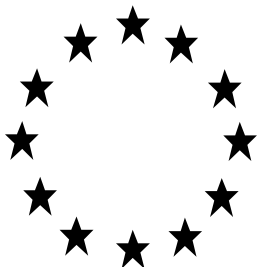
Regulation (EU) n°528/2012 concerning the making available on the market and use of biocidal products

Evaluation of active substances

Assessment Report



Copper sulfate pentahydrate
Product-type 2
(Disinfectants and algaecides not intended for direct application to humans or animals)

September 2013

RMS: France

Copper sulfate pentahydrate (PT2)

Assessment report

Finalised in the Standing Committee on Biocidal Products at its meeting on September 2013

Table of contents

1 STATEMENT OF SUBJECT MATTER AND PURPOSE

1.1 PRINCIPLE OF EVALUATION

This assessment report has been established as a result of the evaluation of copper sulfate pentahydrate for product-type 2 (private area and public health area disinfectants and other biocidal products), carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of biocidal products on the market[1], with the original view to the possible inclusion of this substance into Annex I or IA to that Directive.

The evaluation has therefore been conducted in the view to determine whether it may be expected, in light of the common principles laid down in Annex VI to Directive 98/8/EC, that there are products in product-type 2 containing of copper sulfate pentahydrate that will fulfil the requirements laid down in Article 5(1) b), c) and d) of that Directive. Those requirements and common principles are very similar to those laid down in Article 19(1), (2) and (5) and Annex VI of Regulation (EU) No 528/2012. At the time of finalisation of this assessment report, there was no indication that the conclusions regarding compliance with Directive 98/8/EC would not be valid for the purpose of establishing compliance with the requirements of Regulation (EU) No 528/2012.

1.2 PURPOSE OF THE ASSESSMENT

The aim of the assessment report is to support a decision on the approval of copper sulfate pentahydrate for product-type 2, and should it be approved, to facilitate the authorisation of individual biocidal products in product-type 2 that contain copper sulfate pentahydrate. 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.

The conclusions of this report were reached within the framework of the uses that were proposed and supported by the applicant (see Appendix II). Extension of the use pattern beyond those described will require an evaluation at product authorisation level in order to establish whether the proposed extensions of use will satisfy the requirements of Regulation (EU) No 528/2012.
For the implementation of the common principles of Annex VI, the content and conclusions of this assessment report shall be taken into account.

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 has been granted

1.3 PROCEDURE FOLLOWED

This assessment report has been established as a result of the evaluation of copper sulfate pentahydrate for product-type 2, carried out in the context of the work programme for the review of existing active substances provided for in Article 16(2) of Directive 98/8/EC concerning the placing of

[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

biocidal products on the market[2], with a view to the possible inclusion of this substance into Annex I to the Directive.

Copper sulfate pentahydrate (CAS No. 7758-99-8) was notified as an existing active substance, by Manica, hereafter referred to as the applicant, in product type 2.

Commission Regulation (EC) No 1451/2007 of the 4th of December 2007[3] lays down the detailed rules for the evaluation of dossiers and for the decision-making process in order to include or not an existing active substance into the Annex I or IA of the Directive.

In accordance with the provisions of Article 3 paragraph 2 of that Regulation, France was designated Rapporteur Member State to carry out the assessment of the active substance of copper sulfate pentahydrate on the basis of the dossier submitted by the applicant. The deadline for submission of a complete dossier for copper sulfate pentahydrate as an active substance in product type 2 was the 31th of July 2007, in accordance with Article 9 paragraph 2 of Regulation (EC) No 1451/2007.

On the 27th of July 2007, the French Competent Authority received a dossier from the applicant. The Rapporteur Member State accepted the dossier as complete for the purpose of the evaluation, taking into account the supported uses, and confirmed the acceptance of the dossier on the 31st of January, 2008.

On 31 January 2011, the Rapporteur Member State submitted, in accordance with the provisions of Article 14(4) and (6) of Regulation (EC) No 1451/2007, to the Commission and the applicant a copy of the evaluation report, hereafter referred to as the competent authority report. The Commission made the report available to all Member States by electronic means on 5 April 2011. The competent authority report included a recommendation for the inclusion of copper sulfate pentahydrate in Annex I to the Directive for PT 2.

In accordance with Article 16 of Regulation (EC) No 1451/2007, the Commission made the competent authority report publicly available by electronic means on the [date to be inserted]. This report did not include such information that was to be treated as confidential in accordance with Article 19 of Directive 98/8/EC.

In order to review the competent authority report and the comments received on it, consultations of technical experts from all Member States (peer review) were organized by the Commission. Revisions agreed upon were presented at technical and competent authority meetings and the competent authority report was amended accordingly.

In accordance with Article 15(4) of Regulation (EC) No 1451/2007, the present assessment report contains the conclusions of the Standing Committee on Biocidal Products, as finalized during its meeting held on 27 September 2013.

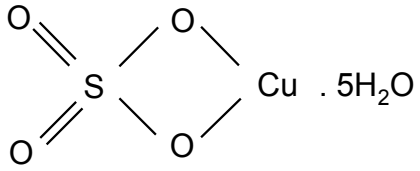
[2] Directive 98/8/EC of the European Parliament and of the Council of 16 February 1998 concerning the placing biocidal products on the market, OJ L 123, 24.4.98, p.1
[3] OJ L 325, 11.12.2007, p. 3

2 OVERALL SUMMARY AND CONCLUSIONS

2.1 GENERAL SUBSTANCE INFORMATION/GENERAL PRODUCT INFORMATION

2.1.1 Identity, Physico-chemical properties & Methods of analysis of the active substance

2.1.1.1 Identity

CAS-No.	7758-99-8
EINECS-No.	231-847-6
Other No. (CIPAC, ELINCS)	All copper compounds have the CIPAC code 44 The CIPAC code for Cu^{2+} ion is 029 The CIPAC code for SO_4^{2-} ion is 306
Chemical Name	Copper II sulfate pentahydrate Sulfuric acid copper (2+) salt (1:1), pentahydrate
Common name, synonyms	No common name (not required by ISO)
Molecular formula	$CuSO_4. 5H_2O$
Structural formula	
Molecular weight (g/mol)	249.68

When “copper sulfate pentahydrate” or “copper sulfate” is written in the dossier, it refers to “copper II sulfate pentahydrate”.

The active substance as manufactured is copper sulfate pentahydrate with a minimum purity of 99.9%. The calculation of the equivalent copper sulfate pentahydrate purity is based on the total copper content of the test material, as the copper represents the active ingredient of the test material. The active element is cupric ion Cu^{2+}, released from copper sulfate. A purity of 99.9% matches with a copper content of approximately 25.4%.
Regarding the setting of the specifications of the reference source of the active substance copper sulfate pentahydrate, the section of this report relating to this issue has been reviewed and amended to be in line with what was agreed for annex I inclusion of copper active substances used in product type 8 – wood preservatives: the agreed approach presented for PT 8 copper dossiers to check if the specifications of the reference sources are covered by the active substances that have been tested in the studies used to perform the risk assessment was followed for copper sulfate pentahydrate too.
In that context, a new 5-batch analysis for copper sulfate pentahydrate has been required by the RMS and provided by the applicant with analytical methods. Based on the submitted data, specifications have been set for the source of copper sulfate pentahydrate supported by the applicant, (see the document Confidential specification of PT2 Manica).

Copper sulfate pentahydrate contains five relevant impurities: lead, cadmium, arsenic, zinc and nickel.

2.1.1.2 Physico-chemical properties

Copper sulfate pentahydrate is a blue crystalline, odorless, solid inorganic salt, which begins to lose water of crystallization at 88°C. It has a bulk density of 2.286 g/cm^3. As an inorganic salt it has no measurable vapor pressure and no Henry's Law Constant.
It is very soluble in water (220 g/L) where it is completely dissociated in ionic species. Copper sulfate pentahydrate is also soluble in methanol (> 20 g/L) and sparingly soluble in organic solvents (< 1 g/L).
Because the mechanisms of absorption of Cu^{2+} into organic matter and living cells are understood to be different from those traditionally attributed to carbon-based pesticides, partition coefficient is not considered relevant to ionic copper. Modelled / measured partition coefficients Kp are used instead.
Copper sulfate pentahydrate is not highly flammable, not oxidizing and not explosive.

2.1.1.3 Methods of analysis

Adequate methodology exists for the determination of the active substance and the known impurities in the technical active substance.

The CIPAC method for the determination of copper in copper sulfate pentahydrate is validated. An analytical method based on ICP-MS is available and validated for the determination of sulfate in the active substance and water content is determined by gravimetric method. Impurities contents can be determined by ICP-MS. The methods are validated. For the determination of Zinc, further validation data are required for the annex I inclusion to fully validate the analytical method.
Adequate methodologies exist for the determination of the active substance in soil and body fluids and tissues. Validation data are missing for the analytical methods for the determination of the active substance in air. However due to the very low vapour pressure of the copper sulfate pentahydrate and the fact that the product is not sprayed, an analytical method for air is not required and no further data will be required.
Validation data for the analytical method for the determination of the active substance in water are required after annex 1 inclusion to show compliance with the requirement (LOQ limit in drinking water and method capable of analysing 1% of the typical applied concentration for PT 2, in surface water) as well as the suitability of the method for drinking and ground water and surface water.
No method is required for analysis of residues in food or feedstuffs.

2.1.2 Identity, Physico-chemical properties & Methods of analysis of the biocidal product

2.1.2.1 Identity

Trade name	Ionx Cu WB50 Laundry disinfectant	
Manufacturer's development code No(s)	Not applicable	
Ingredient of preparation	Function	Content
Copper sulfate pentahydrate	Active substance	15%
Details of the product composition and information on the co-formulants are confidential and are presented in the confidential part of the dossier.		
Physical state of preparation	Blue liquid	

2.1.2.2 Physico-chemical properties

Ionx Cu WB50 is a ready to use light blue liquid containing 15% copper sulfate pentahydrate.
Its pH is acid (pH=2.5). It has a density of 0.999.
It is not flammable or auto-flammable and has neither oxidizing nor explosive properties.
The product is stable during two years of storage.

2.1.2.3 Methods of analysis

Adequate methodology exists for the determination of the active substance in the biocidal product.

2.1.3 Intended Uses and Efficacy

2.1.3.1 Intended uses

MG01: Disinfectants and general biocidal products: Product Type 2.05

Copper sulfate pentahydrate is incorporated into products used with washing machines, where the presence of the Cu^{2+} ion can exert a biocidal effect. The product is dosed through automatic dosing system into the rinse water of industrial washing units. The product is added after the detergent wash and before the final rinse cycle, to reduce the bacterial contamination of clothing or overalls. It is used by professionals only.

The product Ionx Cu WB50 is used as a bactericide. The other activities (fungicide, virucide, sporicide) claimed have been cancelled by the applicant during the evaluation of the dossier and will have to be proved at the product authorization stage.

2.1.3.2 Efficacy and resistance

The product Ionx Cu WB50 has not showed a sufficient efficacy according to the CEN standards tests that have been performed, whatever the dose tested (100 to 5000 ppm). Moreover, it was very difficult to appreciate the efficacy of copper sulfate itself in a product with two other ingredients which have a potential microbiocide activity (hydrochloric acid is notified for PT2 too).
While no efficient dose has been highlighted for the product Ionx Cu WB50, an efficient dose of copper sulfate alone (14000 ppm or 14 g/l) has been proved according to the EN1040 standard. This bactericidal default dose (14000 ppm) has been proposed for the risk assessment.
Nevertheless, the environmental risk evaluation has highlighted a maximum acceptable dose not to exceed of 430 ppm of copper sulfate pentahydrate and the human risk evaluation has highlighted a maximum acceptable dose not to exceed of 6272 ppm of copper sulfate pentahydrate for healthy people and of 314 ppm for enfeebled people. Therefore, to prove a level of efficacy at the maximum acceptable doses set in accordance to the results of the risk evaluation for human health and environment, a laundry test using a Stomacher model has been carried out by the applicant with tested doses of 153 and 430 mg/L. Swatches of nurse's uniform contaminated with meticillin-resistant Staphylococcus aureus (MRSA) were washed in a Stomacher with a detergent or copper sulfate alone or combined in two separate experiments. This study demonstrates a bactericidal activity of copper sulfate pentahydrate at concentrations of 153 and 430 mg/L against MRSA, both alone and in combination with the detergent. It was also observed a synergistic biocidal effect between the detergent and CuSO4, used in combination.

The different efficacy tests with copper sulfate lead in the setting of effective doses significantly different: 14000 ppm with thestandard phase 1 test EN 1040 and 153 ppm with the non-standardised stomacher model test. These differences are probably originating from different susceptibilities of the employed bacterial strains towards the active substance. Whereas in the stomacher test an MRSA-strain of unknown sensitivity was used, obligatory strains used in EN standards are most likely more robust towards copper sulphate treatment.

Mechanisms for microbial inhibition by copper can be summarized as a complexing or an alteration of proteins which disrupts normal cell function resulting in either a reduction in viral activation or lethal (bactericidal) effect on the organism.

There are no known instances of the product failing to confer protection against bio-deterioration as a result of the development of true resistance among the target microorganisms.

2.1.4 Classification and Labelling

There is no harmonized classification for copper sulfate pentahydrate. On the basis of a review of submitted data for this substance, the following classification and labelling is proposed:

2.1.4.1 Active substance

Directive 67/548/EEC	
Class of danger	Xn – Harmful Xi – Irritant N - Dangerous to the environment
R phrases	R22: Harmful if swallowed R41: Risk of serious damage to eyes. R50-R53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
S phrases	S26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice S39: Wear eye/face protection S60: This material and its container must be disposed of as hazardous waste S61: Avoid release to the environment. Refer to special instructions/safety data sheet
Regulation 1272/2008	
Classification and Hazard statements	Acute Tox. 4/H302: Harmful if swallowed Eye dam 1/ H318 : Causes serious eye damage Aquatic. Acute 1: H400 : Very toxic to aquatic life Aquatic. Chronic 1: H410 : Very toxic to aquatic life with lasting effects

2.1.4.2 Biocidal product (Ionx Cu WB50)

Directive 67/548/EEC	
Class of danger	Xi – Irritant N - Dangerous to the environment
R phrases	R41: Risk of serious damage to eyes R50-R53: Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
S phrases	S25: Avoid contact with eyes S26: In case of contact with eyes, rinse immediately with plenty of water and seek medical advice S39: Wear eye/face protection S60: This material and its container must be disposed of as hazardous waste. S61: Avoid release to the environment. Refer to special instructions/safety data sheets.
Regulation 1272/2008	
Classification and Hazard statements	Eye Dam. 1 /H318 Aquatic. Acute 1: H400 : Very toxic to aquatic life Aquatic. Chronic 1: H410 : Very toxic to aquatic life with 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.

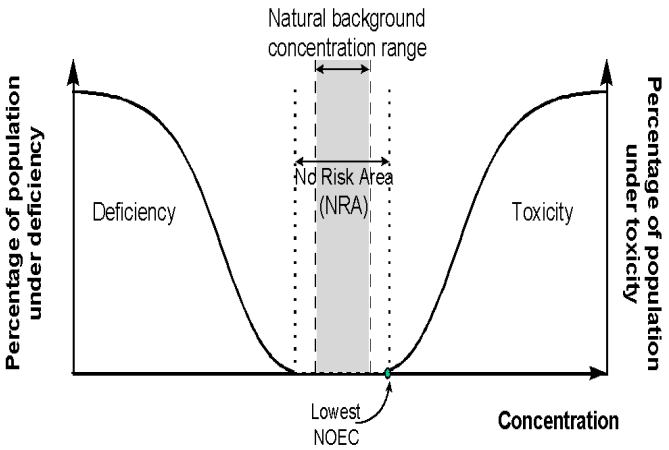


Figure 2.2.1-1: Dose-response curve for copper (adapted from Ralph and McArdle, 2001).

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 sulfate pentahydrate 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 Directive 98/8/EC. 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.

Copper sulfate pentahydrate is harmful if swallowed but does not require any classification by other routes of administration.
Copper sulfate pentahydrate is considered to be a weak skin irritant but does not require classification and it induces risk of serious damage to eyes. Moreover, it is not a skin sensitizer.

The health effects to consider in the risk characterization are effects on kidney (increase in cytoplasmic protein droplets), liver (inflammation) and forestomach, observed in the oral repeated toxicity studies.
The findings are similar to those seen in human intoxications' cases (effects on liver and kidney).

The absence of a genotoxicity/mutagenicity potential of copper sulfate was demonstrated in a battery of *in vitro* and *in vivo* tests. Copper sulfate should not be considered as genotoxic.

Human data on chronic genetic diseases, leading to an accumulation of copper, permit to conclude that copper is likely not carcinogenic. This is supported by the fact that copper is controlled by homeostatic mechanisms and thus, it will not accumulate in organs or tissues.
Finally, copper sulfate should not be classified as reprotoxic. The copper is absorbed across the placenta and is required for healthy growth and development, especially in blood maturation, bone development, heart development and function, brain development and function and the function of several key enzymes.

2.2.1.2 Effect assessment

Metabolism and toxicokinetics

- Absorption

Oral absorption:
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 (A6.2/01).
To determine the systemic NOAEL, as stated in TMIII08, in order to harmonize BPD dossier and 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 absorption:
Dermal absorption of diluted copper hydroxide (1.25 g/L and 20 g/L) to human skin in vitro was 4.06% and 0.52% respectively. It could be argued that soluble copper sulfate may be more readily absorbed than a spray dilution of a less readily soluble material such as copper hydroxide. However, contact with biocidal sprays containing copper sulfate can be anticipated to result in dermal contact with small quantities of the active substance. While some of the active copper may be dermally absorbed, it is likely that on contact with common salt (NaCl) present in sweat, the formation of small quantities of copper chloride will occur on the skin surface. Copper chloride solubility is more akin to copper hydroxide and justifies the use of the dermal delivery data selected for the risk assessment.

[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

A dermal delivery value of 4.06% has been selected by the applicant, but as stated in TMIII08, in order to harmonize BPD dossier and EU RAR, the dermal delivery of copper sulfate pentahydrate retained to be available for the purpose of risk assessment for dermal absorption is 5%.
As accepted at the TM IV 11, for the case of hospitalized enfeebled people, a dermal absorption of 100% was used as a worst case for the risk characterization, in order to take into account a possible higher skin permeability of hospitalized people (e.g. severely burnt people).

Respiratory absorption:
The absorption rate of copper via inhalation was not reported. The distribution of the mean particle diameter of copper sulfate pentahydrate was reported and shows that there are less than 0.01 % of the particles with a diameter < 100 µm.
For the purpose of risk assessment, and if exposure by inhalation is significant, an inhalation absorption level of copper of 100 % will be chosen as a worse case value of copper penetration.

- Distribution

Once absorbed, the body does not distinguish between copper naturally present in food and copper added as a dietary supplement. The hepatic portal system carries the newly-absorbed copper, bound to transcuprein and albumin, directly to the hepatocytes of the liver (IIIA.6.2/01). The liver is the main storage organ for copper, and the principal organ which regulates the secretion of ceruloplasmin into the blood as well as excess of copper in the bile.

- Metabolism

Metabolism does not occur: cupric ion is monatomic and cannot be metabolized. It is however used in every cell in the body, and every cell can regulate its copper content.

- Excretion

The copper is excreted in the bile. The copper surplus is then released in the faeces. Urinary excretion is small, as for skin, hair and sweat.

Acute toxicity

The median lethal dose (LD50 for male and female rats combined): 482 mg/kg (95% confidence limits of 403 to 575 mg/kg) (IIIA6.1.1-01). According to the effects observed in the oral acute study, copper sulfate meets the EU criteria for classification as 'Harmful if swallowed' and should be then classified **Xn/R22**.

The median lethal dermal dose to rats exceeded the limit dose level of 2000 mg/kg (A6.1.2-01).

Acute inhalation toxicity was not investigated. A substance is not considered to be a potential inhalation hazard if the particle size is greater than 100 µm. A particle size analysis for copper sulfate pentahydrate ("grain" grade) (IIIA6.1.3-01), indicated that less than 0.01% (w/w) of the test item was below 125 µm in diameter indicating copper sulfate pentahydrate does not have the potential to be an inhalation hazard and should not therefore be classified according to the directive 67/548/EEC.

Irritation and sensitization

Copper sulfate pentahydrate, was evaluated for its potential to produce primary dermal irritation after a single topical 4-hour application to the skin of rabbits at dose of 0.5 g. Mean values for cutaneous irritation were 0.22 for erythema and 0 for oedema. The lesions observed at 72 hours showed good reversibility at day 7. Copper II sulfate pentahydrate is considered to be a weak irritant and does not require classification (A6.1.4-01).

Copper sulfate pentahydrate is considered to be markedly irritating to the eyes of rabbits as the ocular lesions are still observed after 21 days, a classification as **Xi; R41** "Risk of severe damage to eyes" should be required (A6.1.4-02).
Copper sulfate pentahydrate did not produce a delayed contact sensitization response in the guinea pigs maximization test and is not considered as a dermal sensitizer under the study's conditions (A6.1.5-01).

Repeated administration toxicity

- Oral route

With regard to oral repeated dose toxicity, the 92-day dietary study (A6.4.1-01) was considered to be the pivotal study for Cu^{2+} released from copper sulfate pentahydrate.
Copper sulfate was administered daily in diet at 0, 500, 1000, 2000, 4000 and 8000 ppm to rats (Fisher 344N) and at 0, 1000, 2000, 4000, 8000 and 16 000 ppm to mice (B6C3F1).
Hyperplasia and hyperkeratosis in the forestomach mucosa were observed, although this may be associated with the sulfate ion, rather than the cupric ion. The NOAEL for this lesion was 1,000 ppm for rats and 2,000 ppm for mice.
In rats:

- damage to the liver (inflammation) was produced with a NOAEL of:
  - 1,000 ppm for males and
  - 2000 ppm for females,
- and damage to the kidney (increase in cytoplasmic protein droplets) was produced with a NOAEL of:
  - 1,000 ppm for males and females.

A NOAEL for mice could not be derived for liver and kidney toxicity as lesions were not seen in these organs even at the highest concentration.

The overall NOAEL was:

- 1000 ppm for rats (equivalent to 64 mg/kg bw/day for copper sulfate pentahydrate males and 68 mg/kg bw/day for females) and
- 2,000 ppm (equivalent to 382 mg/kg bw/day for males and 494 mg/kg bw/day for females) for mice.

Copper sulfate pentahydrate has a molecular mass of 249.68 g/mol, and copper 63.55 g/mol.

Therefore, the NOAEL in terms of copper:

- in male and female rats was 16.3 mg Cu/kg bw/day and 17.3 mg Cu/kg bw/day respectively and
- in male and female mice was 97.2 mg Cu/kg bw/day and 125.7 mg Cu/kg bw/day, respectively (IIIA6.4.1-01).

- Dermal route

No experimental assessment of short–term dermal toxicity was conducted. Actually, in vitro data using human skin show that copper is only minimally absorbed via the skin (maximum dermal delivery for tribasic copper sulfate is 4.06 %).

- Inhalation route

No repeated doses study by inhalation is available since the particle size data indicated that < 0.01 % (w/w) of the test item is less than 125 µm.
Subchronic and chronic studies in the dog have been waived, as the dog is an unsuitable animal model for studying copper toxicity to human. 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 (A6.2.01).

Genotoxicity

Copper sulfate has been extensively investigated in a series of mutagenicity studies in various salts. The results of the studies are summarized in the following table.

Summary of genotoxic studies with copper sulfate

Study type	Test material	Result		Reference
		presence of the metabolic activation	absence of the metabolic activation	
In vitro assays				
Ames	Copper sulfate	Negative	Negative	6.6.1-01
Ames	Copper sulfate	Negative	Negative	6.6.1-02
In vitro UDS	Copper sulfate	Positive	Positive	6.6.3-01
In vivo assays				
UDS	Copper sulfate	Negative		6.6.4/01
Mouse micronucleus (CD-1 mice)	Copper sulfate	Negative		6.6.4/02
Bone marrow chromosome aberration study (ip injections) (Swiss albino mice)	Copper sulfate	Positive (significant increase in aberrations)		6.6.4/03
Bone marrow chromosome aberration, mouse micronucleus and sperm abnormality assays (ip injection, oral)(Swiss albino mice)	Copper sulfate	Positive (dose, route and time inflenced significantly the frequency of chromosomal aberration)		6.6.5/01
Mouse micronucleus (ip injection) (CBA mice)	Copper sulfate	Negative		6.6.4/04

Since *in vivo* cytogenetic tests are available and that *in vitro* systems, particularly those involving isolated mammalian cells, may not be valid in the risk assessment of copper, no further *in vitro* tests were conducted. Indeed, copper absorbed by the body is always bound to either proteins such as albumin, transcuprein or ceruloplasmine, or amino acids such as histidine, and transfer from blood to cells is regulated such that copper transferred through the cell membrane is immediately bound to chaperines or metallothionein within the cell, before being incorporated in various enzymes. The in vitro tests bypass these strict control mechanisms and effectively present the isolated mammalian cell with a totally artificial situation of excess free copper ion. The free copper ion is highly reactive, and the presence of high quantities of free ion in cell cultures will cause disruption to the cellular processes. These effects may be manifest as gene mutations, but their occurrence is not an evidence for mutagenic activity of copper in real conditions.

In vivo, mouse micronucleus assays and UDS assay were negative but bone marrow chromosome aberration studies gave positive results. However, in these studies, copper sulfate was administered by intra-peritoneal injection.

Consideration of the provided *in vitro* and *in vivo* mutagenicity data for copper sulfate results in the conclusion that copper sulfate should not be considered as genotoxic.

Long term toxicity and carcinogenicity

It is instructive to consider the consequences and effects of genetic conditions that affect copper regulation, as these conditions lead to accumulation of copper in various tissues. There are two genetic conditions in the human (Wilson's disease and Menkes' disease) that result in major alterations in copper absorption, distribution and excretion. Wilson's disease (where copper is absorbed in the intestine but cannot be pumped out of the liver to bile) leads to accumulation of copper in the principal target organ, the liver, and also in the kidney, brain and the cornea. People with Menkes' disease (where copper is absorbed by intestinal cells but cannot be pumped out of these cells to the hepatic

portal system) can only absorb minimal amounts of copper, and show chronic accumulation of copper in the intestinal epithelium and high levels in kidney and in fibroblasts. Human subjects with these conditions may die of the condition itself (if untreated), but they do not show any increased incidence of cancer. This is significant for the risk assessment of copper. If abnormally high levels of copper are present over long periods in an organ or tissue, yet there is no association between the high copper levels and cancer in these organs or tissues, in chronic disease, then it is reasonable to conclude that copper is not carcinogenic in these tissues. It is also reasonable to conclude that as copper levels in normal humans are actively controlled by homeostatic mechanisms, copper will not accumulate in other organs or tissues. If it does not accumulate, it cannot cause any illness, including increased risk of cancer.

There are in literature, studies in rats that describe the effects of long term administration of copper in various forms. Because of their duration (less than one year) or focus observations, none of them can be considered as a key study. Nevertheless, because of the above arguments, further carcinogenicity studies on animals are considered unnecessary.

Reproductive toxicity and developmental toxicity

There are several studies in the public domain that investigate the reproductive toxicity potential of copper and copper compounds. In many of these studies, positive or equivocal findings have been reported. However, on investigation, it has been shown that these positive findings are the result of inappropriate routes of administration. These are namely intra peritoneal (i.p.) and intravenous (i.v.) routes.
When toxicity studies are conducted with either i.p. and i.v. routes of administration, they bypass the normal uptake and distribution mechanism that is specifically designed to protect the animal from the toxic/reactive Cu^{2+} ion.
Copper sulfate and copper hydroxide are precursor to the actual active substance, Cu^{2+}. In mammalian toxicity, it is also considered that the most toxic form of any copper salt is the Cu^{2+} ion. A metabolism study (A6.2-02) showed that copper hydroxide and copper sulfate pentahydrate were equivalent in terms of absorption, distribution and excretion. It is therefore appropriate to use study on copper hydroxide in support of evaluation of copper sulfate pentahydrate.

Teratogenicity

Copper hydroxide was given by gavage to groups of mated female rabbit during days 7 to 28 of pregnancy at three different doses (6, 9 and 18 mg Cu/kg bw/d) (A6.8.1-02).
Administration of copper to pregnant rabbits at 18 and 9 mg Cu /kg bw/d was associated with marked initial bodyweight loss, inappetance, abortion and death.
Pups in litters from surviving dams showed slightly lower mean foetal weight and slightly increased incidence of retarded ossification of skull and pelvic bones at 18 mg Cu/kg bw/d.
Therefore, the maternal no observed effect level was 6 mg Cu/kg bw/d and the foetal no observed effect level was 9 mg Cu/kg bw/d.

In another study, copper sulfate was administered to groups of male and female mice in the diet, equivalent to 0, 27, 53, 80, 106, 159, 213 mg Cu/kg bw/d. The males and females were paired after one month of treatment and the females were treated during gestation (A6.8.1-03).
A treatment-related effect was noted at higher levels (159, 213 mg Cu/kg bw/d), where decreased foetal weights and a higher mortality were recorded.
At 159 mg Cu/kg bw/d, malformations (last lumbar vertebra included in sacrum and unilateral fused ribs) were observed in 3 foetuses in total. At 213 mg Cu/kg bw/d, hernia of the thoracic wall, hydrocephalus and fusion of thoracic ribs and vertebrae, hemivertebra as part of sacrum were observed.
However, this study shows major methodological deficiencies including no information on maternal toxicity. In addition, the precise identity of the copper sulfate used in this study was not reported. Moreover, there was a lack of details concerning the food consumption and the bodyweight gain.

Although the malformations observed are uncommon, no data allows considering that they are not a secondary non-specific consequence of the maternal toxicity. This study is therefore not considered as reliable.

Fertility
A two-generation oral reproduction study in rats administered with copper sulfate pentahydrate at 0, 100, 500, 1000 and 1500 ppm (A6.8.2/01) has been submitted.
The NOAEL for the parental generation was 1500 ppm for reproductive toxicity (the highest concentration tested corresponding to 23.6 mg/kg bw/d (♂) or 55.7 mg/kg bw/d (♀)) but only 1000 ppm (35.2 mg/kg bw/d) for general toxicity, based on the reduced spleen weight at 1500 ppm in females. 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 sulfate should not be classified as reprotoxic.

It is also important to consider that copper is an essential element to fetal development in humans. At birth, the neonatal human contains about 15 mg of copper. All of this comes from the mother, who supplies it either by increasing absorption or by depleting maternal body stores. The copper is absorbed across the placenta and is required for healthy growth and development, especially in blood maturation, bone development, heart development and function, brain development and function and the function of 20 key enzymes (Ralph and McArdle, 2001).

Neurotoxicity

Acute, short term and long term studies (A6.9-01 and 02) where copper has been administered through diet to laboratory animals have not shown any neurotoxic signs, and histopathology of neural tissues have not shown any adverse effects associated with copper administration.

Human data

Copper has been used in suicide attempts. Most of these have involved copper sulfate. Acute intoxication is associated with emesis, superficial or deep ulcerations of the gastric and intestinal mucosa. Liver histopathology revealed dilatation of central veins, varying degrees of liver cell necrosis and bile thrombi. In kidneys there was congestion of glomeruli swelling or necrosis of tubular cells and haemoglobin casts. These findings are similar to those seen in animal studies.

Chronic symptoms, occurred in a case of self-administration, a 26-year-old Irishman took 30 mg Cu/day for two years (apparently without ill effect), then increased the dose to 60 mg Cu/day in the third year and suffered from liver failure.

2.2.1.3 Exposure assessment

Primary exposure

Ionx Cu WB50 is intended for use by professionals as a disinfectant added to the washing of contaminated clothing or overall. Washing is done by batch units or by a continuous washing process, which are automated. Therefore, exposure of user will be prevented but sometimes, the containers of Ionx Cu WB50 are handled manually and the product is poured into receptacles. During this stage, there is a potential for exposure of professional users by the product containing 15% copper sulfate pentahydrate (equivalent to 38.19 g copper /L). In Tier 1 no Personal Protective Equipment (PPE) is taken into account whereas in tier 2, it was considered that gloves were worn.

Primary exposure of non-professionals and the general public is not expected.

Table 2.2.1-1 : Summary of exposure estimates for pouring concentrate product Ionx Cu WB50 into receptacle
(mixing and loading model 7, modified by HEEG and agreed at TMI 08)

Tier	Time frame	Inhalation exposure		Dermal exposure		Total exposure
PPE	Frequency	External concentration	Systemic dose	Deposit on skin	Systemic dose	Systemic dose
		mg Cu/m^3 air	mg Cu/kg bw/day	mg Cu/day	mg Cu/kg bw/day	mg Cu/kg bw/day
Tier 1 : Without PPE	4 tasks of 10 minutes per day Daily Whole year	negligible	negligible	154.27	0.129	**1.29E-01**
Tier 2 : With gloves	4 tasks of 10 minutes per day Daily Whole year	negligible	negligible	1.54	0.00129	**1.29E-03**

Secondary exposure

The secondary human exposure estimated considers the potential for the exposure of adults, infants and children who wear fabric, disinfected with Ionx Cu WB50 (residues on clothing).
As no efficient dose has been highlighted for the product Ionx Cu WB50, an efficient dose of copper sulfate pentahydrate alone (14000 ppm) will be used for the risk assessment in a first approach.

Two types of population could be exposed to fabrics disinfected with Ionx Cu WB50:
- Healthy person, when fabrics are disinfected in private area, for example in a hotel,
- Enfeebled person in hospital with specific pathology or for example severely burnt person.

For each type of person, different scenarios of exposure could be considered:
- Exposure of adults, children and infants who wear clothing disinfected with Ionx Cu WB50,
- Exposure of adults, children and infants in contact with bedding disinfected with Ionx Cu WB50.

Considering that the body surface in contact with bedding is inferior to the body surface in contact with clothing, the risk assessment, for the case of exposure by contact with bedding, does not seem necessary (contact with clothing is more conservative).

Exposure of adults, children and infants who wear clothing disinfected with Ionx Cu WB50 could be considered as:
- **Chronic exposure** for healthy person (for example for professionals (doctor, nurse, operators) who wear clothing or coat disinfected with Ionx Cu WB50) or for enfeebled person when they are hospitalized during a long term period.
- **Subchronic exposure** for healthy person during for example a medium term stays in a hotel or for enfeebled person when they are hospitalized during a medium term period.
- **Acute exposure** for healthy person during for example a short term stays in a hotel or for enfeebled person when they are hospitalized during a short term period.

Each scenario has to be considered for the washing by continuous washing process or by batch units.

Table 2.2.1-2 : Summary of estimates for indirect exposure scenarios (by residues on clothing) for adults, children and infants:

	Time frame	Inhalation exposure		Dermal exposure		Total exposure
	Frequency	External concentration	Systemic dose	Deposit on skin	Systemic dose	Systemic dose
		mg as /m^3 air	mg as / kg bw /day	mg copper /day	mg copper / kg bw /day	mg copper / kg bw /day
Exposure by residue on clothing, general public and hospitalized public (enfeebled person)						
Continuous washing process						
Adult (healthy)	Wear 1000 g of fabrics Daily, the whole year for professionals (chronic exposure) or during a stay in a hotel (acute or subchronic exposure)	negligible	negligible	14.3	1.19E-02	1.19E-02
Adult (enfeebled)	Wear 1000 g of fabrics Daily, during their hospitalization (acute, subchronic or chronic exposure)	negligible	negligible	14.3	**2.38E-01**	**2.38E-01**
Child (healthy)	Wear fabrics in proportion with their body surface during a stay in a hotel for example (acute, subchronic or chronic exposure)	negligible	negligible	7.89	1.14E-02	1.14E-02
Child (enfeebled)	Wear fabrics in proportion with their body surface Daily, during their hospitalization (acute, subchronic or chronic exposure)	negligible	negligible	7.89	**2.29E-01**	**2.29E-01**
Infant (healthy)	Wear fabrics in proportion with their body surface during a stay in a hotel for example (acute, subchronic or chronic exposure)	negligible	negligible	3.44	1.72E-02	1.72E-02
Infant (enfeebled)	Wear fabrics in proportion with their body surface Daily, during their hospitalization (acute, subchronic or chronic exposure)	negligible	negligible	3.44	**3.43E-01**	**3.43E-01**

	Time frame	Inhalation exposure		Dermal exposure		Total exposure
	Frequency	External concentration	Systemic dose	Deposit on skin	Systemic dose	Systemic dose
		mg as /m^3 air	mg as / kg bw /day	mg copper /day	mg copper / kg bw /day	mg copper / kg bw /day
Exposure by residue on clothing, general public and hospitalized public (enfeebled person)						
Batch units						
Adult (healthy)	Wear 1000 g of fabrics Daily, the whole year for professionals (chronic exposure) or during a stay in a hotel (acute or subchronic exposure)	negligible	negligible	76	6.34E-02	6.34E-02
Adult (enfeebled)	Wear 1000 g of fabrics Daily, during their hospitalization (acute, subchronic or chronic exposure)	negligible	negligible	76	**1.27E+00**	**1.27E+00**
Child (healthy)	Wear fabrics in proportion with their body surface during a stay in a hotel for example (acute, subchronic or chronic exposure)	negligible	negligible	41.92	6.10E-02	6.10E-02
Child (enfeebled)	Wear fabrics in proportion with their body surface Daily, during their hospitalization (acute, subchronic or chronic exposure)	negligible	negligible	41.92	**1.22E+00**	**1.22E+00**
Infant (healthy)	Wear fabrics in proportion with their body surface during a stay in a hotel for example (acute, subchronic or chronic exposure)	negligible	negligible	18.29	9.15E-02	9.15E-02
Infant (enfeebled)	Wear fabrics in proportion with their body surface Daily, during their hospitalization (acute, subchronic or chronic exposure)	negligible	negligible	18.29	**1.83E+00**	**1.83E+00**

2.2.1.4 Risk characterization for the human health

The human health risk characterization is performed using both the AEL and the MOE approaches.
As exposure through food is negligible no food risk assessment was deemed necessary and no ADI was derived. An ADI value of 0.5 mg/kg/d is nevertheless available in the literature (WHO, IPCS).

AELs determination

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

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

In the case of copper sulfate, all AELs ($AEL_{acute\text{-}term}$, $AEL_{medium\text{-}term}$ and $AEL_{long\text{-}term}$) were derived on the basis of the NOAEL of 1000 ppm, corresponding to 16.3 mg Cu/kg bw/day obtained in the 90-day oral rat study with copper sulfate (A6.4.1/01). An oral absorption rate of 25% was taken into account for calculating the systemic NOAEL as follows:

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

The lowest available NOAEL is 6 mg Cu/kg bw/day based on the teratogenicity study (Doc IIIA6.8.1-02), but it cannot be taken into account for the risk assessment calculation because these effects are considered to be local effects on the stomach in rabbits which result from gavage administration of copper hydroxide. The NOAEL of the 2-generation study (15 mg/kg/d is very closed to the NOAEL of the repeated dose toxicity study (16.3 mg/kg/d) which is the most robust study.
Moreover, we selected the 92-day rat study to be in line with the VRA and the PT 8 copper compounds assessment.

Although copper sulfate was considered as a weak dermal irritant and a marked eye irritant, no local AEC was derived as far as no irritating effects were reported in repeated dose toxicity studies in the absence of systemic effects. Local effects are therefore covered by systemic AELs. Acute eye irritation is taken into account by the Xi; R41 classification.

As the indented uses are disinfectants in private area and **public health area**, enfeebled people could be also exposed to the active substance. Therefore, it is necessary to take them into consideration in the risk assessment.
Considering that the intraspecies factor of 10 covers already ill people, it seems not necessary to add a supplementary factor to cover the enfeebled people. (adoption of the SF of 10 at TMIV2011)
In this context, for healthy and enfeebled people, regarding the assessment factors, after refinement, a value of 50 (including an inter-species factor of 5 and an intra-species factor of 10)[5] was applied for deriving $AEL_{acute\text{-}term}$, $AEL_{medium\text{-}term}$. An additional factor of 2 was integrated for taking into account the duration extrapolation from subchronic to chronic exposures. An overall assessment factor of 100

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

was therefore adopted for deriving $AEL_{long\text{-}term}$. These refined assessment factors were agreed by the technical meeting.
These values are used as the reference margin of exposure (MOE_{ref}).

The following AELs were therefore derived:

- $AEL_{acute\text{-}term}$ = 4.1 / 50 = 0.082 mg Cu/kg bw/day
- $AEL_{medium\text{-}term}$ = 4.1 / 50 = 0.082 mg Cu/kg bw/day
- $AEL_{long\text{-}term}$ = 4.1 / 100 = 0.041 mg Cu/kg bw/day

In the AEL approach, a risk is considered as acceptable if AEL > exposure.
In practice, exposure is expressed as a percentage of the AEL (% AEL). The risk is therefore considered as acceptable if % AEL ≤ 100.

In the MOE approach, a risk is considered as acceptable if MOE > MOE_{ref} (where $MOE = \frac{NOAEL}{Exposure}$)

Risk characterization for primary exposure scenarios

- Professional users

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

Table 2.2.1-3 : Summary of Risk assessment for professional users during long-term exposure:

Exposure scenario	systemic total dose [mg/kg bw/day]	MOEref	NOAEL [mg/kg bw/day]	$AEL_{long\text{-}term}$ [mg/kg bw/day]	% AEL	MOE
Pouring product into receptacle Tier 1 (mixing and loading)	**1.29E-01**	100	4.1	0.041	315	32
Pouring product into receptacle Tier 2 (mixing and loading)	**1.29E-03**	100	4.1	0.041	3.15	3178

The % of AEL in the first Tier assessment is > 100 and the MOE is < 100. However, this Tier does not take into account the Personal Protective Equipment (PPE). When PPE (gloves) are worn, it can be seen that the % of AEL and MOE are acceptable.

Conclusion: A risk for professional user under the conditions specified above (without gloves) exists. However, when gloves are worn the risk is acceptable.

- Non-professional users

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

Risk characterization for secondary (indirect) exposure scenarios

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

Table 2.2.1-4 : Summary of risk assessment for indirect exposure by residues on clothing

Exposure scenario	systemic total dose [mg/kg bw/day]	MOEref	NOAEL [mg/kg bw/day]	AEL [mg/kg bw/day]	% AEL	MOE
Continuous washing process						
Acute and subchronic exposure						
Adult (healthy)	**1.19E-02**	50	4.1	0.082	15	345
Adult (enfeebled)	**2.38E-01**	50	4.1	0.082	290	17
Child (healthy)	**1.14E-02**	50	4.1	0.082	14	360
Child (enfeebled)	**2.29E-01**	50	4.1	0.082	279	18
Infant (healthy)	**1.72E-02**	50	4.1	0.082	21	238
Infant(enfeebled)	**3.43E-01**	50	4.1	0.082	418	12
Chronic exposure						
Adult (healthy)	**1.19E-02**	100	4.1	0.041	29	345
Adult (enfeebled)	**2.38E-01**	100	4.1	0.041	580	17
Child (healthy)	**1.14E-02**	100	4.1	0.041	28	360
Child (enfeebled)	**2.29E-01**	100	4.1	0.041	559	18
Infant (healthy)	**1.72E-02**	100	4.1	0.041	42	238
Infant(enfeebled)	**3.43E-01**	100	4.1	0.041	837	12
Batch units						
Acute and subchronic exposure						
Adult (healthy)	**6.34E-02**	50	4.1	0.082	77	65
Adult (enfeebled)	**1.27E+00**	50	4.1	0.082	1549	3
Child (healthy)	**6.10E-02**	50	4.1	0.082	74	67
Child (enfeebled)	**1.22E+00**	50	4.1	0.082	1488	3
Infant (healthy)	**9.15E-02**	50	4.1	0.082	112	45
Infant(enfeebled)	**1.83E+00**	50	4.1	0.082	2232	2
Chronic exposure						
Adult (healthy)	**6.34E-02**	100	4.1	0.041	155	65
Adult (enfeebled)	**1.27E+00**	100	4.1	0.041	3098	3
Child (healthy)	**6.10E-02**	100	4.1	0.041	149	67
Child (enfeebled)	**1.22E+00**	100	4.1	0.041	2976	3
Infant (healthy)	**9.15E-02**	100	4.1	0.041	223	45
Infant(enfeebled)	**1.83E+00**	100	4.1	0.041	4463	2

For healthy people:
For the continuous washing process, considering acute, subchronic and chronic exposure, % AEL are < 100 for adults, children and infants. The MOE are > 50 for acute and subchronic exposure and >100 for chronic exposure.

There is no unacceptable risk observed for these scenarios.

For the batch units washing process, % AEL is < 100 and MOE > 50 only for adults and children for an acute and subchronic exposure. % AEL are > 100 for infants for acute and subchronic exposure and for adults, children and infants for chronic exposure.

There are unacceptable risks observed for chronic exposure (adults, children and infants) and acute, subchronic exposure for infants.

Conclusion: A risk is expected for healthy adults, children and infants who are exposed during a long-term period, when clothing are disinfected with Ionx Cu WB50 at the dose of 14 000 ppm copper sulfate pentahydrate by a batch unit process. Moreover, a risk for infants is also observed when they are exposed during an acute or medium-term period.

For enfeebled person:
For the continuous washing process and for the batch units washing process, considering acute, subchronic and chronic exposure % AEL are > 100 for adult, child and infant.

There are unacceptable risks observed for all the scenarios.

Conclusion: An unacceptable risk exists for enfeebled adults, children and infants who are exposed during acute, medium or long-term period when clothing are disinfected with Ionx Cu WB50 at the dose of 14 000 ppm copper sulfate pentahydrate by a batch unit process or a continuous washing process.

As no efficacy has been highlighted for the product Ionx Cu WB50 at the claimed dose in the CEN standards tests submitted initially in the dossier, efficacy study has been performed with copper sulfate pentahydrate alone. In this study, an efficient dose of copper sulfate pentahydrate alone of 14000 ppm (which is equivalent to 14 g copper sulfate pentahydrate /L and to 3.56 copper g/L) has been set and, therefore used to conduct the risk assessment. This in-use concentration of 14000 ppm leads to unacceptable estimated risks for different categories of people. However, for the uses claimed in this dossier, the active substance presents an interest as it is a non-selective broad spectrum bactericide with efficacy against major germ types and should present a suitable efficacy when used in practical real conditions, and even a synergistic effect in combination with other active substances. In this context, reverse reference scenarios were undertaken to identify the maximum in-use concentration of copper sulfate pentahydrate that would result in acceptable risks for human health. From the acceptable exposure level of copper, a maximal concentration of copper in the rinse water was determined in order to have a secondary exposure by residues on clothing which will lead to an acceptable risk for adults, children and infants when fabrics are disinfected with Ionx Cu WB50.

As chronic exposure could be considered as a worst case for people who are exposed during an acute or a subchronic period, the assessments were performed only from the chronic acceptable exposure level of copper.

As acceptable risk was observed for healthy person when fabrics are disinfected with Ionx Cu WB50 by continuous process, the assessment by reverse scenario was performed only for batch unit process (AEL = 0.041 mg/kg/d).
For enfeebled person, the risk was unacceptable for all scenarios. In this context, the assessment by reverse scenario was performed for batch unit process and continuous process (AEL = 0.041 mg/kg/d).

The results are reported in the table below:

Table 2.2.1-5 : Summary of maximal concentration of copper in wash water of rinse consistent with an acceptable risk

	Maximal concentration of copper sulfate pentahydrate in wash water of rinse (ppm)		
	Batch units process		Continuous process
	Healthy person	Enfeebled person	Enfeebled person
Adult	9059	453	2416
Child	9417	471	2511
Infant	6272	314	1672

The exposure assessment is based on the model from Consexpo fact sheet[6]: cleaning product page 40. It has to be noted that the model is based on consumer washing machine and the possible difference between the number of rinse cycles with a professional washing machine has not been taken into account. This point could be considered for refinement of secondary exposure at the product authorization stage.

Risk characterization for combined exposure scenarios

Combined exposure can be considered for professionals who wear clothing disinfected by Ionx Cu WB50 and who handle the product during pouring into receptacle.
Only the scenarios which lead to an acceptable risk for primary and secondary exposure are considered for the assessment of combined exposure.
In this context, only the combined exposure when gloves are worn during pouring into receptacle for a professional who wear clothing disinfected by Ionx Cu WB50 by a continuous process is considered.

Results are reported in the tables below:

Table 2.2.1-6 : Summary of risk assessment for combined exposure

Exposure scenario	**systemic total dose [mg/kg bw/day]**	**MOEref**	**NOAEL [mg/kg bw/day]**	**AELlong-term [mg/kg bw/day]**	**% AEL**	**MOE**
Continuous washing process						
Combined exposure (Pouring product into receptacle Tier 2 + exposure of professional by residues on clothing)	**1.32E-02**	100	4.1	0.041	32	311

For the continuous washing process, % AEL is < 100 for adult and MOE is > 100. There is no unacceptable risk observed for these scenarios.

[6] RIVM report 320104003/2006 **Cleaning Products Fact Sheet** To assess the risks for the consumer L.C.H. Prud'homme de Lodder, H.J. Bremmer, J.G.M. van Engelen

An unacceptable risk for adults nevertheless exists when they handle product to pour it into a receptacle and they wear clothing disinfected with Ionx Cu WB50 by a batch unit process.

As no efficient dose has been highlighted for the product Ionx Cu WB50, an efficient dose of copper sulfate pentahydrate alone (14000 ppm which is equivalent to 14 g copper sulfate pentahydrate /L and to 3.56 copper g/L) has been used for the risk assessment, leading to unacceptable risks.

The same approach as the one described in paragraph 2.2.1.4 has been applied. Considering the potential interest of the active substance for the uses claimed in this dossier (non selective broad spectrum), it has been proposed to conduct an assessment by reverse scenario to estimate the application dose which could lead to acceptable calculated risks. At the product authorization stage, the applicant will have to demonstrate the efficacy of the product at this acceptable application dose.

For this purpose, an assessment by reverse scenario was realised. From the acceptable exposure level of copper minus the exposure of professionals who wear gloves during pouring product into receptacle, a maximal concentration of copper in the rinse water of a batch unit process was determined in order to have a combined exposure (primary and secondary) which will lead to an acceptable risk.

The results are reported in the table below:

Table 2.2.1-7 : Summary of maximal concentration of copper in wash water of rinse to have an acceptable risk

	Maximal concentration of copper in wash water of rinse (ppm)
	Batch units
Adult	8774

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

Risk assessment has been conducted with the only efficient dose available for copper sulfate pentahydrate alone which is 14000 ppm (equivalent to 14 g copper sulfate pentahydrate /L and to 3.56 copper g/L).
With this high in-use dose, primary exposure leads to an unacceptable risk for professionals if gloves are not worn for pouring product into receptacle. However, if gloves are worn the risk became acceptable.

For secondary exposure, there are no unacceptable risks for healthy adults, infants and children when exposed to residues on clothing for healthy person if fabrics are washed by a continuous process. However, there are unacceptable risks for infants if they are exposed during an acute or medium period and for adults, infants and children if they are exposed during a long period when fabrics are washed by a batch units process.

For enfeebled person, the risks are unacceptable for adults, children and infants who wear clothing washed by a batch units process or by continuous process.
As the in-use dose of 14000 ppm considered to conduct the risk assessment is much higher that the practical real in-use dose, the Rapporteur has determined the maximal concentration of copper that could be considered **acceptable** in wash rinse water, considering each process of washing, for healthy and enfeebled adults, children and infants..

For healthy person:
The maximal dose of copper sulfate pentahydrate in **batch unit** process will have to be lower than:

- 9059 ppm for adults and 8774 ppm (combined exposure) for professionals who pour product into receptacle and who wears fabrics disinfected by Ionx Cu WB50.
- 9417 ppm for children
- 6272 ppm for infants.

For enfeebled person:
The maximal dose of copper sulfate pentahydrate in **continuous process** will have to be lower than:

- 2416 ppm for adults
- 2511 ppm for children
- **1672** ppm for infants

And the maximal dose of copper sulfate pentahydrate in **batch unit** process will have to be lower than:

- 453 ppm for adults
- 471 ppm for children
- **314** ppm for infants

It is worth noting that all the doses which lead to an acceptable risk for human health are markedly higher than the intended dose proposed by the applicant in the original dossier, ie 2 ppm of copper sulfate pentahydrate.

2.2.2 Environmental Risk Assessment

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, biodegradation. It is not applicable to discuss copper in terms of degradation half-lives or possible routes of degradation.

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

Partition coefficient in suspended matter
Kpsusp = 30 246 L/kg (log Kp (pm/w) = 4.48) (50th percentile)
Partition coefficient in sediment
Kpsed = 24 409 L/kg (log Kp(sed/w) = 4.39) (50th percentile)
Partition coefficient in soil
Kpsoil = 2 120 L/kg (log Kp (soil/w) = 3.33) (50th percentile)

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

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

2.2.2.2 Effects assessment

2.2.2.2.1 Freshwater compartment (including sediment and STP)

2.2.2.2.1.1 Freshwater compartment

For the freshwater pelagic compartment, 139 individual NOEC/EC10 values resulting in 27 different species-specific NOEC values, covering different trophic levels (fish, invertebrates and algae) were used for the PNEC derivation. The large intra-species variabilities in the reported single species NOECs were related to the influence of test media characteristics (e.g., pH, dissolved organic carbon, hardness) on the bioavailability and thus toxicity of copper. Species-specific NOECs were therefore calculated after normalizing the NOECs towards a series of realistic environmental conditions in Europe (typical EU scenario's, with well defined pH, hardness and DOC). Such normalization was done by using chronic copper bioavailability models (Biotic Ligand Models), developed and validated for three taxonomic groups (fish, invertebrates and algae) and additional demonstration of the applicability of the models to a range of other species. The species-specific BLM-normalized NOECs were used for the derivation of log-normal Species Sensitivity Distributions (SSD) and HC5-50 values (the median fifth percentile of the SSD), using statistical extrapolation methods.

The HC5-50 values of the typical EU scenarios ranged between 7.8 to 22.1 µg Cu/L. Additional BLM scenario calculations for a wide range of surface waters across Europe further demonstrated that the HC5-50 of 7.8 µg Cu/L, is protective for 90% of the EU surface waters and can thus be considered as a reasonable worst case for Europe in a generic context.

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

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

2.2.2.2.1.2 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.

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 characterization. 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).

2.2.2.2.1.3 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 characterization.

2.2.2.2.2 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 normalized 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 normalized 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 PNECsoil for the risk characterization.

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 PT02 biocidal product dossier, 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).

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.

2.2.2.2.3 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 assessment

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

The application as a laundry disinfectant can be considered as such. It was shown above that for service-life the PEC/PNEC ratio is above 1. **Copper sulfate pentahydrate, as inorganic metal is excluded from the P assessment taking into account the Annex XIII of Reach regulation 1272/2008. Therefore the criterion for persistence in soil is not relevant.**

Due to the homeostatic regulation process of invertebrates and fish of copper, bioaccumulation and biomagnification of copper are considered as not applicable for copper. **Copper sulfate pentahydrate does not fulfil the B criterion.**

Considering the HC5-50 value of 7.8 µg/L for the aquatic compartment, **copper sulfate pentahydrate fulfils the T criterion.**

Conclusion: Copper sulfate pentahydrate does not fulfil the PBT-criteria. Therefore inclusion in Annex I is not restricted by these criteria.

2.2.2.4 Environmental exposure assessment

Ionx Cu WB50 is used as a laundry disinfectant added to the washing of contaminated clothing or overalls in automated washing machines in the medical sector. Two washing processes are typically used: continuous washing process (PT2.05 i) and batch washing process (PT2.05 ii). Ionx Cu WB50 is added during the rinsing cycle of the washing process. The product is delivered to the washing unit in litre polypropylene containers connected via dedicated pipework. Ionx Cu WB50 is added towards the end of the process via an automated dosing system set. The efficient dose/quantity of active substance of 3.56 g Cu^{2+} / L of rinse water (corresponding to the efficient dose of 14 000 ppm according to the chapter 2.1.3 on the efficacy) was used in the scenarios.

The environmental exposure assessment was calculated according to the Emission Scenario Document for product type 2: Private and Public Health area disinfectants and other biocidal products (sanitary and medical sector) during the life cycle stage "Professional Use" of the biocidal product.

For such uses, it was considered that the only relevant environmental exposure pathway is via emission to the STP as wastewater from the machines. The primary environmental compartments that is exposed to Ionx Cu WB50 following its uses as a laundry disinfectant is the STP. The risks were also calculated for the secondary compartments of interest downstream the STP were aquatic compartment (including sediment) and terrestrial compartment (including groundwater).

The risk assessment was carried out on the basis of total concentrations of copper as Cu in the environment. PEC values, initially calculated as "added values" were corrected in order to integrate the background concentrations in copper. Thus, total copper concentrations were calculated in taking into account of the natural/pristine and the regional copper background concentrations (as agreed under the Council Regulation (EEC) 793/93 on Existing Substances - EU-RAR).

In the specific case of copper release in soil, the applicant presented studies on copper toxicity in aged contaminated soils in the evaluation of the terrestrial ecotoxicity. Results from these studies show that, after 18 months ageing, NOECs increased for plants and invertebrates corresponding to a decrease of copper toxicity threshold. For micro-organisms, NOECS increased also but certainly due to an adaptation to copper. 18 months ageing tests were however not long enough to show a total remove of toxicity.
In order to consider the phenomenon of copper ageing in soil, an ageing factor of 2 was applied on the total copper concentrations in soil for the PEC values: the PEC values for soil were divided by 2. This strategy was validated at TMIII08 for PT08 dossiers.

2.2.2.5 Risk characterization

2.2.2.5.1 Aquatic compartment (including surface water, sediment and STP)

Continuous washing process
Considering the natural or the regional background, all the PEC/PNEC ratios for surface water, sediment and STP associated with the use of Ionx Cu WB50 with an efficient dose of 14000 ppm copper sulfate pentahydrate (in rinse water) are more than 1. Hence, there are no acceptable risks for surface water, sediment or STP using the continuous washing process at the efficient dose of 14000 ppm $CuSO_4$, $5H_2O$.
Batch washing process
All the PEC/PNEC ratios for surface water, sediment and STP associated with the use of Ionx CU WB50 with an efficient dose of 14000 ppm copper sulfate pentahydrate (in rinse water) are less than one except for the sediment compartment considering a regional background. Hence, there is an unacceptable risk for the sediment compartment using the batch washing process at the efficient dose of 14000 ppm copper sulfate pentahydrate.

2.2.2.5.2 Atmosphere

The negligible vapor pressure of copper means that exposure to air is insignificant; therefore the risks to the atmosphere are considered to be acceptable.

2.2.2.5.3 Terrestrial compartment (including groundwater)

Continuous washing process
Considering the natural or the regional background, all the PEC/PNEC ratios associated with the use of Ionx Cu WB50 with an efficient dose of 14000 ppm copper sulfate pentahydrate (in rinse water) are more than one for the agricultural soil. Hence, there are no acceptable risks for the **soil** compartment using the continuous washing process at the efficient dose of 14000 ppm copper sulfate pentahydrate.

Considering the natural or the regional background, all the PEC/PNEC ratios associated with the use of Ionx Cu WB50 with an efficient dose of 14000 ppm copper sulfate pentahydrate (in rinse water) are less than one for the groundwater compartment. Hence, there are acceptable risks for the **groundwater** compartment using the continuous washing process at the efficient dose of 14000 ppm copper sulfate pentahydrate.

Batch washing process
Considering natural or regional background, all the PEC/PNEC ratios associated with the use of Ionx Cu WB50 with an efficient dose of 14000 ppm copper sulfate pentahydrate (in rinse water) are less than one for soil and groundwater compartments. Hence, there is no risk for both **soil** and **groundwater** compartments using the batch washing process at the efficient dose of 14000 ppm copper sulfate pentahydrate.

2.2.2.5.4 Reverse scenario

Using the efficient dose of 14 g copper sulfate pentahydrate / L (14000 ppm), the PEC/PNEC ratios derived above lead to unacceptable risks for the environment. The sediment compartment is the most impacted in the two scenarios (continuous and batch washing process).

The same approach as the one described in paragraph 2.2.1.4 has been applied. Considering the potential interest of the active substance for the uses claimed in this dossier (non selective broad spectrum), it has been proposed to conduct an assessment by reverse scenario to estimate the application dose which could lead to acceptable calculated risks.
Hence, based on the compartment which is the most impacted by the emission of copper, the sediment, the RMS used a reverse scenario to determine the efficacy dose that would lead to acceptable risk for the environment for washing biologically contaminated laundry from hospitals both for the continuous process (PT 2.05 i) and the batch process (PT 2.05 ii).
An efficient dose of 110 ppm Cu which is equivalent to 430 ppm copper sulfate pentahydrate (instead of 14000 ppm copper sulfate pentahydrate for which efficacy has been proven according to the chapter 2.1.3 on the efficacy) was defined.

Conclusion: The efficient dose that would lead to acceptable risk for the environment whatever the background used and for the two processes proposed **must not exceed 110 ppm Cu which is equivalent to 430 ppm copper sulfate pentahydrate (instead of 14000 ppm copper sulfate pentahydrate)**.

It is worth noting that the doses which leads to acceptable risk for the environment is markedly higher than the intended dose proposed by the applicant in the original dossier, ie 2 ppm of copper sulfate pentahydrate.

2.2.2.5.5 Non compartment specific effects relevant to the food chain (primary and secondary poisoning)

An in-depth literature search showed the absence of copper biomagnification across the trophic chain in the aquatic and terrestrial food chains. Differences in sensitivity among species were not related to the level in the trophic chain but to the capability of internal homeostasis and detoxification. Field evidence had further provided no indications of secondary poisoning.

Hence, the risks posed via secondary poisoning are considered to be acceptable.

2.2.3 Endocrine disruption criteria

Based on the available data in this dossier, no alert on the endocrine disruption was observed. In the ecotoxicity and toxicity tests with mammals there were no effects in test animals which could be related to possible endocrine disruption.
According to the document "Communication from the Commission to the council and the European parliament on the implementation of the Community Strategy for Endocrine Disrupters - a range of substances suspected of interfering with the hormone systems of humans and wildlife (COM (2001) 262 final) in table 5, copper are deemed not to be EDs.

2.3 OVERALL CONCLUSIONS OF THE EVALUATION

Copper sulfate pentahydrate is not highly flammable, not oxidizing and not explosive. Its physico-chemical properties are deemed acceptable for the appropriate use, storage and transportation of the biocidal product.

Copper sulfate pentahydrate is considered as harmful if it is swallowed and induces serious damage to eyes.

Based on the available data in this dossier, there is no evidence of endocrine effects and the substance cannot be considered as carcinogenic, mutagenic and toxic for the reproduction.

As no efficacy has been highlighted for the product Ionx Cu WB50 at the claimed dose in the CEN standards tests submitted initially in the dossier, efficacy study has been performed with copper sulfate pentahydrate alone. In this study, an efficient dose of copper sulfate pentahydrate alone of 14000 ppm (which is equivalent to 14 g copper sulfate pentahydrate /L and to 3.56 copper g/L) has been set and, therefore used to conduct the risk assessment. This in-use concentration of 14000 ppm leads to unacceptable estimated risks for different categories of people and for the environment.

In this context, the maximal acceptable concentration of copper in wash rinse water was determined to conclude to an acceptable risk, for healthy and enfeebled adults, children and infants, taking into account the process of washing. This approach concludes that the maximal efficient doses of copper sulfate pentahydrate have to be lower than 1672 ppm in the case of a continuous process and than 314 ppm in batch unit process, considering all populations.

The environmental risk assessment indicates that safe use(s) can only be identified if the efficient dose is reduced to 0.11 g Cu / L which is equivalent to 0.43 g copper sulfate pentahydrate / L (instead of 14 g copper sulfate pentahydrate / L, the only dose rate considered efficient by RMS based on provided data). It is recommended that the efficient dose rate does not exceed 0.43 g $CuSO_4$ $5H_2O$ /L (430 ppm of copper sulfate pentahydrate).

A laundry test using Stomacher model demonstrates a bactericidal activity of copper sulfate pentahydrate at concentrations of 153 and 430 mg/L against MRSA, both alone and in combination with the detergent used in the washing process. It was also observed a synergistic biocidal effect between the detergent and $CuSO_4$, used in combination.

The results of this study lead to conclude that the active substance copper sulfate pentahydrate is efficient at the maximum acceptable doses estimated to protect the human health and the environment. However, at the product authorization stage, each applicant will have to demonstrate the efficacy of each product, and the determined efficient dose should be lower than the maximum acceptable doses as calculated in this assessment.

Overall summary

SCENARIO	Human primary exposure		Human secondary exposure						Environmental exposure						
			Healthy person			Enfeebled person			Aquatic compartment			Atmosphere	Terrestrial compartment		primary and secondary poisoning
	Professional	Non professional	Adult	Child	Infant	Adult	Child	Infant	Surface water	sediment	STP		soil	groundwater	
BATCH UNITS PROCESS															
Dose in the product: 150000 ppm $CuSO_4$, $5H_2O$									**Efficient dose : 14000 ppm $CuSO_4$, $5H_2O$**						
Treatment of fabric[1]	Acceptable[2]	Not expected	NR						A	**NA**	A	A	A	A	Not Expected
Efficient dose : 14000 ppm $CuSO_4$, $5H_2O$									NR						
Wearing fabric	Not expected	Not expected	**NA**	**NA**	**NA**	**NA**	**NA**	**NA**							
Reverse scenario : 314 ppm $CuSO_4$, $5H_2O$									**Reverse scenario : 430 ppm $CuSO_4$, $5H_2O$**						
Treatment of fabric[2]	NR	Not expected	NR						A	A	A	A	A	A	Not Expected
Wearing fabric	Not expected	Not expected	A	A	A	A	A	A	NR						
[1] Only mixing and loading are relevant during this phase for human exposure. [2] Risk is acceptable **if gloves are worn** but an unacceptable risk exists when worker does not wear gloves.															
CONTINUOUS PROCESS															
Dose in the product: 150000 ppm $CuSO_4$, $5H_2O$									**Efficient dose : 14000 ppm $CuSO_4$, $5H_2O$**						
Treatment of fabric[3]	Acceptable[4]	Not expected	NR						**NA**	**NA**	**NA**	A	**NA**	A	Not Expected
Efficient dose : 14000 ppm $CuSO_4$, $5H_2O$									NR						
Wearing fabric	Not expected	Not expected	A	A	A	**NA**	**NA**	**NA**							
Reverse scenario : 1672 ppm $CuSO_4$, $5H_2O$									**Reverse scenario : 430 ppm $CuSO_4$, $5H_2O$**						
Treatment of fabric[4]	NR	Not expected	NR						A	A	A	A	A	A	Not Expected
Wearing fabric	Not expected	Not expected	A	A	A	A	A	A	NR						
[3] Only mixing and loading are relevant during this phase for human exposure. [4] Risk is acceptable **if gloves are worn** but an unacceptable risk exists when worker does not wear gloves.															

A: Acceptable NA: Not acceptable NR: Not relevant

3 DECISION

3.1 BACKGROUND TO THE PROPOSED DECISION

The evaluation of the dossier led to the following conclusions for the active substance copper sulfate pentahydrate used in private area and public health area disinfectants (product type 2),:

- The physico-chemical properties of copper sulfate pentahydrate are deemed acceptable for the appropriate use, storage and transportation of the biocidal product.

- The use claim is the disinfection of contaminated clothing by professionals only. The active substance copper sulfate pentahydrate is incorporated into products used with washing machines, where the presence of the copper2+ ion can exert a biocidal effect. The product is added to the rinse water in industrial washing units (added after the detergent wash and before the final rinse cycle). The representative product in this PT2 evaluation contains 15 % copper sulfate pentahydrate as one of 3 active substances that contribute to its overall efficacy.
  The in-use concentration of copper sulfate is 2 mg/l. The product has not showed a sufficient efficacy, at the claimed dose, in the tests submitted in the dossier, performed according to the CEN standards.

- Data were available showing that a concentration 14000 mg/l copper sulfate pentahydrate was efficacious. Consequently, the risk assessment for human health and the environment were conducted based on this in-use concentration. As a result unacceptable risks were identified.

- Reverse reference scenarios were undertaken to identify the maximum in-use concentration of copper sulfate pentahydrate that would result in acceptable risks for human health and the environment. A concentration of 314 mg/l was identified from this exercise (it is noted that this is significantly higher than the 2 mg/l in-use concentration proposed by the Applicant for the representative product).
  The Applicant subsequently submitted data showing that copper sulfate pentahydrate was efficacious in PT2 at a concentration of 153 mg/l. Within the frame of Annex I inclusion under directive 98/8/EC, the submitted tests are sufficient to demonstrate a basic disinfectant activity of the active substance. Moreover, it should be considered that copper sulfate will presumably be applied in combination with other active substances.

- Thus, it has been shown that copper sulphate pentahydrate has innate efficacy at an in-use concentration that results in an acceptable level of risk for both human health and the environment. The proposed in-use concentration of copper sulfate pentahydrate in the representative product also results in an acceptable level of risk for both human health and the environment. However, the Applicant will need to demonstrate the efficacy of products containing copper sulfate pentahydrate in PT2 at product authorisation.

- With regard to human health exposure and effects, based on the conducted risk assessment, it is considered that safe uses can be identified for professional users only if adequate gloves are worn.

- Based on the available data in this dossier, there is no evidence of endocrine effects of copper sulfate pentahydrate. The substance cannot be considered as carcinogenic, mutagenic and toxic

for the reproduction (CMR). Copper sulfate pentahydrate is considered as Toxic for the environment but not Bioaccumulative. Persistence criterion is not relevant for inorganic metal.

3.2 PROPOSED DECISION

The overall conclusion from the evaluation of copper sulfate pentahydrate for use in Product Type 2 (private area and public health area disinfectants and other biocidal products), is that it may be possible to issue authorisations of products containing copper sulfate pentahydrate in accordance with the conditions laid down in Article 5(1) b), c) and d) of Dir. 98/8/EC.

At the time of finalisation of this assessment report, there is no indication that this conclusion would not be valid with regard to compliance with Article 19(1), (2) and (5), and the common principles of Annex VI of Regulation (EU) No 528/2012. As consequence, it can also be concluded that it may be possible to issue authorisations of products containing copper sulfate pentahydrate in accordance with Article 19(1), (2) and (5), and the common principles of Annex VI of Regulation (EU) No 528/2012.

There is no indication that copper sulfate pentahydrate would fulfil the exclusion criteria specified in article 5(1), nor the substitution criteria specified in Article 10 (1) of Regulation (EU) No 528/2012.

The active substance as manufactured, copper sulfate pentahydrate, shall have a minimum of purity of 999 g/kg (99.9% w/w), equivalent to 25.4% w/w copper.

For industrial or professional users, safe operational procedures and appropriate organizational measures shall be established. Only where exposure cannot be reduced to an acceptable level by other means, products shall be used with appropriate personal protective equipment.

3.3 ELEMENTS TO BE TAKEN INTO ACCOUNT WHEN AUTHORIZING PRODUCTS

1. The claims on the compatibility of the product with the material of the packaging must be supported at product authorisation if they will be included on the label. Moreover the material of the packaging should be specified for and no reactivity towards container material should be confirmed.
2. Product containing copper sulfate pentahydrate may only be used as a bactericide. The other activities (fungicide, sporicide and virucide) will have to be proved at the product authorization stage.
3. Efficacy for disinfection of contaminated clothing has not been appropriately demonstrated and should be entirely reviewed at the product authorization stage. Additional studies should be submitted demonstrating efficacy under practical conditions, preferably conducted to current European standards and activities claimed should be in accordance with requirements suggested in PT2 claim matrix.
4. Before authorizing products, attention shall be paid to possible occurrence of resistance.
5. At the product authorization stage, each applicant will have to demonstrate the efficacy of its product with appropriate tests and will have to assess the environmental and human risk with the determined efficient dose rate.
6. When used in rinse water in industrial/professional washing machines in order to disinfect clothes or laundry, the concentration of copper sulfate in rinse water shall not exceed 314ppm, unless it can be demonstrated in the application for product authorisation that risks can be reduced to an acceptable level by other means.

7. The human health exposure assessment is based on the model from Consexpo fact sheet: cleaning product. It has to be noted that the model is based on consumer washing machine and the possible difference between the numbers of rinse cycle with a professional washing machine has not been taken into account. This point could be considered for refinement of secondary exposure at the product authorization stage.
8. At product authorisation stage the different member states have to decide on the maximum acceptable dosage for the environment, taking into account actual background / regional concentrations.
9. Dermal absorption values used in the applications for product authorisation should be justified, if available by the submission of specific dermal absorption data on the product, or by read-across to existing data if scientifically justified, or by using default values.

3.4 REQUIREMENTS FOR FURTHER INFORMATION

For the analytical method for the determination of Zinc in copper sulfate pentahydrate, further validation data are required for the annex I inclusion to fully validate the analytical method.

For the analytical method for the determination of copper in water, validation data are required to confirm the compliance with the requirement: LOQ limit of 2mg/L in drinking water, and method capable of analyzing 1% of the typical applied concentration for PT 2 in surface water as well as the suitability of the method for drinking and ground water and surface water.

These data should preferably be submitted to the original Rapporteur Member State (France) at the latest 6 months before the date of approval.

3.5 UPDATING THIS ASSESSMENT REPORT

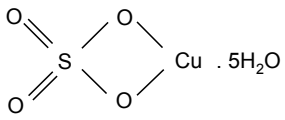
This assessment report may need to be updated periodically in order to take account of scientific developments and results from the examination of any of the information submitted in relation with Regulation (EU) No 528/2012. Such adaptations will be examined and finalised in connection with any amendment of the conditions for the approval of copper sulfate pentahydrate.

Appendix I: List of endpoints

Identity, Physical and Chemical Properties, Details of Uses, Further Information, and Proposed Classification and Labeling

Active substance (ISO common name)	Copper sulfate pentahydrate (No common name, not required by ISO)
Function	Bactericide
Rapporteur Member State	France

Identity (Annex IIA, Point II)

Chemical name (IUPAC)	Copper II sulfate pentahydrate
Chemical name (CA)	Copper II sulfate pentahydrate Sulfuric acid copper (2+) salt (1:1), pentahydrate
CAS No	7758-99-8
EC No (EINECS No)	231-847-6
Other substance No.	All copper compounds have the CIPAC code 44 The CIPAC code for Cu^{2+} ion is 029 The CIPAC code for SO_4^{2-} ion is 306
Minimum purity of the active substance as manufactured (g/kg or g/l)	>99,9%
Identity of relevant impurities and additives (substances of concern) in the active substance as manufactured (g/kg)	Cadmium (0.00017%), Arsenic (0.00017%), Nickel (0.00033%), Zinc (0.0006%) and Lead (0.001%)
Molecular formula	$CuSO_4.5H_2O$
Molecular mass	249.68 g/mol (pentahydrate)
Structural formula	

Physical and Chemical Properties (Annex IIA, Point III)

Melting point (state purity)	Decomposes before melting
Boiling point (state purity)	Decomposes before boiling
Temperature of decomposition	Copper sulfate pentahydrate has first three phases of deshydratation: At 88°C: $CuSO_4$,$5H_2O$ → $CuSO_4$,$3H_2O$ At 114°C: $CuSO_4$,$3H_2O$ → $CuSO_4$, H_2O At 215°C: $CuSO_4$,H_2O → $CuSO_4$ And then, two phases of decomposition: At 340°C: $CuSO_4$ → $3Cu(OH)_2$ $CuSO_4$ At 600-650°C: $3Cu(OH)_2$ $CuSO_4$ → CuO
Appearance (state purity)	Blue triclinic crystalline solid
Relative density (state purity)	2.286 g/cm^3
Surface tension	As it is commonly known that inorganic salts increase the surface tension of water, the result of the test according to EC method A5 would be expected to be

	higher than 72.75mN/m. Therefore inorganic salts are not expected to be surface active.
Vapour pressure (in Pa, state temperature)	Negligible $7{,}31.10^{-17}$ Pa (EPIWIN)
Henry's law constant (Pa m3 mol -1)	Henry's Law constant cannot be calculated without a measurable vapour pressure $1{,}211.10^{-19}$ Pa m^3/mol (EPIWIN)
Solubility in water (g/l or mg/l, state temperature)	220 g/L at 25°C Due to the high solubility in water, effect of temperature is not relevant. And as copper sulfate pentahydrate always remains in solution under a dissociated ionic state, effect of pH is not relevant.
Solubility in organic solvents (in g/l or mg/l, state temperature) (Annex IIIA, point III.1)	At T=22°C n-hexane: <1 g/L Dichloromethane: <1 g/L Xylene: <1 g/L Ethyl acetate: <1 g/L Acetone: <1 g/L Methanol >20 g/L
Stability in organic solvents used in biocidal products including relevant breakdown products (IIIA, point III.2)	Not applicable, the formulation containing copper sulfate pentahydrate does not contains organic solvents.
Partition coefficient (log POW) (state temperature)	Not relevant for copper (mechanisms of absorption of Cu^{2+} into organic matter and living cells are understood to be different from those traditionally attributed to carbon-based pesticides) Modelled / measured partition coefficients Kp are used instead.
Hydrolytic stability (DT50) (state pH and temperature) (point VII.7.6.2.1)	Copper is not degraded by hydrolytic processes and metabolites are not formed.
Dissociation constant (not stated in Annex IIA or IIIA; additional data requirement from TNsG)	Copper sulfate pentahydrate is very soluble in water and it always remains in solution under a dissociated ionic state.
UV/VIS absorption (max.) (if absorption > 290 nm state ε at wavelength)	λ_{max} = 798.1 nm Absorbance = 1.037 ε = 47.8 $M^{-1}.cm^{-1}$
Photostability (DT50) (aqueous, sunlight, state pH) (point VII.7.6.2.2)	Copper is not degraded by photolysis processes and metabolites are not formed.
Quantum yield of direct phototransformation in water at Σ > 290 nm (point VII.7.6.2.2)	Copper is not degraded by photolysis and therefore the determination of quantum yield is not possible.
Flammability	Copper sulfate pentahydrate is not flammable.
Explosive properties	Copper sulfate pentahydrate has not explosive. properties

Classification and proposed labeling (Annex IIA, Point IX)

The proposed classification of copper sulphate pentahydrate according to Directive 67/548/CEE:

Hazard symbol:	N Xn Xi	Dangerous for the environment Harmful Irritant
Risk phrases	R22 R41 R50/53	Harmful if swallowed Risk of serious damage to eyes. Very toxic to aquatic organisms, may cause long-term adverse effects in the aquatic environment
Safety phrases	S26 S39 S60 S61	In case of contact with eyes, rinse immediately with plenty of water and seek medical advice Wear eye/face protection This material and its container must be disposed of as hazardous waste Avoid release to the environment. Refer to special instructions/safety data sheet

Classification according to the CLP, REGULATION (EC) No 1272/2008 is presented as supportive information.

Class of danger	Hazard statement
Acute Tox 4	H302 : Harmful if swallowed
Eye dam 1	H318 : Causes serious eye damage
Aquatic. Acute 1	H400 : Very toxic to aquatic life
Aquatic. Chronic 1	H410 : Very toxic to aquatic life with lasting effects

Chapter 2: Methods of Analysis

Analytical methods for the active substance

Technical active substance (principle of method) (Annex IIA, point 4.1)	A CIPAC analytical method (44/TC/M3.1) is available for the determination of total copper in copper sulfate: samples are heated with nitric acid and copper is determined electrolytically. An analytical method based on ICP-MS is available and validated for the determination of sulfate in the active substance Water content is determined by gravimetric method
Impurities in technical active substance (principle of method) (Annex IIA, point 4.1)	Relevant impurities can be determined by ICP-MS. Aliquots of test material are taken, water and nitric acid are added. The samples are dissolved using ultrasonication and then diluted to volume with water prior to analysis The methods are validated and validation data have been provided. For the determination of Zinc, further validation data are required for the annex I inclusion to fully validate the analytical method.

Analytical methods for residues

Soil (principle of method and LOQ) (Annex IIA, point 4.2)	Acid digestion followed by ICP-AES method or AAS. Methods based on internationally accepted guidelines (US EPA method 220.1, US EPA method 7210, AOAC official method 990.8), LOD: 20µg/l (AAS), 20µg/l (AAS) and 6µg/l (ICP-AES, estimated)
Air (principle of method and LOQ) (Annex IIA, point 4.2)	1) Air is passed through sampling filters (glass fibre, quartz fibre or membrane filter). The filters are digested in acid solution consisting of either H_2F_2/HNO_3 (variant A) or $H_2F_2/HNO_3/HClO_4$ (variant B). Determination of copper is by flame (F) AAS or by graphite tube electrothermal (GF) AAS (wavelength 324.8 nm). Estimated LOQ = 27 ng/m^3 2) Air is passed through sampling filters (glass fibre, quartz fibre or membrane filter). The filters are digested in acid solution consisting of H_2F_2/HNO_3. Determination of copper is by ICP-OES. Estimated LOQ = 1ng/m^3. Validation data are missing. However due to the very low vapour pressure of the copper sulfate pentahydrate (7.31×10-17 Pa) and the fact that the product is not sprayed, an analytical method for air is not required and no further data will be required.
Water (principle of method and LOQ) (Annex IIA, point 4.2)	1) Acid digestion followed by ICP-AES LOD = 6µg/l 2) Acid digestion followed by AAS LOD = 20µg/l 3) Acid digestion followed by AAS furnace technique LOD = 1µg/l Methods based on internationally accepted guidelines (US EPA method 200.7, US EPA method 220.1 and US EPA method 220.2). No LOQ has been provided. Validation data are required after annex I inclusion. Moreover the suitability of the method for drinking and ground water and surface water is required after annex I inclusion..
Body fluids and tissues (principle of method and LOQ) (Annex IIA, point 4.2)	Not required. Copper sulfate is not classified as toxic or very toxic. However internationally accepted guidelines are available for the determination of elements in body fluids and tissues (NIOSH methods…): acid digestion followed by ICP-AES analysis, LOD: 1µg/100g blood, 0.2µg/g tissue and 0.1µg/50ml urine
Food/feed of plant origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	Not applicable for biocidal use.
Food/feed of animal origin (principle of method and LOQ for methods for monitoring purposes) (Annex IIIA, point IV.1)	Not applicable for biocidal use.

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 TMIII08 that oral absorption rates 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 dermal absorption rates of 5% have to be used for diluted solutions and 100% for the concentrated product. As accepted at the TM IV 11, 100% for enfeebled people.
Rate and extent of absorption by inhalation:	A default value of 100% was applied.
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). Accumulation does not occur except in cases of genetic disease or chronic administration of exceptionally high doses (60 mg/person/day), where copper accumulates in the liver.
Rate and extent of excretion:	Biliary excretion is quantitatively the most important route. 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	Male and female LD50 : 482 mg/kg Requires a R22 risk phrase
Rat LD_{50} dermal	Male and female LD50 : > 2000 mg/kg
Rat LC_{50} inhalation	The particle size distribution indicates less than 0.01% w/w particles are less than 125 µm in diameter. A substance is not considered to be a potential inhalation hazard if the particle size is greater than 100 µm.
Skin irritation	Not classified as dermal irritant.
Eye irritation	Severe eye irritant

	Requires a R41 risk phrase
Skin sensitization (test method used and result)	Not sensitising (guinea pig maximisation test)

Repeated dose toxicity (Annex IIA, Point 6.3)

Species/ target / critical effect	The test substance used the following study was copper (II) sulfate. Rat/ liver/ inflammation Rat/ kidney/ cytoplasmic droplets Rat, mouse/ forestomach/ minimal to moderate hyperplasia of the squamous mucosa
Lowest relevant oral NOAEL / LOAEL	NOAEL from a 90-d rat study: Equivalent to 16.3 mg Cu/kg bw/day in male
Lowest relevant dermal NOAEL / LOAEL	Not available
Lowest relevant inhalation NOAEL / LOAEL	Not available

Genotoxicity (Annex IIA, Point 6.6)

In vitro:

1. Ames test - negative in both the presence and absence of S9 mix
2. UDS-positive

The *in vitro* tests bypass the strict control mechanism and present the isolated mammalian cell with a totally artificial situation of excess free copper ion.

In vivo:

1. UDS-negative
2. mouse micronucleus-negative
3. bone marrow chromosome aberration, micronucleus assay and sperm abnormality assay(IP)-positive

Positive results were observed when copper sulfate was administered by intra-peritoneal injection, route which bypasses the natural protective mechanisms in gut.

→ no requirement for classification

Carcinogenicity (Annex IIA, Point 6.4)

Species/type of tumour	There are two genetic conditions in the human (Wilson's disease and Menkes' disease) lead to accumulation of copper Human subjects with these conditions may die of the condition itself (if untreated), but they do not show increased incidence of any cancer. If abnormally high levels of copper are present over long periods in an organ or tissue, yet there is no association between the high copper levels and cancer in these organs or tissues, in chronic disease. It is therefore reasonable to conclude that copper is not carcinogenic in these tissues.

Lowest dose with tumours	n.a.

Reproductive toxicity (Annex IIA, Point 6.8)

Species/ Reproduction target / critical effect	The test substance used in the following study was copper (II) sulfate 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 sulfate cannot be regarded as having adverse effects on fertility in the tested animals. 1500 ppm NOAEL in rat two-generation study = 23.6 (♂) -55.7 (♀) mgCu/kg bw/d (maximal dose tested)
Species/Developmental target / critical effect	Rabbit/developmental toxicity/ Reduced foetal weight and increased incidence of retarded ossification of skull and pelvic bones at dose levels with maternal weight loss, inappetance and death.
Lowest relevant developmental NOAEL / LOAEL	NOAEL maternal = 6 mgCu/kg bw/d NOAEL foetal = 9 mgCu/kg bw/d

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

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

Other toxicological studies (Annex IIIA, VI/XI)

None

Medical data (Annex IIA, Point 6.9)

Direct observation, e.g. clinical cases, poisoning incidents if available; data point 6.12.2.	Acute: Intoxication is associated with emesis, superficial or deep ulcerations of the gastric and intestinal mucosa. Liver histopathology revealed dilatation of central veins, varying degrees of liver cell necrosis and bile thrombi. In kidneys there was congestion of glomeruli swelling or necrosis of tubular cells and haemoglobin casts. Chronic: A case of self-administration, a 26-year-old Irishman took 30 mg Cu/day for two years (apparently without ill effect), then increased the dose to 60 mg Cu/day in the third year and suffered from liver failure.

Summary (Annex IIA, Point 6.10)

	Value	Study	Safety factor
ADI (if residues in food or feed)	Not relevant*		
Healthy and enfeebled persons			
AEL acute and medium term	0.082 mg/kg bw/d	Rat 90-day oral toxicity NOAEL = 16 mg/kg/day (corresponding to a systemic NOAEL of 4.1 mgCu/kg/day)	MOE ref = 50
AEL long-term	0.041 mg/kg bw/d	Rat 90-day oral toxicity NOAEL = 16 mg/kg/day (corresponding to a systemic NOAEL of 4.1 mgCu/kg/day)	MOE ref = 100
Drinking water limit	No data reported		
ARfD (acute reference dose)	Not applicable		

"As exposure through food is negligible no food risk assessment was deemed necessary and no ADI was derived. An ADI value of 0.5 mg/kg/d is nevertheless available in the literature (WHO, IPCS)"

Chapter 4: Fate and Behavior 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 relevant for metals
Photolytic / photo-oxidative degradation of active substance and resulting relevant metabolites	Not relevant for metals
Readily biodegradable (yes/no)	Not relevant for metals
Biodegradation in seawater	Not relevant for metals
Non-extractable residues	Not relevant for metals The vast majority of copper in the sediment will be bound to solid matter and pore water concentrations of bio-available copper will be low. Under anaerobic conditions, which are prevalent in sediment, the formation of Cu_2S and CuS will be responsible for reducing levels of available copper due to the sparingly soluble nature of these compounds.
Distribution in water / sediment systems (active substance)	The distribution of metals between aqueous phase and soil/sediment/suspended matter should preferentially be described on the basis of measured soil/water, sediment/water and suspended matter/water equilibrium distribution coefficient (TECHNICAL GUIDANCE DOCUMENT on Risk Assessment Part II Appendix VIII, 2003; TECHNICAL GUIDANCE DOCUMENT Annex 4-VIII Environmental risk assessment for metals and metal compounds (RIP 3.2-2). From the literature overview, the following partitioning coefficients have thus been derived for Cu metal and Cu compounds: **Partition coefficient in suspended matter** Kp_{susp} = 30,246 l/kg (log Kp (pm/w) = 4.48) (50^{th} percentile) (Heijerick *et al*, 2005)

	Partition coefficient in sediment Kpsed = 24,409 l/kg (log Kp(sed/w) = 4.39) (50th percentile) (Heijerick *et al.,* 2005)
Distribution in water / sediment systems (metabolites)	Not relevant for 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)	Copper does not mineralise as an inorganic metal salt.
Laboratory studies (range or median, with number of measurements, with regression coefficient)	Not relevant for metals
Field studies (state location, range or median with number of measurements)	Not relevant for metals
Anaerobic degradation	Not relevant for metals
Soil photolysis	Not relevant for metals
Non-extractable residues	Not relevant for metals
Relevant metabolites - name and/or code, % of applied a i. (range and maximum)	Not relevant for metals
Soil accumulation and plateau concentration	Although unable to degrade, the affect of ageing on the distribution of copper in soil results in increased immobilisation by long term adsorption and complexation reactions in the soil.

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

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

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

Direct photolysis in air	Copper is not volatile and is not degraded by photolysis processes in air.
Quantum yield of direct photolysis	Not relevant for metals
Photo-oxidative degradation in air	Not applicable. Not relevant for metals
Volatilization	Copper is not volatile at environmentally relevant temperatures.

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

Soil (indicate location and type of study)	No monitoring data available.
Surface water (indicate location and type of study)	No monitoring data available.
Ground water (indicate location and type of study)	No monitoring data available.
Air (indicate location and type of study)	No monitoring data available.

Chapter 5: Effects on Non-target Species

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

Acute toxicity to aquatic organisms	No acute toxicity data are presented as the toxicity was evaluated using a SSD based on chronic toxicity data.
Chronic toxicity to aquatic organisms in the FRESHWATER COMPARTMENT	**SSD result: HC5-50 = 7.8 µg Cu / l as reasonable worst case** **Freshwater algae and higher plants:** Lowest NOEC used in the SSD = 15.7 µg Cu /L (growth of *Pseudokirchneriella subcapitata*) Highest NOEC used in the SSD = 510.2 µg Cu /L (growth of *Chlorella vulgaris*) **Freshwater Invertebrates:** Lowest NOEC used in the SSD = 4 µg Cu /L (mortality and reproduction of *Ceriodaphnia dubia*) Highest NOEC used in the SSD = 181 µg Cu /L (reproduction of *Daphnia magna)* **Freshwater Fishes:** Lowest NOEC used in the SSD = 2.2 µg Cu /L (growth of *Oncorhynchus mykiss***)** Highest NOEC used in the SSD = 188 µg Cu /L (mortality of *Perca fluviatilis)*
Chronic toxicity to aquatic organisms in the SEDIMENT COMPARTMENT	**SSD result: HC5-50 = 1741 mg Cu/kg OC,** corresponding to **87 mg Cu/kg dry weight for a sediment with 5 % O.C**.(TGD default value) **Sediment organisms:** Lowest NOEC used in the SSD = 18.3 mg Cu /kg d.w. (growth and reproduction of *Tubifex tubifex*) Highest NOEC used in the SSD = 580.9 mg Cu /kg d.w. (survival of *Tubifex tubifex*)

Chronic toxicity to Sewage microorganisms	The lowest reliable observed **NOEC** value was noted for the inhibition of respiration **= 0.23 mg/l**

Effects on earthworms or other soil non-target organisms

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

Effects on terrestrial vertebrates

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

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

Acute oral toxicity	No data
Acute contact toxicity	No data

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

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

Bioconcentration (Annex IIA, Point 7.5)

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

Chapter 6: Other End Points

Not applicable.

Appendix II: List of Intended Uses

Product Type/Object and situation	Product name	Pests or Group of pests controlled	Formulation		Application	Remarks:
			Type	Conc. of as	Professional use **Dose rate [mg a.s.L]**	
PT2.05 : other biocidal products within product type 2	copper sulfate	bacteria	NR	NR	153	added to the rinse water in industrial washing units (added after the detergent wash and before the final rinse cycle)

NR: not relevant

Appendix III: List of studies

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

Part A: Reference list of studies submitted (by Section No.)

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
Section 1	No studies submitted.				
Section 2					
IIIA2.7 IIIA2.8	XXXX	2012a	Copper sulfate pentahydrate: analytical profile of batches XXXX Unpublished report **CONFIDENTIAL REPORT**	Y	Manica S.p.A
Section 3					
IIIA, 3.1.1, 3.1.2, 3.1.3, 3.3.1, 3.3.2, 3.5, 3.7	Anon	2006	CRC Handbook of Chemistry and Physics, 87th Edition, 2006, CRC Press. Non-GLP, Published.	No	Public domain
IIIA, 3.4.1-01	Saliou, C.	2000	Tribasic Copper Sulphate spectral data UV/Visible, IR. CFPI Nufarm, OT 09/C/2910. GLP, Unpublished.	Y	Nufarm
IIIA, 3.4.1-02	Nyquist, R., Kagel, R., Putzig, C., Leugers, M.	1996	Handbook of infrared and raman spectra of inorganic compounds and salts. Volume 4 Nyquist et al 1996 Non-GLP, Published.	No	Public domain
IIIA, 3.7-01	Garofani, S	2008	Copper sulphate pentahydrate: determination of the solubility in organic solvents Chem Service Srl, Study No. 467/2007 GLP, Unpublished.	Y	Manica S.p.A
Section 4					
IIIA, 4.1-01	XXXX	2003	Copper oxychloride and Bordeaux mixture: Analytical method validation. XXXX GLP, Unpublished. **CONFIDENTIAL REPORT**	Y	Manica S.p.A
IIIA, 4.1-02	XXXX	2012a	Copper sulphate pentahydrate – analytical profile of batches XXXX GLP, Unpublished. **CONFIDENTIAL REPORT**	Y	Manica S.p.A

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA, 4.1-03	XXXX	2012b	Copper sulfate pentahydrate: analytical method validation. XXXX GLP, Unpublished. **CONFIDENTIAL REPORT**	Y	Manica S.p.A
IIIA, 4.2(a)-01	Kiefer, R.	2003	Validation of an analytical method for the determination of bioavailable copper in soil samples. GAB Biotechnologie GmbH & IFU Umweltanalytik GmbH, Report No. 20031084/02-UVX. GLP, Unpublished.	Y	Manica S.p.A
IIIA, 4.2(a)-03	Anon	1996	Method 3050B. Acid digestion of sediments, sludges and soil. USEPA. Not GLP, Published.	N	Public
IIIA, 4.2(a)-04	Anon	1983	Method 220.1. Methods of chemical analysis of water and wastes. USEPA. Not GLP, Published.	N	Public
IIIA, 4.2 (c) 0.5, 06, 07	Anon	1983, 1992	4.2(c)-05: Method 220.2. Methods of chemical analysis of water and wastes. USEPA March 1983 4.2(c)-06: Method 7211. Copper (atomic absorption, furnace technique). USEPA July 1992 4.2(c)-07: Method 200.7. Inductively coupled plasma - Atomic emission spectrometric method for trace element analysis of water and wastes. USEPA, 1983 Not GLP, Published.	No	Public domain
IIIA 4.2 (d)	NIOSH	1987	Method 8005. NIOSH Manual of Analytical Methods, Fourth Edition, 8/15/94. Not GLP, published. Method 8310. NIOSH Manual of Analytical Methods, Fourth Edition, 8/15/94. Not GLP, published.	No	Public domain
Section 5					
IIIA, 5.3.1-01	Brambilla, L.	2009	Basic bactericidal activity on copper sulphate pentahydrate. eurofins Pharma Services, Biolab S.p.A, Italy. Report no. 2009/1026 Ami, GLP, Unpublished.	Y	Manica S.p.A
IIIA, 5.3.1(02)	Hall, T.	2011	Copper sulphate laundry rest using a Stomacher model.	Y	Manica S.p.A
IIIA, 5.4.1	Thurman, R.B., Gerba, C.P.	1989	The Molecular Mechanisms of Copper and Silver Ion Disinfection of Bacteria and Viruses, CRC Critical Reviews in Environmental Control, Vol 18, Issue 4, p. 295-314. Non-GLP, Published.	No	Public domain
Section 6					

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA, 6.1.1-01	Lheritier, M.	1994	Test to evaluate the acute toxicity following a single oral administration (LD50) in the rat. Pharmakon Europe., Report no. 44193. GLP, Unpublished.	Y	Manica S.p.A
IIIA, 6.1.2-01	Lheritier, M.	1993	Test to evaluate the acute toxicity following a single cutaneous administration (limit test) in the rat. Pharmakon Europe., Report no. 44293 GLP, Unpublished.	Y	Manica S.p.A
IIIA, 6.1.3-01	Janssoone, M.M. and Brachet, A.	2006	Determination of the particle size distribution of copper sulphate pentahydrate. Geneva Research Centre. Report no. P-76-06-01 GLP, Unpublished	Y	Manica S.p.A
IIIA, 6.1.4-01	Mercier, O.	1994a	Test to evaluate the acute primary cutaneous irritation and corrosivity in the rabbit (3 animals). Pharmakon Europe. Report no. 44493. GLP, Unpublished	Y	Manica S.p.A
IIIA, 6.1.4-02	Mercier, O.	1994b	Test to evaluate acute ocular irritation and reversibility in the rabbit (3 animals). Pharmakon Europe. Report no. 44393. GLP, Unpublished	Y	Manica S.p.A
IIIA, 6.1.5-01	Mercier, O.	1994c	Test to evaluate sensitizing potential in the guinea pig: Guinea-pig maximisation test. Pharmakon Europe. Report no. 44093. GLP, Unpublished	Y	Manica S.p.A
IIIA, 6.2-01	Leeming, N.M.	2003	Absorption, Distribution, Metabolism and excretion of copper in humans and in domestic and laboratory animals. European Union Copper Task Force. Non-GLP, Unpublished.	Y	EUCuTF
IIIA, 6.2-02	Himmelstein, M	2004	Five Copper Substances: absorption, distribution, and excretion in male rats. DuPont Haskell Laboratories. Report number 11784. GLP, Unpublished	Y	EUCuTF
IIIA, 6.3.1-01	Hébert, C.D., Elwell, M.R., Travlos, G.S., Fitz, C.J. and Bucher, J.R.	1993	Subchronic toxicity of cupric sulfate administered in drinking water and feed to rats and mice. National Institute of Environmental Health Sciences, North Carolina and Biotechnical Services Inc, Arkansas. *Fund and App Tox*, **21**, 461-475. GLP, Published	N	Published literature

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA, 6.4.1-01	Hébert, C.D.	1993	National Toxicology Program Report Number 29 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 Institute of Health Publication 93-3352. Non-GLP, Published	N	Published literature
IIIA, 6.4.1-02	Haywood, S.	1980	The effect of excess dietary copper on the liver and kidney of the male rat. J. Comp. Path Vol 90, 217-232. Non-GLP, Published	N	Published literature
IIIA, 6.4.1-03	Haywood, S.	1985	Copper toxicosis and tolerance in the rat, Changes in copper content of the liver and kidney. J. Path Vol. 145, 149-158. Non-GLP, Published	N	Published literature
IIIA, 6.4.1-04	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. Dept of Veterinary Pathology, University of Liverpool. *J Comp Path*, **90**, 233-238. Non-GLP, Published	N	Published literature
IIIA, 6.5-01	Harrisson, J.W.E., Levin, S.E. and Trabin, B.	1954	The safety and fate of potassium sodium copper chlorophyllin and other copper compounds. Lawall and Harrisson Research Laboratories, Philadelphia. *J Amer Pharm Ass*, Vol. XL111, **12**, 722-737. Non-GLP, Published	N	Published literature
IIIA, 6.6.1-01	Ballantyne, M.	1994	Study to determine the ability of copper II sulphate pentahydrate to induce mutation in five histidine-requiring strains of *Salmonella typhimurium*. Hazleton Europe. Report number 456/31. GLP, Unpublished	Y	EUCuTF
IIIA, 6.6.1-02	Marzin, D.R. and Phi, H.V	1985	Study of the mutagenicity of metal derivatives with Salmonella typhimurium TA102. Institute Pasteur de Lille, Laboratoire de Toxicologie Génétique, Lille. *Mutation Research*, **155**, 49-51 Non-GLP, Published	N	Published literature
IIIA, 6.6.3-01	Denizeau, F. and Marion, M.	1989	Genotoxic effects of heavy metals in rat hepatocytes. Dept of Chemistry, University du Québec à Montréal. Cell Biology and Toxicology, 5 (1), 15-25. Non-GLP, Published	N	Published literature
IIIA, 6.6.4-01	Ward, P. J.	1994	Copper II sulphate pentahydrate: measurement of unscheduled DNA synthesis in rat liver using an *in vivo/in vitro* procedure. Hazleton Europe. Report number 456/32 GLP, Unpublished	Y	EUCuTF

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA, 6.6.4-02	Riley, S. E.	1994	Copper II sulphate pentahydrate: induction of micronuclei in the bone marrow of treated mice. Hazleton Europe. Report number 456/33 GLP, Unpublished	Y	EUCuTF
IIIA, 6.6.4-03	Agarwal, K., Sharma, A. and Talukder, G.	1990	Clastogenic effects of copper sulphate on the bone marrow chromosomes of mice in vivo. Centre for Advanced Study in Cell and Chromosome Research, University of Calcutta. *Mutation Research*, **243**, 1-6. Non-GLP, Published	N	Published literature
IIIA, 6.6.4-04	Tinwell, H. and Ashby, J.	1990	Inactivity of copper sulphate in a mouse bone marrow micronucleus assay. ICI Central Toxicology Laboratory, Macclesfield. *Mutation Research*, **245**, 223-226. Non-GLP, Published	N	Published literature
IIIA, 6.6.5-01	Bhunya, S.P. and Pati, P.C.	1987	Genotoxicity of an inorganic pesticide, copper sulphate in mouse *in vivo* test system. Laboratory of Genetic Toxicology, Utkal University, Vani Vihar, India. *Cytologia*, **52**, 801-808. Non-GLP, Published	N	Published literature
IIIA, 6.7-02	Haywood, S.	1980	The effect of excess dietary copper on the liver and kidney of the male rat. J. Comp. Path Vol. 90, 217-232. Non-GLP, Published	N	Published literature
IIIA, 6.7-03	Haywood, S.	1985	Copper toxicosis and tolerance in the rat, I. Changes in copper content of the liver and kidney. J. Path Vol 145, 149-158. Non-GLP, Published	N	Published literature
IIIA, 6.7-04	Haywood, S., and Loughran M.	1985	Copper toxicosis and tolerance in the rat, II Tolerance – a liver protective adaptation. Liver Vol. 5 267-275. Non-GLP, Published	N	Published literature
IIIA, 6.8.1-01	Munley S. M.	2003a	Copper hydroxide: pilot developmental toxicity study in rabbits. Du Pont Haskell Laboratory, report number 11861 GLP, Unpublished	Y	EUCuTF
IIIA, 6.8.1-02	Munley S. M.	2003b	Copper hydroxide: developmental toxicity study in rabbits. Du Pont Haskell Laboratory, report number 11862 GLP, Unpublished	Y	EUCuTF
IIIA, 6.8.1-03	Lecyk, M.	1980	Toxicity of CuSO4 in mice embryonic development. Dept. of Comparative Anatomy, Wrocław University. *Zoologica Poloniae*, **28**, 101-105. Non-GLP, Published	N	Published literature
IIIA, 6.8.2-01	Mylchreest, E.	2005	Copper Sulfate Pentahydrate: Multigeneration Reproduction Study in Rats. Du Pont Haskell Laboratory. Report number 14226 GLP, Unpublished	Y	EUCuTF

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA, 6.9-02	Malhotra, K.M., Shukla, G.S. and Chandra, S.V.	1982	Neurochemical changes in rats co-exposed to lead and copper. Industrial Toxicology Research Centre, Lucknow-226, India. *Archives of Toxicology*, **49**, 331-336. Non-GLP, Published.	N	Published literature
IIIA, 6.12.2-02	Chowdhury, A.K.R., Ghosh, S. and Pal, D	1961	Acute copper sulphate poisoning. J. Indian M.A., **36(8)**, 330- 336. Non-GLP, Published	N	Published literature
IIIA, 6.12.2-03	Chuttani, H.K., Gupta, P.S., Gulati, S. and Gupta, D.N.	1965	Acute copper sulfate poisoning. Dept of Medicine and Pathology, Maulana Azad Medical College, New Delhi. American Journal of Medicine, Vol 39, 849-854. Non-GLP, Published	N	Published literature
IIIA, 6.12.2-04	Walsh, F.M., Bayley, M. and Pearson, B.J.	1977	Acute copper intoxication. Pathophysiology and therapy with a case report. Am J. Dis. Child, **131**, 149 – 151. Non-GLP, Published	N	Published literature
IIIA, 6.12.2-05	Mittal, S.R.	1972	Oxyhaemoglobinuria following copper sulphate poisoning: a case report and review of the literature. Forens.Sci. **1** 245-248. Non-GLP, Published	N	Published literature
IIIA, 6.12.2-06	Araya, M., McGoldrick, M.C., Klevay, L.M., Strain, J.J., Robson, P., Nielsen, F., Olivares, M., Pizarro, F., Johnson, L-A. and Poirier, K	2001	Determination of an acute no-observed adverse effect level (NOAEL) for copper in water. Regulatory Toxicology and Pharmacology **34**, 137-145. Non-GLP, Published	N	Published literature
IIIA, 6.12.2-07	O'Donohue, J.W., Reid, M.A., Varghese, A., Portmann, B. and Williams, R.	1993	Micronodular cirrhosis and acute liver failure due to chronic copper self-intoxication. European Journal of Gastroenterology & Hepatology **5**:561-562 Non-GLP, Published	N	Published literature
IIIA, 6.12.3-02a and 02b	Senter, M.	2007	Personal statement relating to medical surveillance records	N	Manica S.p.A
IIIA, 6.12.4-01	Araya, M., McGoldrick, M.C., Klevay, L.M., Strain, J.J., Robson, P., Nielsen, F., Olivares, M., Pizarro, F., Johnson, L-A. and Poirier, K	2001	Determination of an acute no-observed adverse effect level (NOAEL) for copper in water. Regulatory Toxicology and Pharmacology **34**, 137-145. Non-GLP, Published	N	Published literature

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA, 6.12.4-02	Maddy, K.T, Edmiston, S. and Richmond, D.	1990	Illness, injuries and deaths from pesticide exposures in California 1949-1988. CDPA, Sacramento, USA. Reviews of Environmental Contamination and Toxicology, **114**, 58-122. Non-GLP, Published	N	Published literature
IIIA, 6.12.6-01	Wöhrl, S., Hemmer, W., Focke, M., Götz, M. and Jarisch, R.	2001	Copper Allergy revisited. J. Am. Acad. Dermatol.**45:**863-70. Non-GLP, Published.	N	Published literature
IIIA, 6.13-01	Auerlich, 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. Dept of Animal Science, Michigan State University. (Part Mink Farmer's Research Foundation and Heger Co). *J Anim Sci*, **55**, 337-343. Non-GLP, Published	N	Published literature
IIIA, 6.14-01	Roper, C.S.	2003	The *in vitro* percutaneous absorption of copper from various formulations through human skin. Inveresk Research. Report number 22829. GLP, Unpublished	Y	EUCuTF
IIIA, 6.14-01	Toner, F. and Roper, C.S.	2004	The *in vitro* percutaneous absorption of copper from various formulations through human skin – dermal delivery. Inveresk Research. Report number 23873. GLP, Unpublished.	Y	EUCuTF
IIIA, 6.14-02	Giampietro, Z.	2006	Operator exposure study in copper sulphate and copper plant protection product production area, Manica SpA. Lachiver Laboratori srl, Via Leida, Verona, Italy. Non-GLP, Unpublished	Y	Manica S.p.A
Section 7					
IIIA, 7.1.2.2.2/01	Schäfers, C.	2000	Community level study with copper hydroxide 50% WP in aquatic microcosms. Fraunhofer-Institut for Molecular Biology and Applied Ecology, Report No. URA-001/4-50. GLP, Unpublished.	Y	EUCuTF
IIIA, 7.1.2.2.2/02	Wagemann, R., Barica, J.	1979	Speciation and rate of loss of copper from lakewater with implications to toxicity. Water Research, Vol. 13, pp. 515-523. Non-GLP. Published.	N	Published literature
IIIA, 7.1.2.2.2/03	Masuda, K., Boyd, C.E.	1993	Comparative evaluation of the solubility and algal toxicity of copper sulphate and chelated copper. Aquaculture, Vol. 117, pp. 287-302. Non-GLP, Published.	N	Published literature

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA, 7.1.4.1/02	Allison, J.D. and Allison, T.L.	2005	Partition coefficients for Metals in Surface Water, Soil and Waste. US Environmental Protection Agency, EPA/600/R-05/074, July 2005. Non-GLP, Published.	N	Published literature
IIIA, 7.2.1-01	Cetois, A., Quesnoit, M., Hinsinger, P.	2003	Soil copper mobility and bioavailability – a review, Section 1 and 2. ENSA.M-INRA-UMR Rhizosphère & Symbiose. Non-GLP, Unpublished.	Y	EUCuTF
IIIA, 7.2.1-02	Ferrier, F.	Not stated	Fate and behaviour of copper in soil. Elf Atochem Agri S.A. Non-GLP, Unpublished.	Y	EUCuTF
IIIA, 7.2.1-03	Chlopecka, A.	1993	Forms of trace metals from inorganic sources in soils and amounts found in spring barley, Water, Air and Soil Pollution, Vol. 40, pp 127-134. Non-GLP, Published.	N	Published literature
IIIA, 7.2.1-04	Römkens, P.F., Salomons, W.	1993	The non-applicability of the simple K_d - approach in modelling trace metal behaviour; a field study. Heavy metals in the environment, International conference, Vol. 2, pp 496-499. Non-GLP, Published.	N	Published literature
IIIA, 7.2.1-05	Strumpf, Th., Traulsen, B.D., Pestemer, W.	2000a	Final report on the study: Availability of copper in soils used for agriculture. BBA Institute of Ecological Chemistry, Berlin. Non-GLP, Unpublished.	Y	EUCuTF
IIIA, 7.2.2.3-01	Lock, K., Janssen, R.	2003	Influence of ageing on metal availability in soils. Reviews of environmental contamination and toxicology, Vol. 178: pp 1-21. Non-GLP. Published.	N	Published literature
IIIA, 7.2.3.1-01	McLaren, R.G., Crawford D.V	1973	Studies on soil copper II. The specific adsorption of copper by soils. Journal of Soil Science, Vol. 24, No. 4, pp. 443-452. Non-GLP, Published.	N	Published literature
IIIA, 7.2.3.1-02	Alberti, G., Cristini, A., Loi, A., Melis, P., Pilo, G.	1997	Copper and lead sorption by different fractions of two Sardinian soils. Proceedings of the 3rd International Conference on the Biogeochemistry of Trace Elements, INRA. Paris. Non-GLP, Published.	N	Published literature
IIIA, 7.2.3.1-03	Díaz-Barrientos, E., *et al.*	2003	Copper and zinc retention by an organically amended soil. Chemosphere, Vol. 50, pp. 911-917. Non-GLP, Published.	N	Published literature

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA, 7.2.3.1-04	Bolan. N, Adriano, D., Mani, S., Khan, A.	2003	Adsorption, complexation and phytoavailability of copper as influenced by organic manure. Environmental toxicology and chemistry, Vol. 22, No. 2, pp-450-456. Non-GLP, Published.	N	Published literature
IIIA, 7.2.3.1-05	Sauvé, S., Hendershot, W. and Allen, H.	2000	Solid-Solution Partitioning of Metals in Contaminated Soils: Dependence on pH, Total Metal Burden, and Organic Matter. Environmental Science and Technology Vol 34 No. 7, pp-1125-1131. Non-GLP, Published.	N	Published literature
IIIA, 7.2.3.2-01	Cetois, A., Quesnoit, M., Hinsinger, P.	2003	Soil copper mobility and bioavailability – a review, Section 3. ENSA.M-INRA-UMR Rhizosphère & Symbiose. Non-GLP, Unpublished.	Y	EUCuTF
IIIA, 7.2.3.2-02	Mathur, S.P., Sanderson, R.B.	1984	The effect of copper applications on the movement of copper and other elements in organic soils. Water, Air and Soil Pollution, Vol. 22, pp. 277-288. Non-GLP, Published.	N	Published literature
IIIA, 7.2.3.2-03	Strumpf, Th., Traulsen, B.D., Pestemer, W.	2000b	Quantification of copper by compact lysimeters test after Funguran application in highly copper-contaminated farmland soil. BBA Institute for Ecological Chemistry, Berlin. Non-GLP, Unpublished.	Y	EUCuTF
IIIA, 7.2.3.2-04	Antic, T.	1992	Part A: Leaching test for the following preparations: URA-08740-F-0-WP – URA-06180-F-0-SC. Experimental part of study. Establishment of leaching water for the validation of the method of analysis. Spiess-Urania Agrochem GmbH, Report No. C91VSF01 GLP, Unpublished. Part B: Final report. Analysis by residue U91AWF01. Determination of copper in leaching water, Report No. U91AWF01. Spiess-Urania Agrochem GmbH. GLP. Unpublished.	Y	EUCuTF
IIIA, 7.2.3.2-05	Lemnitzer, B.	2000	Soil leaching study with URA-08740-F-0-WP. Spiess-Urania Chemicals GmbH, Report No. 00 10 35 901. GLP, Unpublished.	Y	EUCuTF
IIIA, 7.4.1.1-01	Murray-Gulde, C.L., Heatley, J.E., Schwartzman, A.L., Rodgers Jr., J.H.	2002	Algicidal effectiveness of Clearigate, Cutrine-Plus and copper sulfate and margins of safety associated with their use. Archives of Environmental Contamination and Toxicology, 43, 19 – 27. Non-GLP, Published	N	Published literature

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA, 7.4.1.2-01	Mastin, B.J., Rodgers Jr., J.H.	2000	Toxicity and bioavailability of copper herbicides (Clearigate, Cutrine-Plus, and copper sulfate) to freshwater animals. Archives of Environmental Contamination and Toxicology, 39, 445 – 451. Non-GLP, Published.	N	Published literature
IIIA, 7.4.1.3-01	Murray-Gulde, C.L., Heatley, J.E., Schwartzman, A.L., Rodgers Jr., J.H.	2002	Algicidal effectiveness of Clearigate, Cutrine-Plus and copper sulfate and margins of safety associated with their use. Archives of Environmental Contamination and Toxicology, 43, 19 – 27. Non-GLP, Published	N	Published literature
IIIA, 7.4.1.3-02	Radix, P., Léonard, M., Papantoniou, C., Roman, G., Saouter, E., Gallotti-Schmitt, S., Thiébaud, H., Vasseur, P.	2000	Comparison of four chronic toxicity tests using algae, bacteria, and invertebrates assessed with sixteen chemicals. Ecotoxicology and Environmental Safety 47, 186 – 194 (2000) Non-GLP, Published	N	Published literature
IIIA, 7.4.1.4-01	Noack, M.	2000	Copper oxychloride: Respiration inhibition test with activated sludge. Dr U. Noack Laboratorium, Report number BBR73981. GLP, Unpublished	N	Published literature
IIIA, 7.4.1.4-02	Fiebig, S., Noack, U.	2004	The use of copper (II) sulphate pentahydrate as reference substance in the activated sludge respiration inhibition test acc. to the OECD guideline 209. Fresenius Environmental Bulletin, Volume 13, No. 12b, 1556 - 7 Non-GLP, Published	N	Published literature
IIIA, 7.4.2-01	Janus, J.A., Canton, J.H., van Gestel, C.A.M., Heijna-Merkus, E.	1989	Integrated Criteria Document Copper, Effects. Appendix to Report No. 758474009. National Institute of Public Health and Environmental Protection, Bilthoven, The Netherlands. Non-GLP, Unpublished.	N	Published literature
IIIA, 7.4.2-02	McGreer, J.C., Brix, K.V., Skeaff, J.M., DeForest, D.K., Brigham, S.I., Adams, W.J., Green, A.	2003	Inverse relationship between bioconcentration factor and exposure concentrations for metals: implications for hazard assessment of metals in the aquatic environment. Environmental Toxicology and Chemistry, Vol. 22, No.5, 1017 – 1037, 2003 Non-GLP, Published.	N	Published literature
IIIA, 7.4.3-01	Schäfers, C.	2000	Community level study with copper hydroxide 50% WP in aquatic microcosms. Fraunhofer-Institut for Molecular Biology and Applied Ecology, Report No. URA-001/4-50. GLP, Unpublished.	Y	EUCuTF

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA, 7.4.3.1-01	Mudge, J.E., Northstrom, T.E., Jeane, G.S., Davis, W., Hickam, J. L.	1993	Effects of varying environmental conditions on the toxicity of copper to salmon Environmental Toxicology and Risk Assessment: 2nd Volume, STP 1216 Gorsuch, J.W., Dwyer, F.J., Ingersoll, G.G., La Point, T.W. eds. American Society for Testing Materials, Philadelphia Non-GLP, Published	N	Published literature
IIIA, 7.4.3.2-01	Marr, J.C.A., Lipton, J., Cacela, D., Hansen, J.A., Bergman, H.L., Meyer, J.S. & Hogstrand, C.	1996	Relationship between copper exposure duration, tissue concentration and rainbow trout growth Aquatic Toxicology 36 (1996) 17-30 Non-GLP, Published	N	Published literature
IIIA, 7.4.3.4-01	Radix, R., Leonard, M., Papantoniou, C., Roman, G., Saouter, E., Gallotti-Schmitt, S., Thiebald, H., Vasseur, P.	2000	Comparison of four chronic toxicity tests using algae, bacteria, and invertebrates assessed with sixteen chemicals. Ecotoxicology and Environmental Safety 47, 186 – 194 (2000). Non-GLP, Published	N	Published literature
IIIA, 7.5.1.1-01	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 Pollut. 4, 159 – 163, 1973 Non-GLP, Published.	N	Published literature
IIIA, 7.5.1.2-01	Phillips, C.T., Checkai, R.T.	1996	Standardized earthworm toxicity testing: comparison of artificial soil vs natural soil using selected chemical pollutants on the earthworm *Eisenia foetida* Proceedings of the ERDEC Scientific Conference on Chemical and Biological Defense Research, Aberdeen Proving Ground, Md., Nov. 14-17, 1995, Meeting Date 1995, 685-691. Editor: Berg, Dorothy A. Non-GLP, Published	N	Published literature
IIIA, 7.5.1.3-01	International Copper Association	1999	Effects of Copper in terrestrial systems, a literature summary International Copper Association (1999) ISBN: 0-943642-12-7 Non-GLP, Published	N	Published literature
IIIA, 7.5.1.3-02	Hunter, B.A., Johnson, M.S., Thompson, D.J.	1987	Ecology of copper and cadmium in a contaminated grassland ecosystem. I – Soil and vegetation contamination Journal of Applied Ecology (1987) 24, 573 - 586 Non-GLP, Published	N	Published literature

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIA, 7.5.1.3-03	Powell, J.C., Lyons, C.G.	1995	Effects of copper, zinc, and sulfur application to peach trees on coastal plain soil. Commun. Soil Sci. Plant Anal. (1995) 26 (9&10), 1637-1648 Non-GLP, Published	N	Published literature
IIIA, 7.5.1.3-04	Tikhomirov, F.A., Magina, L.G., Kiseleva, E.V.	1988	Effect and after effect on plants of high copper and nickel concentrations in soil. Moscow University Soil Science Bulletin (1988) 43, 24 - 27 Non-GLP, Published	N	Published literature
IIIA, 7.5.1.3-05	Wong, M.H., Bradshaw, A.D.	1982	A comparison of the toxicity of heavy metals, using root elongation of rye grass, *Lolium perenne*. New Phytologist (1982) 91, 255 – 261 Non-GLP, Published	N	Published literature
IIIA, 7.5.1.3-06	Mozaffari, M, Alva, A.K., Chen, E.Q.	1996	Relation of copper extractable from soil and pH to copper content and growth of two citrus rootstocks Soil Science (1996) 161, 786 – 792 Non-GLP, Published	N	Published literature
IIIA, 7.5.1.3-07	Graham, J.H., Timmer, L.W., Fardelmann, D.	1986	Toxicity of fungicidal copper in soil to citrus seedlings and vesicular-arbuscular mycorrhizal fungi. Phytopathology (1986) 76, 66 – 70 Non-GLP, Published	N	Published literature
IIIA, 7.5.1.3-08	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 (1994) 64, 285 – 289 Non-GLP, Published	N	Published literature
IIIA, 7.5.1.3-09	Ali, N.A., Ater, M., Sunahara, G.I. and 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 57 (2004) 64, 363-374 Non-GLP, Published	N	Published literature
IIIA, 7.5.2.1-01	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 (1994) 123 – 130. Non-GLP, Published	N	Published literature
Section 8	No studies submitted				
Section 9	No studies submitted.				
Section 10	No studies submitted.				

Part B: Reference list of studies submitted (by Section No.)

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
Section 1	No studies submitted.				
Section 2	No studies submitted.				
Section 3					
IIIB, 3.1.1-01	Garofani, S.	2008a	IONX CU WB50: determination of the physico-chemical properties ChemService Srl Report number CH – 319/2007 GLP, Unpublished.	Y	Manica S.p.A.
IIIB, 3.1.2-01	Garofani, S.	2008a	IONX CU WB50: determination of the physico-chemical properties ChemService Srl Report number CH – 319/2007 GLP, Unpublished.	Y	Manica S.p.A.
IIIB, 3.1.3-01	Garofani, S.	2008a	IONX CU WB50: determination of the physico-chemical properties ChemService Srl Report number CH – 319/2007 GLP, Unpublished.	Y	Manica S.p.A.
IIIB, 3.4-01	Garofani, S.	2008a	IONX CU WB50: determination of the physico-chemical properties ChemService Srl Report number CH – 319/2007 GLP, Unpublished.	Y	Manica S.p.A.
IIIB, 3.5-01	Garofani, S.	2008a	IONX CU WB50: determination of the physico-chemical properties ChemService Srl Report number CH – 319/2007 GLP, Unpublished.	Y	Manica S.p.A.
IIIB, 3.5-02	Garofani, S.	2008a	IONX CU WB50: determination of the physico-chemical properties ChemService Srl Report number CH – 319/2007 GLP, Unpublished.	Y	Manica S.p.A.
IIIB, 3.6-01	Garofani, S.	2008a	IONX CU WB50: determination of the physico-chemical properties ChemService Srl Report number CH – 319/2007 GLP, Unpublished.	Y	Manica S.p.A.
IIIB, 3.7-01	Garofani, S.	2008a	IONX CU WB50: determination of the physico-chemical properties ChemService Srl Report number CH – 319/2007 GLP, Unpublished.	Y	Manica S.p.A.
IIIB, 3.7-02	Garofani, S.	2008b	IONX CU WB50: determination of the accelerated storage stability and corrosion characteristics ChemService Srl Report number CH – 319/2007 GLP, Unpublished.	Y	Manica S.p.A.

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIB, 3.7-03	Garofani, S.	2009	IONX Cu WB 50: Two years storage stability and corrosion characteristics ChemService Srl Report number CH – 322/2007 GLP, Unpublished.	Y	Manica S.p.A.
		2010	& Amendment 1		
IIIB, 3.8-01	Garofani, S.	2008a	IONX CU WB50: determination of the physico-chemical properties ChemService Srl Report number CH – 319/2007 GLP, Unpublished.	Y	Manica S.p.A.
IIIB, 3.8-02	Garofani, S.	2008a	IONX CU WB50: determination of the physico-chemical properties ChemService Srl Report number CH – 319/2007 GLP, Unpublished.	Y	Manica S.p.A.
IIIB, 3.10-01	Garofani, S.	2008a	IONX CU WB50: determination of the physico-chemical properties ChemService Srl Report number CH – 319/2007 GLP, Unpublished.	Y	Manica S.p.A.
IIIB, 3.11-01	Garofani, S.	2008a	IONX CU WB50: determination of the physico-chemical properties ChemService Srl Report number CH – 319/2007 GLP, Unpublished.	Y	Manica S.p.A.
Section 4					
IIIB, 4.1-02	Garofani, S.	2008c	Ionx CU WB50: Validation of the analytical method for the determination of the active ingredient content. ChemService Srl Report number CH – 320/2007 GLP, Unpublished.	Y	Manica S.p.A.
Section 5					
IIIB, 5.10.2-01	Anon	nd	Final report on the testing of copper compounds coded AL42; PC 33; WB 50 versus the following target organisms: Methicillin resistant *Staphylococcus aureus* (MRSA) *Acinetobacter calcoaceticus-baumanii* (ACCB) *Enterococcus sp.* (vancomycin resistant) (VRE) Spores of *Clostridium difficile* (CDIFF) *Legionella pneumophila* (LPn) Non-GLP, Unpublished.	Y	Ionx Technologies

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIB, 5.10.2-02	Wren, M.W.D, Hall, T.J	2006	Preliminary studies on the effect of a copper metallo-ion formulation on washing of contaminated nursing uniform material with Ariel detergent University College Hospital, London Report number UCL 002/2006 Non-GLP, Unpublished.	Y	Ionx Technologies
IIIB, 5.10.2-03	Crane, E.	2008	Chemicals, disinfectants and antiseptics – basic bacterial activity (phase 1) MGS Laboratories, Report No. 16114/SO No. 1568 Non-GLP, Unpublished.	Y	Healthcare Initial
IIIB, 5.10.2-04	Crane, E.	2008	Chemicals, disinfectants and antiseptics – basicfungicidal activity (phase 1) MGS Laboratories, Report No. 16114/SO No. 1568 Non-GLP, Unpublished.	Y	Healthcare Initial
IIIB, 5.10.2-05	Crane, E.	2008	Quantitative suspension test for the evaluation of fungicidal activity of chemical disinfectants and antiseptics (phase 2/step 1) MGS Laboratories, Report No. 16114/SO No. 1568 Non-GLP, Unpublished.	Y	Healthcare Initial
IIIB, 5.10.2-06 (a) – (k)	Hall, T.J.	2008	Are EN tests outdated and preventing the development of innovative new biocides? Positon paper , supporting letter and papers	N	Public domain
IIIB, 5.10.2-07	Woodall, C.	2009	EN 14476:2005 Chemical disinfectants and antiseptics – Virucidal quantitative suspension test for chemical disinfectants and antiseptics used in human medicine – Test method and requirements (phase 2/step 1). BuScientific Test Data, Glasgow, UK, Report No. BS-MGS-002	Y	Healthcare Initial
IIIB, 5.10.2-08	Humphreys, P.	2009	Bactericidal activity of the Remedy Research Products CuWB50 determined using the European Standard Test Method BS EN 1040:2005 University of Huddersfield Report No. HMS/RR/8/09 Non-GLP, Unpublished.	Y	Remedy Research Ltd.
IIIB, 5.11-01	Hall, T.J.	2009	Bacterial resistance to copper – Summary report Positon paper	N	Public domain
Section 6					

Section No / Reference No	Author(s)	Year	Title. Source (where different from company) Company, Report No. GLP (where relevant) / (Un)Published	Data Protection Claimed (Yes/No)	Owner
IIIB, 6.1.1-01	Wolf, T.	2007a	Ionx CUWB50: Acute oral toxicity study with rats (Acute toxic class method) Austrian Research Centers GmbH, ARC Life Sciences / Toxicology Study number ARC- L-2715 GLP, Unpublished.	Y	Manica S.p.A.
IIIB, 6.1.2-01	Wolf, T.	2007b	Ionx CU WB50: Acute dermal toxicity study with rats Austrian Research Centers GmbH, ARC Life Sciences / Toxicology Study number ARC- L-2716 GLP, Unpublished.	Y	Manica S.p.A.
IIIB, 6.2-01	Wolf, T.	2007c	Ionx CUWB50: Acute dermal irritation/corrosion study with rabbits Austrian Research Centers GmbH, ARC Life Sciences / Toxicology Study number ARC- L-2717 GLP, Unpublished	Y	Manica S.p.A.
IIIB, 6.3-01	Eberhart-Sattler, K	2008	Ionx CU WB50: Skin sensitisation study (Guinea pig Maximisation Test) Austrian Research Centers GmbH, ARC Life Sciences / Toxicology Study number ARC- L-2806 GLP, Unpublished	Y	Manica S.p.A.
Section 7	No studies submitted				
Section 8	No studies submitted				
Section 9	No studies submitted.				
Section 10	No studies submitted.				

.