a Standard Laboratory Test System. Chemosphere. 33: 12; 2475-2486. Not GLP, Published.	No	Public domain
A 7.5.6	Augustsson, A. K., & Rundgren, S*	1998	The Enchytraeid Cognettia sphagnetorum in Risk Assessment: Advantages and Disadvantages. Ambio. 27; 62-69. Not GLP, Published.	No	Public domain
A 7.5.6	Bogomolov, D.M., Chen, S.K., Parmalee, R.W, Subler, S. & Edwards, C.A.*	1996	An Ecosystem Approach to Soil Toxicity Testing: A Study of Copper Contamination in Laboratory Soil Microcosms. Applied Soil Ecology. 4; 95-105. Not GLP, Published.	No	Public domain
A 7.5.6	Jaggy, A. & Streit, B.*	1982	Toxic Effects of Soluble Copper on Octolasium cyaneum sav. (lumbricidae). Rev. Suisse De Zoologie. 89; 4: 881-889. Not GLP, Published.	No	Public domain

A 7.5.6	Kahil, M.A., Abdel-Lateif, H.M., Bayoumi, B.M, van Straalen, N.M. & van Gestel, C.A.M.*	1996 b	Effects of Metals and Metal Mixtures on Survival and Cocoon Production of the Earthworm Aporrectodea caliginosa. Pedobiology. 40; 548-556 .Not GLP, Published.	No	Public domain
A 7.5.6	Khalil, M.A., Abdel-Lateif, H.M., Bayoumi, B. M. & van Straalen, N.M.*	1996 a	Analysis of Separate and Combined Effects of Heavy Metals on the Growth of Aporrectodea caliginosa (Oligochaeta; Annelida), Using the Toxic Unit Approach. Applied Soil Ecology. 4; 213-219.Not GLP, Published.	No	Public domain
A 7.5.6	Korthals, G.W, Van de Ende, A., Van Megen, H., Lexmond, T.M., Kammenga, J.E. & Bongers, T.	1996 b	Short-Term Effects of Cadmium, Copper, Nickel and Zinc on Soil Nematodes from Different Feeding and Life-History Strategy Groups. App. Soil. Ecology. 4, 107-117. GLP, published	No	Public domain
A 7.5.6	Korthals, G.W., Alexiev, A.D., Lexmond, T.M., Kammenga, J.E. & Bongers, T.*	1996 a	Long Term Effects of Copper and pH on the Nematode Community in an Agrosystem. Environ. Toxicol. Chem. 15 (6): 979-985. Not GLP, Published.	No	Public domain
A 7.5.6	Korthals, G.W., van de Ende, A., van Megen, H., Lexmond, T.M., Kammenga, J. & Bongers, T. *	1996	Short-Term Effects of Cadmium, Copper, Nickel and Zinc on Soil Nematodes from Different Feeding and Life History Strategy Groups. Applied Soil. Ecology. 4; 107-117. Not GLP, Published.	No	Public domain
A 7.5.6	Ma, W.C. *	1982	The Influence of Soil Properties and Worm Related Factors on the Concentration of Heavy Metals in Earthworms. Pedobiologica. 24; 109-119. Not GLP, Published.	No	Public domain

A 7.5.6	Parmalee, R. W., Wentsel, R.S., Phillips, C.T., Simini, M. & Checkai, R.T.*	1993	Soil Microcosm for Testing the Effects of Chemical Pollutants on Soil Fauna Communities and Trophic Structure. Environ. Toxicol. Chem. 12; 1477-1486. Not GLP, Published.	No	Public domain
A 7.5.6	Scott-Fordsmand, J.J., Krogh P.H. & Weeks, J.M.*	1997	Sublethal Toxicity of Copper to a Soil-Dwelling Springtail (Folsomia fimetaria) (Collembola: Isotomidae). Environmental Toxicology and Chemistry, 16: 12; 2538-2542.Not GLP, Published.	No	Public domain
A 7.5.6	Svendsen, C. & Weeks, J. M.*	1997 b	Relevance and Applicability of a Simple Earthworm Biomarker of Copper Exposure. II Validation and Applicability Under Field Conditions in a Mesocosm Experiment with Lumbricus rubellus. Ecotoxicol. Environ. Saf. 36, 80-88. Not GLP, Published.	No	Public domain
A 7.5.6/ 7.5.2.1	Kula, H. & Larink, O.*	1997	Development and Standardisation of Test Methods for the Prediction of Sublethal Effects of Chemicals on Earthworms. Soil Biology and Biochemistry. 29: 3/4; 635-639. Not GLP, Published.	No	Public domain
A 7.5.6/ 7.5.2.1	Spurgeon, D.J., Hopkin, S.P. & Jones, D.T.*	1994	Effects of Cadmium, Copper, Lead and Zinc on Growth, Reproduction and Survival of the Earthworm Eisenia fetida (Savigny): Assessing the Environmental Impact of Point-Source Metal Contamination in Terrestrial Ecosystems. Environmental Pollution. 84; 123-130. Not GLP, Published.	No	Public domain
A 7.5.6/ 7.5.2.1	Bengtsson G., Gunnarsson, T. & Rundgren, S.*	1986	Effects of Metal Pollution on the Earthworm Dendrobaena rubida (Sav) in Acified Soils. Water, Air and Soil Pollution. 28; 361-383	No	Public domain

A 7.5.6/ 7.5.2.1	Krogh, P.H. & Axelsen, J.A.*	1998	Test on the Predatory Mite Hypoaspis aculeifer Preying on the Collembolan Folsomia fimetaria. In: Handbook of Soil Invertebrate Toxicity Tests. pp 239-251. Ed. H. Lokke and C.A.M. Van Gestel. J. Wiley and Sons Ltd, Chichester, UK. Not GLP, Published.	No	Public domain
A 7.5.6/ 7.5.2.1	Rundgren S. & Van Gestel, C.A.M	1998	Comparison of Species Sensitivity. In: Handbook of Soil Invertebrate Toxicity Tests. pp 95-112 Ed. H. Lokke and C.A.M. Van Gestel. J. Wiley and Sons Ltd, Chichester, UK. Not GLP. (published).	No	Public domain
A 7.5.6/ 7.5.2.1	Rundgren S. & Van Gestel, C.A.M.*	1998	Comparison of Species Sensitivity. In: Handbook of Soil Invertebrate Toxicity Tests. pp 41-55. Ed. H. Lokke and C.A.M. Van Gestel. J. Wiley and Sons Ltd, Chichester, UK. Not GLP, Published.	No	Public domain
A 7.5.6/ 7.5.2.1	Kula, H. & Larink, O.*	1998	Tests of the Earthworms Eisenia fetida and Aporrectodea caliginosa. In: Handbook of Soil Invertebrate Toxicity Tests. pp 95-112 Ed. H. Lokke and C.A.M. Van Gestel. J. Wiley and Sons Ltd, Chichester, UK. Not GLP, Published.	No	Public domain
A 7.5.6/ 7.5.2.1	Sandifer, R.D & Hopkin, S.P.*	1997	Effects of Temperature on the Relative Toxicities of Cd, Cu, Pb and Zn to Folsomia candida (Collembola). Ecotoxicology and Environmental Safety. 37; 125-130. Not GLP, Published.	No	Public domain

A 7.5.6/ 7.5.2.1	Ma, W-C.*	1984	Sublethal Toxic Effects of Copper on Growth, Reproduction and Litter Breakdown Activity in the Earthworm Lumbricus rubellus, with Observations on the Influence of Temperature and Soil pH. Environmental Pollution (Series A). 33; 207-219. Not GLP, Published.	No	Public domain
A 7.5.6/ 7.5.2.1	Scott-Fordsmand, J.J., Krogh, P.H & Weeks, J.M.*	2000 a	Responses of Folsomia fimetaria (Collembola: Isotomidae) to Copper Under Different Soil Copper Contamination Histories in Relation to Risk Assessment. Environmental Toxicology and Chemistry. 19: 5; 1297-1303 Not GLP, Published	No	Public domain
A 7.5.6/ 7.5.2.1	Scott-Fordsmand, J.J., Weeks, J.M & Hopkins, S.P.*	2000 b	Importance of Contamination History for Understanding Toxicity of Copper to Earthworm Eisenia fetica (Oligochaeta: Annelida), Using Neutral Red Retention Assay. Environmental Toxicology and Chemistry. 19: 7; 1774-1780. Not GLP, Published.	No	Public domain
	Ralph A. & McArdle H.	2001	Copper metabolism and copper requirements in the pregnant mother, her fetus and children.	No	Public domain
B3.1.1 - 3.3	Willis, C.V.	1994	Physical and Chemical Characteristics of ACQ-C2D: Color, Physical State, Odor, Specific Gravity, pH, Oxidising or Reducing, Explodability and Viscosity. Case Consulting Laboratories, Inc. Study Number 900-02	Yes	Wood Preservative Copper Taskforce

B3.5 - 3.7	Willis, C.V.	1995	Physical and Chemical Characteristics of ACQ-C2D: Storage Stability and Corrosion Characteristics – 1 Year at Room Temperature. Case Consulting Laboratories, Inc. Study Number 900-03. GLP, Unpublished	Yes	Wood Preservative Copper Taskforce
B3.6	Anonymous	2000	ASTM Method D891-95 (Reapproved 2000). Standard Test Methods for Specific Gravity, Apparent, of Liquid Industrial Chemicals	No	N/A
B3.10	Willis, C.V.	1995	Physical and Chemical Characteristics of ACQ-C2D: Storage Stability and Corrosion Characteristics – 1 Year at Room Temperature. Case Consulting Laboratories, Inc. Study Number 900-03. GLP, Unpublished	Yes	Wood Preservative Copper Taskforce
B3.10	Anonymous	2004	ASTM Method D446-04. Standard Specifications and Operating Instructions for Glass Capillary Kinematic Viscometers	No	N/A
B4.1/01	Willis, C.V.	1994	Preliminary Analysis and Precision and Accuracy of Analytical Method Used to Validate Certified Limits. Case Consulting Laboratories. Study Number 900-01. Not GLP, Unpublished	Yes	Wood Preservative Copper Taskforce
B5.10	Connell M, Cornfield J A and Williams G R	1993	A New Timber Preservative. Rec of the Annual Convention of the British Wood Preserving and Damp-proofing Association pp 28-36	No	N/A
B5.10	Preston A, Walcheski P, Archer K, Zahora A and Jin L	2000	The Ground Proximity Decay Test Method, International Research Group on Wood Preservation Doc No. 00-20205	No	N/A

B5.11	Pohleven, F., Miha, H., Sam, A & Jaka, B.	2002	Tolerance of wood decay fungi to commercial copper based wood preservatives. IRG Document No. 02-30291.	No	N/A
B6.1.1	[redacted]	1994	Acute Oral Toxicity Test in the Rat. [redacted] Project Number 577/17. GLP, Unpublished	Yes	Wood Preservative Copper Taskforce
B6.1.2	[redacted]	1994	Acute Dermal Toxicity (Limit Test) in the Rat. [redacted] Project Number 577/18. GLP, Unpublished	Yes	Wood Preservative Copper Taskforce
B6.1.3	[redacted]	1994	Acute Inhalation Toxicity Study Four-Hour Exposure (Nose Only) in the Rat. [redacted] Project Number 577/19. GLP, Unpublished	Yes	Wood Preservative Copper Taskforce
B6.2	[redacted]	1994	Acute Dermal Irritation Test in the Rabbit. [redacted] Project Number 577/20. GLP, Unpublished	Yes	Wood Preservative Copper Taskforce
B6.3	[redacted]	1994	Buehler Delayed Contact Hypersensitivity Study in the Guinea Pig. [redacted] Project Number 577/22. GLP, Unpublished	Yes	Wood Preservative Copper Taskforce
B6.5	Gangolli S	1999	The Dictionary of Substances and their Effects (DOSES). 2nd Edition, vol. 4, The Royal Society of Chemistry, p95-96 (published)	No	N/A
B7.1/01	van der Zee, M.E.	2001	Submersion tests (NEN 7345) of Tanalith 3494 treated timber. Foundation for Timber Research SHR. Report number 98.214; not GLP; Not published.	Yes	Arch Timber Protection

B7.1/02	Caswell S	2000	Determination of the Emission Profile from Tanalith E Treated Timber. Laboratory Metho to Simulate Exposure from Tanalith E (3491) Treated Timber in an Above Ground (Hazard Class 3) Environment. Hickson Timber Products Limited, Technical Centre. Report No. W20/001a; not GLP; Not published.	Yes	Arch Timber Protection
B7.1/03	Hohman W.J.	1993	Assessing the losses of copper and boron from Tanalith 3485 treated timber with the shower test. Foundation for Timber Research SHR. Report number 92.040 ; not GLP; Not published.	Yes	Arch Timber Protection
B7.1/04	Lindegaard, B.	2003	Test Methods to Evaluate the leaching of Wood Preservatives from Preservative Treated Wood. Phase II Laboratory Tests. Status Report after 1st Test Round. Danish Technological Institute, Timber. Report No. 1175742-02 ; not GLP; not published.	Yes	Arch Timber Protection