EFSA Scientific Report **(2008) 187, 1-101**
Conclusion on the peer review of copper compounds

CONCLUSION ON PESTICIDE PEER REVIEW

Conclusion regarding the peer review of the pesticide risk assessment of the active substance

Copper (I), copper (II) variants namely copper hydroxide, copper oxychloride, tribasic copper sulfate, copper (I) oxide, Bordeaux mixture.

Issued on 30 September 2008

SUMMARY

Copper (I), copper (II) variants (formerly referred to as copper compounds) are one of the 79 substances of the third stage Part A of the review programme covered by Commission Regulation (EC) No 1490/2002[1]. This Regulation requires the European Food Safety Authority (EFSA) to organise upon request of the EU-Commission a peer review of the initial evaluation, i.e. the draft assessment report (DAR), provided by the designated rapporteur Member State and to provide within six months a conclusion on the risk assessment to the EU-Commission.

France being the designated rapporteur Member State submitted the DAR on copper (I), copper (II) variants in accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, which was received by the EFSA on 7 June 2007. The peer review was initiated on 17 September 2007 by dispatching the DAR for consultation of the Member States and the sole applicant the European Union Copper Task Force. Subsequently, the comments received on the DAR were examined and responded by the rapporteur Member State in the reporting table. This table was evaluated by EFSA to identify the remaining issues. The identified issues as well as further information made available by the applicant upon request were evaluated in a series of scientific meetings with Member State experts in May – June 2008.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in July – August 2008 leading to the conclusions as laid down in this report.

This conclusion was reached on the basis of the evaluation of the representative uses as a fungicide/bactericide on grapes and tomatoes. Full details of the GAP can be found in the attached list of endpoints.

[1] OJ No L 224, 21.08.2002, p. 25, as amended by Regulation (EC) No 1095/2007 (OJ L 246, 21.9.2007, p. 19)

The representative formulated products for the evaluation were "Kocide 101" (copper hydroxide), a wettable powder formulation containing 500 g/kg of Cu; “Macc 80” (Bordeaux mixture), a wettable powder formulation containing 200 g/kg of Cu; “Cuprocaffaro WP” (copper oxychloride), a wettable powder formulation containing 500 g/kg of Cu; “Cuproxat SC” (tribasic copper sulfate), a suspension concentrate formulation containing 193 g/L of Cu and “Nordox 75 WG “ (copper (I) oxide), a wettable granule formulation containing 750 g/kg Cu.

Only single methods for the determination of residues are available since a multi-residue-method like the German S19 or the Dutch MM1 is not applicable due to the nature of the residues.
Sufficient data relating to physical, chemical and technical properties are available to ensure that at least some quality control measurements of the plant protection product are possible. The methods of analysis for the technical materials and the formulations are not accepted at this time as the identity of the various variants of copper are in question. The specifications and batch data are not accepted. In addition to this, there are some missing physical and chemical properties as well as storage stability data for the variants of copper.

In the mammalian metabolism studies, bioequivalence was established for the five representative copper (I) and (II) variants with copper sulphate pentahydrate, with which most of the toxicological studies were conducted. As a micronutrient essential for life, copper follows a specific homeostatic regulation mechanism, which allows excess copper to be excreted mainly through the bile; once absorbed, copper is bound to proteins so that free copper is normally not found neither in the blood, nor in the cells.
Copper hydroxide is toxic by inhalation, harmful if swallowed and present a risk of serious damage to eyes. Bordeaux mixture is harmful by inhalation and presents a risk of serious damage to eyes. Copper oxychloride and copper (I) oxide are harmful by inhalation and if swallowed. Tribasic copper sulphate is harmful if swallowed. Target organs of excess copper after oral administration are the liver and the kidneys. A concern was raised over inhalation of copper as lung lesions found in operator exposure were reproducible in guinea pigs; a data gap was identified for a short term inhalation toxicity study. Genotoxicity was not of concern upon oral administration, however, there was insufficient evidence to exclude a genotoxic potential of copper after non-oral exposure, and a critical area of concern was raised after inhalation of copper (I) and (II) variants. No carcinogenic potential was attributed to copper, neither in rats nor in humans. Copper did not produce adverse effect on fertility, reproductive parameters or on the development; no neurotoxicity was attributed to copper ingestion, either. Four categories of copper poisoning were identified in the literature, namely direct oral ingestion as suicide attempts, cases where food or drinking water had become contaminated with copper, cases where home-made Bordeaux mixture had resulted in lung disease, and a single case of long term administration of excess copper as a dietary supplement resulting in liver failure.

Based on the WHO values established for human copper intake, the Acceptable Daily Intake (ADI) – or more appropriately designated as “upper limit for copper intake” - for copper (I) and (II) variants was 0.15 mg Cu/kg bw/day, the Acceptable Operator Exposure Level (AOEL) was 0.072 mg Cu/kg bw/day and no Acute Reference Dose (ARfD) was allocated. Default value of 10 % for dermal absorption was set for the five concentrate representative formulations and the in-use spray dilutions. Operator exposure calculated for field applications was below the AOEL only, if personal protective equipment (PPE) was used; for greenhouse applications, estimated operator exposure was below the AOEL only, if a respiratory protective equipment (RPE) was added to the PPE. Unprotected bystander exposure was calculated to be below the AOEL for all proposed uses and all representative formulations. Estimates of worker exposure indicated that exposure to copper (I) and (II) variants may exceed the AOEL for workers wearing protective gloves, long sleeved shirt and long trousers in some scenarios of application. Therefore, a refinement of worker risk assessment is required for those specific scenarios.

Data presented and evaluated on the uptake, translocation and nature of copper residues in plants consist mainly of a review of public scientific literature. To determine the magnitude of residues in the treated raw agricultural commodities, residue trials in grapes and tomatoes were submitted. Also data on the residue levels in processed tomato and grape products were made available, but only found valid and acceptable for grapes. The data allow for MRL proposals and for a consumer exposure assessment with regard to the notified representative uses.
As exposure to copper is not only due to residues from the use as a plant protection product, an aggregate exposure assessment was performed by the rapporteur Member State, including in addition background levels of copper in food and drinking water, based on a recent French dietary survey. This aggregate estimate shows that, in particular for children, the overall dietary copper exposure is not negligible and approximates the established toxicological reference value. Additional potential sources of dietary copper intakes have not been considered. Moreover, the estimate is not representative for all European consumers and therefore situations may arise where the overall copper intake of some consumer groups exceeds the toxicological reference value.

The data presented in the dossier and summarized in the DAR on the fate and behaviour of copper in soil consist mainly of a review of public scientific literature. Although the information is qualitatively complete, it does not allow deriving quantitative parameters to perform a proper environmental risk assessment. Data gaps have been identified by the rapporteur Member State for accumulated PEC soil, $PEC_{SW/SED}$ and PEC_{GW} values as well as for the experimental (laboratory, field or monitoring) data to asses them. The data gaps have been confirmed by the peer review.

The representative uses of the various copper variants are applications to vines and tomatoes (outdoor and indoor). The risk to herbivorous birds from the use in tomatoes was considered low since the tomato foliage is not palatable to birds. The first-tier acute, short-term and long-term TERs for insectivorous birds were below the Annex VI trigger values for all representative uses. The refined risk assessment suggests a low acute and short-term risk to birds, but further refinement is needed for the long-term risk assessment.

The first-tier long-term TERs for earthworm-eating birds and mammals were below the Annex VI trigger of 5. No further information was provided to refine the risk assessment and a data gap was identified in the meeting of experts.

The first-tier risk assessment for mammals indicated a potential high acute and long-term risk. The refined risk assessment submitted by the applicant was not transparent. It was not clear which refinements were taken into account and no information/data were provided to support the refined acute and long-term risk assessment. Therefore, a data gap was identified for a refined risk assessment for mammals where all refinement steps are transparent and supported by information/data. The risk to birds and mammals from the use in tomatoes in glasshouse is considered to be low because of negligible exposure.

Copper is very toxic to the aquatic organisms. An indoor-microcosm study was submitted to address the risk to aquatic invertebrates. The experts suggested using a NOEC of 3.12 µg Cu (dissolved)/L together with a safety factor of 3-5 to take into account uncertainties related to effects on chironomids and possible favourable exposure conditions in the microcosm (high pH). Information from public literature suggests a high potential of bioaccumulation of copper in some aquatic organisms. The potential risk of bioaccumulation in fish needs to be addressed further. A data gap was identified in the meeting to address the risk from bioaccumulation in aquatic organisms.

The risk assessment for aquatic organisms needs to be finalized once reliable PECsw/sed values are established for the outdoor uses of copper in tomato and vines. The risk to aquatic organisms from the use in tomato in glasshouse is considered to be low.

The risk to bees from contact exposure was assessed as low, except for copper oxychloride and the Bordeaux mixture. The risk to bees from oral exposure was assessed as high in the first-tier risk assessment, and the experts suggested a data gap to address the risk to bees further.

A high long-term risk to earthworms was indicated on the basis of the available information. A data gap was identified to address the long-term risk to earthworms.

Information from published studies with soil macro-organisms was submitted by the applicant. The studies were considered as reliable and robust enough to be considered in the risk assessment.

No effects of >25% on soil nitrification were observed up to the highest tested application rate of 20 kg Cu/ha. A reduction of 29 % in carbon mineralization was observed on day 28, at an application rate of 12.5 kg Cu/ha in a study with copper hydroxide. However, a final conclusion on the risk to soil macro- and micro-organisms can only be drawn after reliable PECsoil values have been established.

The assessment of the risk to non-target plants is based on information from public literature. It was not possible for the experts to draw a conclusion on the reliability of the studies. The experts agreed that a more comprehensive summary of the literature information is needed. Furthermore, the accumulation of copper in the off-field area should be considered in the risk assessment.

The risk to non-target arthropods and to biological methods of sewage treatment was assessed as low for the representative uses evaluated.

Key words: Copper (I), copper (II) variants, peer review, risk assessment, pesticide, fungicide, bactericide.

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BACKGROUND

Commission Regulation (EC) No 1490/2002 laying down the detailed rules for the implementation of the third stages of the work program referred to in Article 8(2) of Council Directive 91/414/EEC and amending Regulation (EC) No 451/2000, as amended by Commission Regulation (EC) No 1095/2007 regulates for the European Food Safety Authority (EFSA) the procedure of evaluation of the draft assessment reports provided by the designated rapporteur Member State. Copper (I), copper (II) variants are one of the 79 substances of the third stage, part A, covered by the Regulation (EC) No 1490/2002 designating France as rapporteur Member State.

In accordance with the provisions of Article 10(1) of the Regulation (EC) No 1490/2002, France submitted the report of its initial evaluation of the dossier on copper (I), copper (II) variants, hereafter referred to as the draft assessment report, received by EFSA on 7 June 2007. Following an administrative evaluation, the draft assessment report was distributed for consultation in accordance with Article 11(2) of the Regulation (EC) No 1490/2002 on 17 September 2007 to the Member States and the main applicant, the European Union Copper Task Force, as identified by the rapporteur Member State.

The comments received on the draft assessment report were evaluated and addressed by the rapporteur Member State. Based on this evaluation, EFSA identified and agreed on lacking information to be addressed by the notifier as well as issues for further detailed discussion at expert level.

Taking into account the requested information received from the notifier, a scientific discussion took place in experts' meetings in May-June 2008. The reports of these meetings have been made available to the Member States electronically.

A final discussion of the outcome of the consultation of experts took place during a written procedure with the Member States in July-August 2008 leading to the conclusions as laid down in this report.

During the peer review of the draft assessment report and the consultation of technical experts no critical issues were identified for consultation of the Scientific Panel on Plant Protection Products and their Residues (PPR).

In accordance with Article 11c (1) of the amended Regulation (EC) No 1490/2002, this conclusion summarises the results of the peer review on the active substance and the representative formulation evaluated as finalised at the end of the examination period provided for by the same Article. A list of the relevant endpoints for the active substance as well as the formulation is provided in appendix 1.

The documentation developed during the peer review was compiled as a **peer review report** comprising of the documents summarising and addressing the comments received on the initial evaluation provided in the rapporteur Member State's draft assessment report:

- the comments received;
- the resulting reporting table (revision 1-2 of 1 April 2008)

as well as the documents summarising the follow-up of the issues identified as finalised at the end of the commenting period:

- the reports of the scientific expert consultation;
- the evaluation table (revision 2-1 of 29 September 2008).

Given the importance of the draft assessment report including its addendum (compiled version of July 2008 containing all individually submitted addenda) and the peer review report with respect to the examination of the active substance, both documents are considered respectively as background documents A and B to this conclusion.

By the time of the presentation of this conclusion to the EU-Commission, the rapporteur Member State has made available amended parts of the draft assessment report which take into account mostly editorial changes. Since these revised documents still contain confidential information, the documents cannot be made publicly available. However, the information given can be found in the original draft assessment report together with the peer review report, both of which are publicly available.

THE ACTIVE SUBSTANCE AND THE FORMULATED PRODUCT

The active substance is the Cu ion; it is currently unclear if its oxidative state has a bearing on its biological activity. There is no ISO common name. The variants of copper that were considered in the DAR were copper hydroxide, Bordeaux mixture, copper oxychloride, tribasic copper sulfate and copper (I) oxide.

The meeting concluded that the generic term 'copper compounds' was not a proper way of describing what had been considered in the DAR. The meeting of experts agreed that the active substance should be called copper (I), copper (II) variants.

Copper-(II) ion (Cu++) is taken up by the spores during germination and accumulates until a sufficiently high concentration is achieved to kill the spore cell; the activity is limited to the prevention of spore germination. It is a foliar fungicide with preventive action. Deposits must be on the crop before fungal spores begin to germinate. Similar behaviour is expected in bacterial cells. The activity of copper (I) is probably achieved by conversion to copper (II).

The evaluated representative uses are as a fungicide/bactericide on grapes and tomatoes. Full details of the GAP can be found in the attached list of endpoints.

SPECIFIC CONCLUSIONS OF THE EVALUATION

1. Identity, physical/chemical/technical properties and methods of analysis

The minimum purities of the copper variants as manufactured were not agreed by the PRAPeR 46 meeting of experts. The identity of the copper variants was not proven, and all the batch data were unacceptable as the closure was very poor. FAO specifications exist for copper hydroxide, copper oxychloride and copper (I) oxide; there is no FAO specification for Bordeaux mixture and tribasic copper sulfate. It is probable that the heavy metal impurities in these compounds will be relevant impurities, however, this cannot be concluded on at this point. It was also considered that the methods of manufacture for Bordeaux mixture and copper (I) oxide are missing.

Beside the specification and identity, the assessment of the data package revealed no issues that need to be included as critical areas of concern with respect to the physical, chemical and technical properties of the copper variants or their respective formulations. However, the following data gaps were identified:

<u>Bordeaux mixture formulated plant protection product “Macc 80 WP”</u>
A 2-year shelf-life study was identified as a data gap, although it is noted that a study is available but not peer reviewed. This is also the case for particle size distribution. It was also noted in the peer review that the wettability is poor.

<u>Copper hydroxide formulated plant protection product “Kocide 101”</u>
A 2-year shelf-life study was identified as a data gap, although it is noted that a study is available but not peer reviewed. It was also noted in the peer review that the wettability is poor.

<u>Copper oxychloride formulated plant protection product “Cuprocaffaro WP”</u>
A 2-year shelf-life study was identified as a data gap, although it is noted that a study is available but not peer reviewed. This is also the case for particle size distribution.

<u>Tribasic copper sulfate formulated plant protection product “Cuproxat SC”</u>
The meeting concluded that, since this is a liquid based formulation, it could be possible that the copper variant could change during storage (the other formulations are solid WP and WG). The following data gap was identified: Evidence must be produced showing that the copper variant tribasic copper sulfate is stable over a two-year period.

Copper (I) oxide formulated plant protection product "Nordox 75 WG"

A 2-year shelf-life study was identified as a data gap, although it is noted that a study is available, but not peer reviewed. Also attrition and dispersibility were identified as data gaps.

A specific method to identify copper (I) oxide in the formulation was identified as a data gap. Also the conversion rate of copper (I) to copper (II) was not available for the peer review, however, it is noted that a position paper is available.

The main data regarding the identity of the copper variants, as well as their physical and chemical properties are given in appendix 1.

The methods of analysis for the formulation and the technical material in general are not concluded on because of the issue of identity. Therefore, insufficient data are available for the full quality control of the plant protection products.

Adequate methods are available to monitor total copper in plant material (tomato and grapes), total copper in soil and air and soluble copper in water.

Plants are analysed by atomic absorption spectrophotometry (AAS) with an LOQ of 2 mg/kg for tomatoes and 5 mg/kg for grapes. Soil and air are also analysed by AAS with an LOQ of 40 mg/kg for soil (it is currently not clear if the LOQ for soil is low enough), and an LOQ of 0.5 ng/m^3 for air. A second method for air is available by ICP/OES with a LOQ of 0.3 ng/m^3. The method for water is the published method DIN 38406 with an LOQ of 0.1 µg/L. A method of analysis for products of animal origin is not required because no MRLs will be set.

As the variant copper hydroxide is classified as toxic, a method of analysis for body fluids and tissues is available. The method is inductively coupled plasma optical emission spectrometer (ICP-OES) with an LOQ of 0.02 mg/L.

2. Mammalian toxicology

Copper (I) and (II) variants were discussed at the PRAPeR meeting of experts on mammalian toxicology (PRAPeR 49) in June 2008.

No analysis of the impurity profile of the batches used in the toxicological studies is available; it was noted by the meeting on physical and chemical properties, section 1 (PRAPeR 41) that there is no agreed technical specification. Apart from heavy metals, the experts did not foresee any concern over impurities declared in the proposed technical specification; therefore no further information was required on the toxicological batches. However, as no information is available on heavy metals, a data gap was set for the applicant to present a statement on the maximum concentration levels of heavy metals in copper specification considering the available toxicological data.

2.1. ABSORPTION, DISTRIBUTION, EXCRETION AND METABOLISM (TOXICOKINETICS)

The following considerations for copper as a micronutrient are highlighted:
Copper has been the subject of extensive research. It is widely distributed in biological tissues, where it occurs largely in the form of organic complexes, many of which are metalloproteins and function as enzymes. Copper enzymes are involved in a variety of metabolic reactions, such as the utilization of oxygen during cell respiration and energy utilization. They are also involved in the synthesis of essential compounds, such as the complex protein of connective tissues of the skeleton and blood vessels, and in a range of neuroactive compounds concerned in nervous tissue function.
Copper is present in almost all foods, most human diets naturally include between 1 to 2 mg/person/day of copper, with some containing up to 4 mg/person/day. Copper levels in blood and tissues are generally stable; the body is able to maintain a balance of dietary copper intake and excretion that allows normal physiological processes to take place. Up to 93 % of the copper in the blood is bound to the enzyme caeruloplasmin, while the majority of the rest are bound to albumin and amino acids; there is strong evidence that absorbed copper is never released free in the blood or in the cells.

A bioequivalence study was performed to compare the five variants of copper, copper hydroxide, copper oxychloride, Bordeaux mixture, tribasic copper sulphate and copper (I) oxide with copper sulphate pentahydrate on bile cannulated rats to demonstrate that toxicological studies on copper sulphate could be used in the toxicological risk assessment of the five variants. Absorption, distribution and excretion rates were similar between the six variants of copper following oral ingestion of 20 mg Cu/kg bw; liver was the principal organ of regulation of copper, and main excretion was via the bile. Liver copper levels increased significantly following dosing with T_{max} at 12 hours; depuration was rapid, with levels returning to control by 48 hours after dosing. Plasma concentrations in both control and dosed rats remained unchanged. These findings were consistent with the homeostatic bio-regulation of copper found in the open literature.
Oral absorption of copper varies according to the diet; for humans a copper-adequate diet results in 36 % absorption, while a low-copper diet results in 56 % absorption and a high-copper diet in 12 % absorption. Similar figures were found in rat; 50 % oral absorption was considered for this species. Distribution occurs directly from the intestine to the liver, which controls the distribution of copper to the rest of the body via the bloodstream, bound to caeruloplasmin. Metabolism does not occur. Copper does not accumulate, except in cases of genetic disease or chronic administration of high doses, where copper accumulates in the liver. Excretion is rapid, via the bile, in a trypsin-independent protein fragment, therefore entero-hepatic circulation does not occur. Significant amounts of copper

are excreted bound to metallothioneins contained in intestinal brush border cells, sloughed off and lost in faeces; minor amounts are also excreted in urine and from skin and hair.

2.2. ACUTE TOXICITY

Acute toxicity studies were conducted on the different copper (I) and (II) variants, leading to the following classifications:

Copper (I) and (II) variant	Classification
Copper hydroxide	T, Xn, Xi; T, R23 "Toxic by inhalation" Xn, R22 "Harmful if swallowed" Xi, R41 "Risk of serious damage to eyes"
Copper oxychloride	Xn; Xn, R20/22 "Harmful by inhalation and if swallowed"
Bordeaux mixture	Xn, Xi; Xn, R20 "Harmful by inhalation" Xi, R41 "Risk of serious damage to eyes"
Tribasic copper sulphate	Xn; Xn, R22 "Harmful if swallowed"
Copper (I) oxide	Xn; Xn, R20/22 "Harmful by inhalation and if swallowed"

Copper hydroxide presented a rat LC_{50} of 0.5 mg/L air for a 4-hour exposure of the whole body, while copper oxychloride, Bordeaux mixture and copper (I) oxide presented an LC_{50} of about 2-3 mg/L air for a nose-only 4-hour exposure in rat; it was not possible to generate a proper inhalable atmosphere from the dense aqueous paste of tribasic copper sulphate.

Acute oral LD_{50} of copper hydroxide was found to be between 490 and 1280 mg/kg bw in rat; for copper oxychloride, it was between 950 and 1860 mg/kg bw, and for tribasic copper sulphate and copper (I) oxide the LD_{50} was between 300 and 500 mg/kg bw; the oral LD_{50} of Bordeaux mixture was higher than 2000 mg/kg bw.

Slight eye irritation resulted from application of copper oxychloride, tribasic copper sulphate and copper (I) oxide, but severe irritation was found upon copper hydroxide and Bordeaux mixture application to eyes. Acute dermal toxicity was low for all variants of copper (I) and (II), no skin irritation was found, and none of the copper variants showed potential for skin sensitisation.

2.3. SHORT TERM TOXICITY

According to the metabolism/bioequivalence study, it was agreed that all five variants of copper (I) and (II) were equivalents; therefore studies conducted with copper sulphate were used to assess the short term toxicity of the five representative variants of copper.

Target organs of copper upon oral administration were the liver (inflammation), the kidneys (histopathological changes), and hyperplasia and hyperkeratosis of the stomach in rats; haematological changes were also observed in this species, while mice were less sensitive, showing adverse effects only in the stomach. A study performed with copper glutamate (not representative in this dossier) in dogs confirmed the data from the open literature that dog is not an appropriate species for human risk assessment, as copper accumulates more easily in dogs than in other species (rats and humans) due to different binding affinity of albumin to copper in dogs and also because dogs are thought to be unable to excrete copper through bile, resulting in a ten-fold higher liver copper concentrations.

The lack of studies conducted with non-rodent species was not considered as a data gap due to the extensive data available on humans.

The relevant NOAEL in rat was the dose level of 16 mg Cu/kg bw/day; in mouse, the relevant NOAEL was 97 mg Cu/kg bw/day and in dog, 15 mg Cu/kg bw/day.

In a dermal 21-day study with copper hydroxide performed on rabbits, the NOAEL was 1000 mg copper hydroxide/kg bw/day equivalent to 500 mg Cu/kg bw/day, based on weight loss and increased incidence of dermal findings.

No short term toxicity by inhalation was submitted. This issue was intensively discussed by the experts considering the operator exposure and its link to Vineyard Sprayer Lung (see points 2.8 and 2.9 below). The lesions found upon inhalation of Bordeaux mixture in humans were reproducible in non-standard guinea pig studies, showing interstitial pulmonary lesions, possibly leading to respiratory insufficiency (without a NOAEL). This was identified as a critical area of concern and a data gap was set for a short term toxicity study by inhalation.

2.4. GENOTOXICITY

Copper has been extensively investigated in a series of mutagenicity tests performed with several copper variants; the majority of the studies were obtained from the open literature, but there were three core-guideline compliant GLP studies.

The overall results of genotoxicity studies performed *in vitro* and *in vivo* were equivocal.

After oral ingestion copper is bound to several proteins, and there were no positive results in genotoxicity studies performed *in vivo*. However, it is recognised that free copper is highly reactive and binds easily to DNA, similarly to other proteins. Following non-oral exposure, as by the intraperitoneal route, positive results were obtained *in vivo* in bone marrow chromosome aberration, micronucleus and sperm abnormality assays, although these studies had some limitations. The experts discussed in detail the results of the genotoxicity studies, their relevance in the case of inhalation exposure as concerns operators and bystanders, and the inconclusive epidemiological data on lung tumours. The meeting concluded that there is insufficient evidence to exclude genotoxic potential of copper after non-oral administration and raised a critical area of concern on the genotoxic potential of copper (I) and (II) variants by inhalation.

2.5. LONG TERM TOXICITY

The long term toxicity studies included typical long term studies, special studies to investigate effects of copper when administered together with known carcinogens, investigations on specific effects and adaptations to prolonged administration of high levels of copper; the studies were generally old, non-compliant with guidelines and performed before the adoption of GLP principles.

In rat, long term administration of high level of dietary copper resulted in death, progressive liver toxicity (hypertrophy of the periportal parenchyma cells, inflammatory reaction and necrosis), bile duct hyperplasia and kidney toxicity, followed by some recovery – among surviving animals. The NOAEL was 27 mg Cu/kg bw/day from a 2-year rat study conducted with potassium sodium copper chlorophyllin.

No long term toxicity study in mice was available and was not considered necessary, as short term toxicity showed that mice were much more tolerant to high doses of copper than rats.

Two genetic conditions in humans (Wilson’s disease and Menkes’ disease) result in major alterations in copper absorption, distribution and excretion, leading to accumulation of copper in the principal target organ, the liver, but also in the kidneys, brain and cornea of the eyes. No association was found between the high levels of copper in these organs and carcinogenicity. No link could either be sufficiently demonstrated between Vineyard Sprayer Lung (derived from copper exposure) and lung cancer, as the epidemiological data analysis identified several confusing situations (such as smoking or exposure to other known carcinogens).

Overall, no carcinogenic potential was attributed to copper (I) and (II) variants either in rats or in humans.

2.6. REPRODUCTIVE TOXICITY

Reproductive toxicity of copper (I) and (II) variants was tested in a well conducted, GLP compliant two-generation reproduction toxicity study in rat and a developmental toxicity study in rabbit. Other fertility, developmental and investigative studies were reported in rat, mink, mouse, hamster and rabbit; these studies were not compliant with guidelines or GLP principles. A comprehensive review of copper in pregnancy and childhood was presented for humans, along with other published studies on testicular morphology, as well as developmental studies with copper administered parentally, via intravenous (iv), subcutaneous or intraperitoneal (ip) injections.

Reproduction toxicity

The main effect observed on parents and offsprings was reduced spleen weight at 23 mg Cu/kg bw/day; the parental and offspring's NOAEL was the dose level of 15.2 mg Cu/kg bw/day. No adverse effect on reproductive parameters was observed, therefore the NOAEL for reproductive effects in the rat was the highest dose tested of 23-56 mg Cu/kg bw/day.

Developmental toxicity

In rats, no maternal or foetal adverse findings were observed up to the highest dose tested of 30 mg Cu/kg bw/day.

In rabbits, maternal and foetal NOAELs were 6 mg Cu/kg bw/day based on reduced maternal and foetal weight and increased incidence of common skeletal variations at maternally toxic dose. It was noted however, that the rabbit is not an adequate species to characterise copper toxicity due to the rabbit's coprophagy habits, which results in higher actual copper exposure through "auto re-administration" of copper present in faeces.

Published studies demonstrated that administration of copper via iv or ip routes to mice or hamsters or direct exposure of embryos in culture resulted in death of embryos, neural tube-, cranial and heart defects. Arguments were presented regarding the protective mechanisms and homeostasis following oral ingestion of copper variants, as these effects were not observed after oral administration even at much higher dose levels of copper. The experts discussed the non-dietary routes of exposure in reproductive studies in the context of operators who may be exposed via the inhalation route. Considering that once systemically available, copper would bound to proteins and follow the homeostatic control mechanism characteristic for copper; a similar behaviour was expected for copper administered either by inhalation or by the oral route. No concern was raised by the meeting of experts concerning reproductive toxicity to operators or bystanders exposed to copper by inhalation.

2.7. NEUROTOXICITY

No study was provided. Limited evidence indicates that excess copper does not adversely affect the function of brain mitochondria. In the many toxicity studies in animals, there have been no indication that copper is selectively neurotoxic. However, in humans with genetic condition where the gene for copper transporter protein is inactive (as in Wilson's disease), copper progressively accumulates in the liver and the brain and, in the later stages of the disease (which is fatal through liver failure if not treated), it shows signs of neurotoxicity. In genetically normal humans and in normal laboratory animals, the natural homeostatic mechanisms that regulate copper prevent any accumulation in brain and neural tissues so that copper does not show a neurotoxic potential. No study was required.

2.8. FURTHER STUDIES

Thousands of studies are available in the open literature, some were chosen by the rapporteur Member State as being relevant for the risk assessment of copper (I) and (II) variants.

Direct injection of copper sulphate into the testis of rats and mice caused significant histological degeneration of the seminiferous epithelium and interstitium, and destruction of the spermatozoa, while subcutaneous injection showed no adverse effect. The study demonstrates that even following subcutaneous administration, the natural protective binding and homeostatic mechanisms prevent adverse effects of copper from being manifest.

Guinea pigs exposed to a saturate atmosphere of home-made Bordeaux mixture in a crude experiment assessing daily whole-body exposure over a six-month period showed similar lung lesions to those described for human subjects with Vineyard Sprayer's Lung (see point 2.9 below). A second study with 70 days exposure showed similar liver changes to those seen in human subjects with Vineyard Sprayer's Lung.

Copper (acetate) was negative in a pulmonary tumour response assay in mice.

2.9. MEDICAL DATA

There are four categories of copper poisoning in the literature: direct oral ingestion of copper salts, usually as a suicide attempt, cases where food or drinking water has become contaminated with copper, cases where home-made Bordeaux mixture has resulted in lung disease and a single case of long-term administration of excess copper as a dietary supplement.

Intoxication upon suicidal attempt (as copper sulphate pentahydrate) was associated with emesis, superficial or deep ulcerations of the gastric and intestinal mucosa, liver and kidney histopathology. Elevated serum copper levels are only seen in moderate to severe cases of intoxication. These findings were similar to those seen in animal studies.

Relatively low concentrations of free copper in water induced nausea in humans, although this could represent a taste effect, or, as copper sulphate is a gastric irritant, the nausea could be associated with irritation of the stomach.

A single case of dietary supplement of 30 mg Cu/day for two years (apparently without ill effect), and then with increased dose to 60 mg Cu/day in the third year resulted in liver failure.

The condition known as Vineyard Sprayer's Lung (VSL) is characterised by lung lesions and hepatic changes. This condition was linked mostly to *on-site* preparation of Bordeaux mixture, as a copper sulphate solution neutralised with hydrated lime, and to application techniques at higher rates than those used in modern agriculture. Most of the published findings date back to the 1970s and 1980s. Some of the papers were compromised because the authors did not adequately describe the smoking habits of the subjects, however, there were indications of adverse effects in users of Bordeaux mixture that were exacerbated by smoking.

There was no evidence for adverse effects from oral exposure through customary diets world-wide, nor for any adverse effects of copper on pregnancy, parturition, lactation or growth and development in humans. There was evidence of toxicity particularly to neonates repeatedly exposed to milk heated in copper vessels, or exposure to acid fruit stewed in copper vessels.

2.10. Acceptable daily intake (ADI), acceptable operator exposure level (AOEL) and acute reference dose (ARfD)

ADI

Natural copper intake in Europe is about 1-2 mg Cu/person/day. The upper limit of copper intake without adverse effect is not well defined, but is well recognised to be between 10 and 12 mg Cu/person/day; although some reports described the exposure to upper doses for long period of time as being not adverse in a few individuals.

Based on the values established by the WHO for copper intake (1996) based on human data in children (adults: 0.2 mg Cu/kg bw/day and children: 0.15 mg Cu/kg bw/day), and supported by animal data (1-year dog study, 1982) with a NOAEL of 15 mg Cu/kg bw/day, the meeting set an **upper limit for copper intake of 0.15 mg Cu/kg bw/day**.

Based on human intake, no safety factor was attributed to set the upper limit; for the NOAEL from the 1-year dog study, a standard safety factor of 100 was applied.

Initially in the draft assessment report, the rapporteur Member State proposed to base the ADI on the 1-year dog study. The experts agreed that it should be mentioned that copper (I) and (II) variants are a specific situation, in which it is justified to set reference values based on human data, as they are more relevant than the animal data.

Note: it was felt by the meeting of experts that the term “ADI” was not adequate to copper as an essential micronutrient essential for life; the term “upper limit” was considered as more appropriate.

AOEL

The rapporteur Member State proposed an AOEL of 0.25 mg Cu/kg bw/day based on the 90-day rat study and applying safety factor of 30 (10 for interspecies and 3 for intraspecies variability), considering the homeostasis mechanisms and the limited intraspecies differences in copper metabolism. The rabbit developmental study was excluded for setting the AOEL because of the coprophagy habits of rabbits that led to a doubled intake of copper and overestimated toxicity.

The meeting did not consider appropriate to use a safety factor of 30, as the database is not sufficiently complete to assume this level of certainty; it was agreed to use the standard safety factor of 100 for the animal studies.

The experts proposed to set the AOEL based on the WHO data for adults (adults: 0.2 mg Cu/kg bw/day) without the use of a safety factor, but considering a correction for limited oral absorption of 36 % (from human data under normal copper intake), thus resulting in an **AOEL of 0.072 mg Cu/kg bw/day.**

This AOEL is supported by the 90-day rat study with a NOAEL of 16 mg Cu/kg bw/day, using a safety factor of 100 and a correction for limited oral absorption of 50 % from animal data.

ARfD

Copper is not acutely toxic if swallowed; it is not a neurotoxic compound, and it does not show developmental toxicity after oral administration.

The meeting concluded that no ARfD was warranted. **No ARfD was allocated**.

Drinking water limit

According to Council Directive 1998/83/EC[2] of 3 November 1998 on the quality of water intended for human consumption, **the maximum concentration of copper in drinking water is 2 mg Cu/L**.

2.11. Dermal absorption

An *in vitro* percutaneous absorption study of copper was performed with the five representative variants of copper (I) and (II). However, the study reported that up to 25 tape strips were used to remove the stratum corneum and discarded. Therefore, no information on the amounts present in tape strips was available. The experts agreed to set the dermal absorption as a 10 % conservative default value (for the concentrate and the in-use spray dilution), based on the lack of information on the tape strips amounts and having in mind the relatively low percentage of oral absorption

2.12. Exposure to operators, workers and bystanders

The rapporteur Member State revised the calculations for operator, worker and bystander risk assessment in addendum 2 and addendum 3 to Volume 3 of the DAR (June and July 2008) considering the parameters agreed at the PRAPeR 49 meeting.

Copper (I) and (II) variants are sprayed on grapes and tomatoes; regarding grapes, one treatment program is performed in post-flowering till harvest (with a maximum application rate of 2.0 kg Cu/ha and up to four applications) and another is performed in post-harvest and early spring (with a maximum application rate of 3.0 kg Cu/ha and up to two applications). Use on tomatoes is proposed for both field- and greenhouse treatments with a maximum application rate of 1.25 kg Cu/ha and up to six applications. Default dermal absorption is 10 % for the concentrate and for the in-use spray dilution; inhalation absorption is assumed to be 100 %.

Operator exposure

Field application

The UK POEM model and the German model were considered for field applications by tractor-mounted/trailed broadcast air-assisted sprayer in grapes or tractor-mounted/trailed boom sprayer with hydraulic nozzles in tomatoes. According to the UK POEM assumptions, bodyweight of operators is 60 kg, packaging consists of 25 kg bags; for the German model, the bodyweight of operators is 70 kg.

[2] Official Journal of the European Communities, 05.12.1998, L 330/32

"Kocide 101" (Copper hydroxide, WP formulation with 500 g Cu/kg),
"Cuprocaffaro WP" (copper oxychloride, WP formulation with 500 g Cu/kg) and
"Macc 80 WP" (Bordeaux mixture, WP formulation with 200 g Cu/kg)

Estimated operator exposure presented as % of AOEL (0.072 mg Cu/kg bw/day) – field applications

Use and application rate	Model	No PPE	Gloves M+L & Application	Gloves M+L & Application & coverall	Coverall, broad-brimmed headwear and gloves M+L & application
Grapes max. 3.0 kg Cu/ha	German 8 ha	875 %	559 %	125 %	96.5 %
	POEM 15 ha	2627 %	1037 %	-	-
Tomatoes 1.25 kg Cu/ha	German 20 ha	434 %	121 %	45.3 %	43.8 %
	POEM 50 ha	3065 %	1014 %	-	-

M+L: mixing and loading

"Cuproxat SC" (tribasic copper sulphate, SC formulation with 193 g Cu/L)

Estimated operator exposure presented as % of AOEL (0.072 mg Cu/kg bw/day) – field applications

Use and application rate	Model	No PPE	Gloves M+L	Gloves M+L & application	Gloves M+L & application & coverall
Grapes max. 2.0 kg Cu/ha	German 8 ha	446%	371 %	349 %	60 %
	POEM 15 ha	524%	357 %	232 %	-
Tomatoes 0.80 kg Cu/ha	German 20 ha	141%	65.9 %	54 %	5.8 %
	POEM 50 ha	398%	168 %	37.7 %	-

M+L: mixing and loading

"Nordox 75 WG" (copper (I)oxide, WG formulation with 750 g Cu/kg)

Estimated operator exposure presented as % of AOEL (0.072 mg Cu/kg bw/day) – field applications

Use and application rate	Model	No PPE	Gloves M+L	Gloves M+L & application	Gloves M+L & application & coverall
Grapes max. 3.0 kg Cu/ha	German 8 ha	655%	561%	528%	93.7%
	POEM 15 ha	1372%	782%	594%	-
Tomatoes 1.125 kg Cu/ha	German 20 ha	184%	96.0%	79.2%	11.3%
	POEM 50 ha	1279%	542%	359%	-

M+L: mixing and loading

The estimated systemic exposure resulting from the field use of the five representative formulations for operators exceeded the AOEL according to the UK POEM even when considering the use of personal protective equipment (PPE); when using the German model, estimated operator exposure was below the AOEL only, if a high level of personal protective equipment (PPE) was used such as gloves during mixing and loading, and gloves and coverall during application.

Greenhouse application (tomatoes)

Operator exposure from greenhouse application (hand-held) was estimated according to the Dutch model with the maximum application rate for all formulations. This corresponds to the use of copper hydroxide WP, copper oxychloride WP and Bordeaux mixture WP, and covers the use of tribasic copper sulphate SC and copper (I) oxide WG that have a lower application rate.

The following input parameters were considered: maximum application rate of 1.25 kg Cu/ha (covering all representative formulations), spray volume of 500 L, reduction factor for RPE of 4 (P1-filter, most conservative), reduction factor for PPE of 6 (gloves and coverall, default value) and area treated of 1 ha.

Estimated operator exposure after hand-held spraying on tomatoes, using the Dutch model, was below the AOEL only if suitable mask, gloves and coverall were worn:

Estimated operator exposure presented as % of AOEL (0.072 mg Cu/kg bw/day) – greenhouse applications

Route of exposure	without RPE/PPE	with RPE/PPE
Inhalation	25	6
Dermal	496	83
Total exposure	**521**	**89**

Worker exposure

Estimation of worker exposure was performed according to the model developed by the German BBA. Transfer factor of 15000 cm^2/person/hour was considered for grapes, penetration factor through clothing (long-sleeved shirt and long trousers) and gloves was 5 %, work rate of 8 hours and bodyweight of workers of 60 kg were assumed.

Estimated worker exposure presented as % of AOEL (0.072 mg Cu/kg bw/day)

Worker exposure	**No PPE**	**With PPE** [(a)]
*Kocide 101, Cuprocaffaro WP, Macc 80 WP (grapes, 2.0 kg Cu/ha, 4 applications) – **8 kg***	2222	**111**
*Kocide 101, Cuprocaffaro WP, Macc 80 WP (grapes, 3.0 kg Cu/ha, 2 applications) – **6 kg***	1667	83.5
Kocide 101, Cuprocaffaro WP, Macc 80 WP	2083	**104**

*(tomatoes, 1.25 kg Cu/ha, 6 applications) – **7.5 kg***		
*Cuproxat SC (grapes, 1.5 kg Cu/ha, 4 applications) – **6 kg***	1667	83.5
*Cuproxat SC (grapes, 2.0 kg Cu/ha, 2 applications) – **4 kg***	1111	55.5
*Cuproxat SC (tomatoes 0.8 kg Cu/ha, 6 applications) – **4.8 kg***	1333	66.5
*Nordox 75 WG (grapes, 1.5 kg Cu/ha, 4 applications) – **6 kg***	1667	83.5
*Nordox 75 WG (grapes, 3.0 kg Cu/ha, 2 applications) – **6 kg***	1667	83.5
*Nordox 75 WG (tomatoes 1.125 kg Cu/ha, 6 applications) – **6.75 kg***	1875	93.8

[(a)] PPE : protective gloves, long-sleeved shirt and long trousers

Estimations of worker exposure exceeded the AOEL for workers without PPE. Considering the use of PPE as long-sleeved shirt, long trousers and gloves, the exposure is expected to decrease to levels below the AOEL for most of the proposed uses; however, some scenarios remained above the AOEL and therefore, a study to measure the exposure of workers in the field or to measure realistic foliar dislodgeable residues after several applications should be requested.

Bystander exposure

Estimation of bystander exposure considered both dermal exposure derived from available drift data (Rautmann *et al.*, 2001), and inhalation exposure derived from the German model operator exposure. At 10 m from the spray application, the maximum drift estimate for grapes and tomatoes (90th percentile data, single application; late application for grapes; vegetable crop greater than 50 cm in height for tomatoes) is 1.23%. A default surface area of 2 m^2/person and bodyweight of 60 kg were assumed.

Estimated bystander exposure presented as % of AOEL (0.072 mg Cu/kg bw/day)

Bystander exposure	**No PPE**
Kocide 101, Cuprocaffaro WP, Macc 80 WP	20.5
Cuproxat SC	13.75
Nordox 75 WG	20.5

Bystander exposure was estimated to be below the AOEL for all uses, with all representative formulations.

3. Residues

Copper (I), copper (II) variants were discussed at the PRAPeR meeting of experts in residues (PRAPeR 50, round 10) in June 2008.

3.1. Nature and magnitude of residues in plant

3.1.1. Primary crops

Specific studies to evaluate metabolism and distribution of residue in plants following the use of copper as a plant protection product have not been conducted by the applicant. However, extensive literature exist on the uptake, translocation and effects of copper in plants; data presented in the dossier and summarised in the DAR to address this point consist mainly of a review of this public scientific literature.

In plants, copper is absorbed from soil through the roots. From the roots, copper is transported in the sap to the rest of the plant. Upon foliar application, transportation and distribution of copper in plants are limited.

Copper is a monoatomic element and inherently stable. Therefore, it does not metabolise or form degradation products. However, due to the high reactivity of copper ions, it is able to react with most of the plant cellular constituents. From literature it is found that both free and bound copper exist in plants. However, very few information is available on the relative amount of each form in the different plant compartments, and on the different toxicity of free and bound copper. Copper is made available in the rhizosphere and transported in the plant cell membranes as copper ions. Copper found in roots might accumulate as free copper in the apoplasm. In the cytoplasm, however, entering copper ions are immediately chelated by chaperones, and in chloroplasts they are bound to specific proteins (e.g. plastocyanin). In the vacuole, copper may accumulate in both the free and the bound form.

All the methods used to generate residue data for both tomato and grapes include a mineralisation of the samples by acid digestion. In this condition, all forms of copper present in the plant are converted to Cu^{2+}.

The meeting of experts concluded that the plant residue definition for monitoring and risk assessment should be total copper.

Supervised trials were conducted to determine residue levels of total copper following application to grapes and tomatoes. Field trials were conducted in commercial crops grown in representative countries in the northern and southern EU over several seasons. In addition, trials with indoor-grown/ protected tomatoes were submitted. All five variants of copper, i.e. copper hydroxide, copper oxychloride, Bordeaux mixture, tribasic copper sulfate and copper (I) oxide were applied in their representative formulations and at rates equivalent to the notified GAP. Fruit samples were analysed for residues of total copper using fully validated analytical methods. Due to copper being ubiquitous in the environment in significant levels, the principles of determining the LOQ according to standards usually applicable to synthetic organic pesticides were considered inappropriate for the determination of copper residues in crops. The meeting of experts agreed that, in order to establish the actual residue levels resulting from a treatment with copper variants, the determined copper levels in crops from the treated and untreated plot would have to be compared. Residue levels in treated tomatoes (field and protected) ranged from 1.9 to 3.9 mg/kg, in treated table grapes from 2.2 to 12 mg/kg, and in treated wine grapes from 2.2 to 56 mg/kg. These results are not corrected for background levels. Levels of copper in untreated crops (background) ranged from 0.15 to 1.2 mg/kg in tomatoes and 0.54 to 4.8 mg/kg in grapes. It is however noted, that in viticulture there is a long history of copper use and therefore ‘elevated’ background concentrations might have been found in some grape samples.

A statistical analysis of the residue trial data demonstrated that each of the five variants, when applied at comparable rates and conditions, gave equivalent residue levels on the crops.
In tomatoes, trials were carried out in field-grown and protected crops in southern Europe, and with different PHIs. Overall, there was only a slight decline in residue levels from application until harvest of tomatoes. The trials were sufficient to establish a common MRL proposal for field-grown and protected tomatoes in southern Europe in accordance with the notified representative use on tomatoes for southern Europe only.
To support the uses in grapevine, trials were carried out in wine grapes in southern and northern EU countries and also in table grapes in southern Europe. Residue levels of copper declined only slowly after application. Residue levels at harvest varied according to the location of the trials. The highest residue levels on grapes were found in four trials from Germany, which were likely due to the practice of defoliation of the vines, i.e. removing leaves around the grape bunches prior to application of copper.
Due to the clear differences seen between the northern and southern Europe data sets, it has been proposed to set separate MRLs for table grapes and wine grapes. It was presumed by the RMS that table grapes were grown only in southern Europe and thus, the MRL for table grapes could be based only on the results of trials from South-Europe. The proposed MRL for wine grapes was based on the more critical northern European trials. The meeting of experts recommended that further residue trials in accordance with the German use (defoliation) should be provided in order to support the proposed MRL.

Processing studies (balance and follow-up studies) were carried out in tomatoes, wine- and table grapes. The study with tomatoes could not be considered as a valid study.
Residues of copper were determined in all commodities and fractions following the production of raisins, grape juice and wine, and transfer factors were established. In wine grapes, residues of copper in the treated must and pomace were higher than in the corresponding unprocessed fruit, and the mean transfer factors for these two commodities were 1.9 and 2.8, respectively. Residues of copper in treated juice and wine were lower, resulting in mean transfer factors 0.4 and 0.19, respectively. Copper concentrated in raisins by a mean concentration factor of 2.7.

3.1.2. SUCCEEDING AND ROTATIONAL CROPS

Specific studies to evaluate reside uptake from soil, metabolism and residue levels in succeeding crops have not been conducted and submitted.

Copper is naturally present in soil and is essential for normal plant growth and development. Consequently, all soil-grown crops contain copper. However, at high soil concentrations copper may have significant phytotoxicity. From literature it is also known that plants can accumulate copper to various extents, depending on plant species and copper content and pH of the supporting soils.

Grapevines are perennial plants and are usually not followed by other crops. Tomatoes are annual crops that, depending on the region, are grown on the same ground each year or in rotation with other crops. The RMS made considerations and estimates on copper levels in soil available for uptake by following crops after a treatment according to the notified GAP. These estimated concentrations of copper hitting the ground during application were found insignificant compared to the concentration of copper naturally present in soil. In conclusion, assuming no rotation, residues in grapes and tomatoes grown in the following season are expected to be lower than in the crops directly treated with copper. For the same reason, residues of copper in succeeding crops are not expected to be present at levels higher than background levels, when tomatoes are grown in rotation with other crops.

It is however noted that this estimates and considerations do not take into account the potential of accumulation of copper in soils following repeated use. Specific data or an estimation of the accumulated concentration of copper in soil after several years of use and data on bioavailability is missing (refer to chapter 4.1), and consequently, information as to how these accumulated concentrations may affect the copper levels in crops grown in this soil is not available. Depending upon the results of the evaluation of the data to address this data gap, further information on rotational crops may be necessary.

3.2. NATURE AND MAGNITUDE OF RESIDUES IN LIVESTOCK

Grapes and tomatoes are not considered as potential feed items for livestock animals. Therefore, studies to assess metabolism and distribution and levels of residues in livestock are not required with regard to the notified use of copper as a plant protection product.

3.3. CONSUMER RISK ASSESSMENT

It is noted that a sound consumer risk assessment needs to consider not only the exposure to copper residues from the use of copper on grapes and tomatoes, but all sources of copper exposure. In order to estimate how the dietary exposure from the use of copper as a plant protection product relates to the general copper exposure of consumers (due to ubiquitous levels in food and drinking water), and to conclude whether an exceedance of the toxicological reference value may be possible in a 'combination situation', an aggregate risk assessment needs to be carried out.

It is noted that a final assessment covering all European consumers may be difficult to obtain, in particular, since the copper content in water may vary significantly among countries and regions, and comprehensive information on average and maximum concentrations in water for all Europe was not available for the peer review.

In a fist step (DAR), the RMS estimated the chronic dietary exposure for the consumption of tomatoes and grapes treated with copper using consumption data from WHO (GEMS/ Food European diet), UK, Germany and France.
Estimates on the basis of the proposed MRLs for tomatoes and grapes showed that the Theoretical Maximum daily intake (TMDI) would be 245%, 38% and 22% of the ADI of 0.15 mg/kg bw/day for French adults, toddlers and infants, respectively. Wine was by far the highest contributor to the copper intake estimated for adults. The TMDI for the general population based on the WHO consumption data was estimated as 62 % of the ADI.
In a refined assessment with further national consumption data (UK, Germany) and with consideration of the STMR and processing factors, the estimated intakes (NEDI) for adults, children, toddlers and infants were highest for the UK toddler (26% of the ADI).
In a second step, based on the opinion of the Scientific Committee on Food (SCF)[3] the RMS considered estimates on daily copper intakes of adult european consumers through food, which may range between 0.02 mg/kg bw and 0.06 mg/kg bw, corresponding to 13 to 40% of the proposed ADI, that should be considered in addition to the copper exposure through treated grapes and tomatoes. However, no copper intake data were reported in the SCF opinion with regard to children.

In the addendum of April 2008 the RMS assessed dietary exposure to copper based on the ‘First French total diet study’ that also includes children and considers copper intake from drinking-water on an average content of 0.05 mg/L. The average intake of copper for children of 3-14 years was 0.81 mg/day, corresponding to 51% of the ADI for a French toddler (10.5 kg bw). When in addition, the residue levels (STMR) in treated grapes and tomatoes are considered, and the average content in water is replaced by a highest copper content of 0.5 mg/L in drinking water in France, the calculated NEDI represent 40%, 103% and 92 % of the ADI for French adults, infants and toddlers, respectively. Again, it was noted that according to Council Directive 1998/83/EC of 3 November 1998 on the quality of water intended for human consumption, the maximum concentration of copper in drinking water is 2 mg/L and therewith higher than the value used in the estimates by the RMS. According to comments received by Member State experts this level is realistic in some European regions and could lead to an exceedance of the toxicological reference value in an aggregate assessment. Moreover, it was noted by the experts that not all possible sources of copper (e.g. use as feed

[3] European Commission. Opinion of the Scientific Committee on Food on Tolerable Upper Intake Level of Copper (expressed on 5 March 2003). SCF/CS/NUT/UPPLEV/57 Final, 27 March 2003

additives resulting in residues higher than background levels in animal products; copper levels in seafood) have been taken into account in the presented estimates yet.

The meeting concluded that the overall copper exposure in diet from sources other than residues of plant protection products on food is not negligible. Considering mean residue levels from tomatoes and grapes, natural background levels in food and concentrations in drinking water (0.5 mg/kg) corresponding to 25% of the legally permitted value, the daily exposure of vulnerable consumer groups may approximate the proposed ADI of 0.15 mg/kg bw. Higher copper levels in drinking water and additional sources of exposure may lead to an exceedance of the ADI for some European consumers or consumer sub-groups.

3.4. PROPOSED MRLS

Based on the agreed residue definition and the available residue trial data the following MRLs are proposed:

Tomatoes (based on trials from southern Europe)	5 mg/kg
Table grapes (based on trials from southern Europe)	20 mg/kg
Wine grapes (based on trials from northern and southern Europe)	50 mg/kg

4. Environmental fate and behaviour

Fate and behaviour of copper (I), copper (II) variants was discussed in the PRAPeR 47 meeting of experts (May 2008) on the basis of the DAR as amended in corrigendum of April 2008 and the addendum 1 (April 2008).

4.1. FATE AND BEHAVIOUR IN SOIL

The data presented in the dossier and summarized in the DAR on the fate and behaviour of copper in soil consist mainly of a review of public scientific literature. Although the information is qualitatively complete, it does not allow deriving quantitative parameters to perform a proper environmental risk assessment.

Evidences of accumulation of copper in soil due the agricultural use are presented. Values of up to 200 – 1280 mg/kg in agricultural fields are reported in contrast to background average values of 6 – 25 mg/kg. However, high variability in the copper levels is observed in both agricultural and non-agricultural soils. The level of 35 mg/kg is proposed as the upper level for natural pedo-geochemical background, considering that most soils would normally exhibit lower concentrations. The meeting of experts discussed whether the data in the dossier were robust enough to determine a background level that may be considered to be representative of the EU. The rapporteur Member State noted that the information in the dossier does not allow confirming the background levels proposed. The RMS provided in an addendum soil copper maps of the EU (FOREGS). These maps show a high variability

in the concentrations of copper and it was not feasible to define an EU-wide background level. Furthermore, it is expected that the concentrations reported in the maps encompass natural occurring cupper as well as copper of anthropogenic origin.
An environmental risk assessment should be performed in order to assess potential harmful effects of levels exceeding the natural background produced by the agricultural uses. Applicants claim that total copper concentration in soil should not be directly used in the risk assessment since only a fraction of it is soluble and bioavailable and, therefore, susceptible to leach and/or have biological effects. There is a considerable amount of qualitative information in the dossier (from public scientific literature) on the physicochemical speciation of copper in soil and on different factors having an impact on it. However, some crucial points remain unresolved:

- Accumulation: an estimation of the accumulated concentration of copper in soil after several years of use is missing. The meeting of experts concluded that the information provided by the applicant was generic and not supported by the information already included in the dossier. The plateau of available copper in soil needs to be addressed.

- Bioavailable fraction: according to the applicant, only the water soluble fraction should be considered bioavailable. The meeting of experts agreed that this may be the case for some organisms like plants but it does not necessary apply to other organisms like earthworms. Additionally, the information available does not allow making a quantitative estimation of the soluble fraction that could be used to perform a sound risk assessment.

The applicant indicated that there is an ongoing study to address the potential accumulation of copper in soil. The preliminary information available from this study cannot be used at this stage. Therefore, a data gap was identified by the meeting of experts to address the accumulated PEC soil, a worst case soluble fraction estimate, and a worst case bioavailable fraction estimate (taking into consideration that bioavailability may differ in different organisms). Available monitoring data of copper residues in areas where it has been used for many years should be compared to background levels in areas without agricultural use of copper. The meeting noted that the applicant has provided information on an ongoing study that could eventually address part or the entire data gap, once finalized. Due to the lack of information on the relative amounts of soluble copper in soil and on the bioavailability of non-soluble copper, the meeting of experts proposed that the risk assessment should be based on the total amount of copper and not only on the soluble fraction.

4.1.3. MOBILITY IN SOIL OF THE ACTIVE SUBSTANCE AND THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

The RMS identified a data gap for adsorption/desorption studies or for more appropriate data from scientific literature to address mobility of copper in soil. Information to assess the leaching potential of copper was not provided in the dossier. The applicant provided a justification during the peer review in the evaluation table and offered to submit a study in the future. The experts questioned whether a guideline study (OECD 106) would provide useful information to assess leaching potential of copper. Nevertheless, the meeting of experts agreed that additional experimental data will be needed to derive input parameters that allow estimating PEC_{GW}.

4.2. FATE AND BEHAVIOUR IN WATER

4.2.1. SURFACE WATER AND SEDIMENT

No guideline study was conducted to assess the behaviour of copper (I), copper (II) variants in water/sediment systems. An aquatic microcosm study, where copper hydroxide (formulated as 50 % WP) was applied to the water surface, is available in the dossier. A rate of dissipation of 30.5 days was calculated for the transfer of copper from water to sediment. The majority of copper in the sediment was found to be bound to solid matter. Additionally, some scientific literature studies were presented, in which both speciation of copper and solubility of copper in water are investigated. The information regarding fate and behaviour provided by these studies is not of general application for the risk assessment and was considered as supporting information by the rapporteur Member State.

A review on public domain studies that investigate the transfer of copper from soil to water bodies (leaching, drainflow run-off and erosion) was presented in the dossier. Among the different routes of potential contamination of surface water by copper, erosion seems to be the most important contributor. Data available do not allow concluding on parameters that allow a sound estimate of PEC_{SW}/PEC_{SED} values. The applicant presented FOCUS step 2 calculations. These calculations were considered sufficiently worst case to be used as a screening tool; however, higher tier $FOCUS_{SW}$ modelling was considered inappropriate to model fate and behaviour of inorganic salts. The RMS informed the meeting that with the FOCUS step 2 PEC_{SW}/PEC_{SED} calculated by the applicant, high risk had been identified for the aquatic environment. Therefore, the meeting of experts confirmed the data gap already identified by the rapporteur Member State for more realistic surface water assessment based on modelling and/or field and monitoring data. However, the meeting of experts agreed that $FOCUS_{SW}$ modelling is not appropriate to asses copper salts, and that accumulation and speciation in the sediment will need to be considered in the new assessment. The meeting agreed that for the risk assessment only soluble copper should be considered for surface water. However, for the sediment total copper should be considered.

4.2.2. POTENTIAL FOR GROUND WATER CONTAMINATION OF THE ACTIVE SUBSTANCE, THEIR METABOLITES, DEGRADATION OR REACTION PRODUCTS

No estimation of PEC_{GW} was provided in the dossier. The rapporteur Member State has already identified a data gap for adsorption/desorption data to be used to assess potential contamination of ground water. The meeting of experts agreed that a robust estimation of PEC_{GW} for copper resulting from its agricultural use needs to be provided to ensure that the legal trigger of 2 mg/L is not exceeded. Therefore, the data gap for an estimation of PEC_{GW} for the representative uses was confirmed by the meeting of experts.

4.3. Fate and behaviour in air

Copper is used as copper (I), copper (II) variants and it is not expected to volatilize under environmental conditions.

5. Ecotoxicology

Copper (I) and copper (II) variants were discussed in the PRAPeR 47 meeting of experts on ecotoxicology (May 2008) on the basis of the DAR as amended in corrigendum of April 2008 and the addendum 1 (April 2008). The addendum 2 of June 2008 was not peer-reviewed. Copper ion is the biologically active part of the copper compounds. There was no consistent pattern that would allow a conclusion on the differences in toxicity of the different copper variants. Therefore, the lowest available toxicity endpoints from all tests with the different copper variants were used in the risk assessment instead of using the toxicity endpoints of each of the copper variants separately in the risk assessment. This approach was agreed by the meeting of experts.

5.1. Risk to terrestrial vertebrates

The representative uses of the various copper variants are applications to vines and tomatoes (outdoor and indoor use). The risk to herbivorous birds from the use on tomatoes was considered low since the tomato foliage is not palatable to birds. Birds may peck at ripe tomato fruits. However, the amount of tomato fruit eaten was considered as too low to pose a significant risk to birds or mammals. The scenario of uptake of residues in weeds growing in the field is not included in the guidance document on birds and mammals (SANCO 4145/2000). The experts agreed that no risk assessment for herbivorous birds needs to be conducted for the vineyard and tomato use. The first-tier acute, short-term and long-term TERs for insectivorous birds, and the long-term TERs for earthworm-eating birds were below the Annex VI trigger values for all representative uses. The risk to fish-eating birds and mammals was assessed as low. The risk from exposure via contaminated drinking water was assumed to be low since accumulation of water in the leaf axils is considered as unlikely due to the morphology of the tomato and vine leaves.

The endpoint for the acute risk assessment (LD_{50} of 173 mg Cu/kg bw) was confirmed in the meeting of experts. The study of Grimes and Jaber (1988) on the acute toxicity of copper tribasic sulphate to birds was assessed as not valid.

Three focal species, partridge (no species proposed), skylark (*Alauda arvensis*) and starling (*Sturnus vulgaris*) were suggested to refine the acute and short-term risk to birds. The refined risk assessment was based on a mixed diet (PD refinement). The acute TERs were 6.3, 9.3 and 45, and the short-term endpoints were 2.5, 4.9 and 25 for partridge, skylark and starling for the use in vineyards. The experts agreed on the choice of the focal species. However, it was not clear as to how the composition of the diet was derived. The experts recommended that the TERs should also be calculated for one food type since it cannot be excluded that a bird feeds only on one food type on the acute time scale. It was noted that the TERs were lower for birds with a higher percentage of plant material in the diet. The acute risk to omnivorous birds such as skylark or starling with a high percentage of large invertebrate food items is considered sufficiently addressed. Uncertainty remains for birds with a more herbivorous diet. However, it was considered that green parts of the treated crop plants would not be an attractive food source for birds.

It was not possible to derive reliable LC_{50} values from most of the short-term studies since food avoidance was observed. The rapporteur Member State presented a re-evaluation of the short-term studies in addendum 2 of June 2008. The RMS suggested no changes in the regulatory endpoint for the risk assessment (NOEL = 31.9 mg Cu/kg bw/day). However, there may be a possibility of further refinement of the short-term toxicity endpoint. Only temporary toxic symptoms but no mortality was observed at the next three higher dose levels tested (up to 509 mg Cu/kg bw/day). The highest NOEL (based on concentrations where no food avoidance was observed) from all available short-term studies, which did not exceed the LOEC (mortality), is 107.5 mg Cu/kg bw/day. The EFSA suggests that the NOEL of 107.5 mg Cu/kg bw/day could be used in a refined risk assessment. The resulting short-term TERs would be 8.4 and 16.5 for partridge and skylark. This refinement step is not peer-reviewed but may be taken into consideration as an indication that the short-term risk to insectivorous/omnivorous birds is low for the representative uses of copper.

No focal species were proposed to refine the long-term risk assessment. Instead, the TERs were calculated for different taxonomic groups/guilds of birds (*Phasianidae*, group A; *Passeridae* and *Fringillidae*, group B; *Alaudidae*, *Emberizidae*, *Motacillidae* and *Prunellidae*, group C; *Corvidae* and *Sturdidae*, group D; *Columbidae*, group E). The long-term TERs for all groups of birds were significantly below the Annex VI trigger of 5. Since no real focal species were suggested to refine the long-term risk assessment, it was not possible to agree on any PD or PT refinement. The experts identified a data gap for a new long-term risk assessment based on focal species.

The first-tier long-term TERs for earthworm-eating birds and mammals were below the Annex VI trigger of 5. No further information was provided to refine the risk assessment. The experts suggested that a refined risk assessment for earthworm-eating birds and mammals should be based on blackbird (*Turdus merulus*) and shrew (*Sorex araneus*) as a focal species.

Overall, it is concluded that the acute and short-term risk to insectivorous birds is low, but a high long-term risk to insectivorous birds and earthworm-eating birds cannot be excluded.

The risk assessment for herbivorous mammals was questioned during the peer-review. A new risk assessment was presented in addendum 1 of April 2008. The first-tier acute and long-term TERs were below the Annex VI triggers. The refined risk assessment submitted by the applicant was not transparent. It was not clear which refinements were taken into account and no information/data were provided to support the refined acute and long-term risk assessment. No further clarification was submitted by the applicant. A data gap was identified by the experts for a refined risk assessment for mammals where all refinement steps are transparent and supported by information/data.

It was argued that the long-term risk to mammals is sufficiently addressed since copper is an essential micro-nutrient, and that the level of copper in the organism is regulated by homeostatic mechanisms. However, such mechanisms to regulate the copper uptake and excretion are already taken into account in the toxicity endpoints and hence, cannot be used as an argument that the risk would be overestimated on the basis of the endpoints from the available studies.

Overall it is concluded, that the risk to birds and mammals from the use in tomatoes in glasshouse is considered to be low because of negligible exposure. A potential high long-term risk to birds and a potential high risk to mammals cannot be excluded for the outdoor uses in tomatoes and vines.

5.2. RISK TO AQUATIC ORGANISMS

Copper is very toxic to the aquatic organisms. There was no consistent pattern in differences in toxicity between the different copper variants. Organisms are considered to be exposed to dissolved copper in the aquatic phase. Therefore, the lowest observed toxicity endpoints for all copper variants were used in the risk assessment.

The lowest endpoints on the acute time scale were 96h LC_{50} = 0.008 mg Cu (dissolved)/L for fish, EC_{50} = 0.0266 mg Cu (dissolved)/L for *D. magna*. The lowest endpoints on a long-term time scale were a NOEC (growth) of 0.0017 mg Cu (dissolved)/L for fish and a NOEC (reproduction) of 0.0076 mg Cu (total)/L for *D. magna*. The lowest E_bC_{50} for algae was 0.00939 mg Cu (total)/L. The TERs for all groups of organisms were significantly below the Annex VI triggers on the basis of PECsw/sed values calculated with FOCUS step 2. However, the calculations of PECsw/sed with FOCUS were considered as not reliable (see data gap in point 4.2. above).

The available data on the toxicity of copper to *Chironomus riparius* were discussed. The experts agreed that the available studies (water spiked) are valid and can be used in the risk assessment once reliable PECsed values are established.

An indoor-microcosm study was submitted to address the high risk to aquatic invertebrates. The rapporteur Member State proposed a NOEC of 12µg Cu (total)/L, equivalent to 3.12µg Cu (dissolved)/L without a safety factor. The experts agreed that the results of the microcosm should be based on mean measured concentrations. It was noted that the variability in the controls was high, and that the exposure conditions in the microcosm were probably favourable due to the high pH (decreasing toxicity with increasing pH). Uncertainty remained with regard to effects on sediment-dwelling chironomids. The experts proposed that a safety factor of 3-5 should be applied to the endpoint derived from the study to account for the identified uncertainties.

Available information from public literature suggested a high potential of bioaccumulation of copper in some aquatic organisms. No study was submitted to determine the bioconcentration factors in fish. The experts agreed that the potential risk of bioaccumulation in fish should be addressed, and that information from published literature would be acceptable. A data gap was identified in the meeting for the applicant to address the risk from bioaccumulation in aquatic organisms.

The risk to aquatic organisms from the use in tomato in glasshouse is considered to be low.
The risk assessment for aquatic organisms needs to be finalised once reliable PECsw/sed values are established for the outdoor uses of copper in tomatoes and vines.

5.3. RISK TO BEES

The HQ values for bees were calculated separately for each of the copper variants. This was rejected for the oral toxicity since no clear pattern in differences in toxicity was observed, and since the copper speciation in the digestive tract is likely to be independent from the respective copper salt. For contact risk assessment, separate risk assessments were accepted since the bees were exposed in the contact toxicity tests directly to the different copper variants.
The LD_{50} values ranged from 12.1 - >116 µg Cu/bee for oral toxicity, and >22 to >82.5 µg Cu/bee for contact toxicity to bees. Most of the contact HQ values were below the Annex VI trigger of 50, except for copper oxychloride and the Bordeaux mixture, where the contact HQ values for the use in vine were above the trigger of 50. The oral HQ values for the uses in vine and tomato (based on separate endpoints for each of the variants) were below the trigger of 50 except for copper oxychloride and the Bordeaux mixture. Based on the lowest observed oral toxicity endpoint, none of the oral HQ values are below the trigger of 50 for the different uses. Vineyards as well as tomatoes are attractive foraging habitats for bees. The experts suggested a data gap for the applicant to address the potential high risk to bees further.

5.4. RISK TO OTHER ARTHROPOD SPECIES

The risk to non-target arthropods was conducted for each of the copper variants separately since the tested animals were exposed in the test systems via direct contact to the different copper variants. A new risk assessment taking into account multiple application factors was presented in addendum 1 of April 2008.

The in-field HQ value for *T. pyri* was below the Annex VI trigger of 2, but not for *A. rhopalosiphi* for the uses of copper hydroxide. Mortality rates of 66.9 % was observed for *A. rhopalosiphi* when exposed to fresh residues of copper hydroxide at an application rate of 2000g Cu/ha. Additional species (*Trichogramma cacoeciae*, *Diaeretiella rapae*, *Chrysoperla carnea* and *Poecilus cupreus*) were tested. No significant effects were observed. However, the applied rates are lower than the proposed in-field application rates. The off-field risk to non-target arthropods was assessed as low. The experts agreed that impacts on sensitive groups of non-target organisms will occur in the in-field area, but recolonisation within one year is likely to occur since the risk in the off-field area was assessed as low.

The in-field and off-field HQ values for *A. rhopalosiphi* and *T. pyri* were <2 for the uses of copper oxychloride, Bordeaux mixture and copper (I) oxide. *C. carnea*, *Coccinella septempunctata* and *T. cacoeciae* were also tested with copper oxychloride. The results support the expected low risk to non-target arthropods.

The in-field HQ values for both *A. rhopalosiphi* and *T. pyri* were above the trigger of 2 for the uses of tribasic copper sulphate. The effects were <50% in extended laboratory tests, at application rates higher than the suggested rates in vines and tomatoes. The off-field risk was assessed as low.

Overall, it is concluded that the risk to non-target arthropods is low for all representative uses. However, temporary impacts on the abundance of sensitive non-target arthropod species are expected for the representative uses of copper hydroxide.

5.5. RISK TO EARTHWORMS

The acute toxicity to earthworms from all copper variants is low. The acute TERs were significantly above the Annex VI trigger of 10. However, exposure to copper resulted in reproductive effects. In a study with copper oxychloride effects were observed even at the lowest tested concentration (NOEC < 15 mg Cu/kg soil dry weight). The study was considered as valid by the experts. The TERs were calculated as <0.8 and <1.5 for the uses in vine and tomato based on PECsoil values of 18.7 mg/kg and 10 mg/kg (not taking accumulation in soil into account). A data gap was identified in the meeting to refine the long-term risk assessment for earthworms for the uses in vine and tomato. The applicant informed the rapporteur Member State that a field study with earthworms is ongoing.

5.6. RISK TO OTHER SOIL NON-TARGET MACRO-ORGANISMS

Information from published studies with soil macro-organisms and copper chloride, copper nitrate, copper sulphate was submitted by the applicant. The studies were considered as reliable and robust enough to be considered in the risk assessment. The lowest endpoint (NOEC = 32 mg Cu/kg soil) was observed for nematodes (*Plectus acuminatus*). It was questioned during the peer-review whether the risk from multi-annual application would be sufficiently addressed. The experts agreed that a reliable PEC soil needs to be established before a final conclusion on the risk to soil non-target macro-organisms can be drawn. A data gap was identified for the applicant to address the risk to soil non-target macro-organisms from multi-annual application.

5.7. RISK TO SOIL NON-TARGET MICRO-ORGANISMS

No effects of >25% on soil nitrification were observed up to the highest tested application rate of 20 kg Cu/ha. A reduction of 29% in carbon mineralization was observed on day 28 at an application rate of 12.5 kg Cu/ha in a study with copper hydroxide. However, no effects of >25% were observed in the second soil type used in the study. No effects of >25% on carbon mineralization were observed in the other studies up to the highest tested application rates of 20 kg Cu/ha. The risk to soil micro-organisms was considered as low. However, a final conclusion on the risk to soil micro-organisms can be drawn after reliable PECsoil values are established.

5.8. RISK TO OTHER NON-TARGET-ORGANISMS (FLORA AND FAUNA)

The assessment of the risk to non-target plants is based on information from public literature. The sensitivity of the different plant species to copper varies to a great extent and depends also on soil conditions (pH). A concentration of 12.5 mg Cu/kg soil was toxic to peach seedlings, while effects on other plant species (e.g. *Avena sativa*) became apparent at concentrations of 400mg Cu/kg soil. However, no assessment of the studies was provided. It was not possible for the experts to draw a conclusion on the reliability of the studies. The experts agreed that a more comprehensive summary of the literature information is needed. Furthermore, the accumulation of copper in the off-field area should be considered in the risk assessment. A data gap was suggested to address the risk to non-target plants for several years of application and accumulation of copper in the off-field area.

5.9. RISK TO BIOLOGICAL METHODS OF SEWAGE TREATMENT

The EC_{50} for effects on respiration of sewage sludge ranged from 15.5 to 337 mg Cu/L. It is not expected that copper would reach sewage treatment plants at concentrations exceeding 15.5 mg Cu/L, if applied according to the proposed GAP. The risk to sewage treatment plants is considered to be low for the representative uses in vine and tomato.

6. Residue definitions

Soil

Definition for risk assessment:	total copper
Definition for monitoring:	total copper

Water

Ground water

Definition for exposure assessment:	soluble copper
Definition for monitoring:	soluble copper

Surface water

Definition for risk assessment:	soluble copper
Definition for monitoring:	soluble copper

Air

Definition for risk assessment:	total copper
Definition for monitoring:	total copper

Food of plant origin

Definition for risk assessment:	total copper
Definition for monitoring:	total copper

Food of animal origin

Definition for risk assessment:	not required for the representative uses assessed
Definition for monitoring:	not required for the representative uses assessed

Overview of the risk assessment of compounds listed in residue definitions for the environmental compartments

Soil

Compound (name and/or code)	Persistence	Ecotoxicology
Total copper	No degradation or dissipation proved	A high long-term risk to earthworms (data gap)

Ground water

Compound (name and/or code)	Mobility in soil	> 2 mg / L 1m depth for the representative uses	Pesticidal activity	Toxicological relevance	Ecotoxicological activity
Soluble copper	Data gap	Data gap	Yes	Yes	Yes

Surface water and sediment

Compound (name and/or code)	Ecotoxicology
Soluble copper	Very toxic and a high risk to aquatic organisms.

Air

Compound (name and/or code)	**Toxicology**
Total copper as copper hydroxide	Rat LC_{50} inhalation = 0.5 mg/L air/4 hour, whole body exposure: toxic by inhalation (R23)
Total copper as copper oxychloride	Rat LC_{50} inhalation = 2.83 mg/L air/4 hour, nose-only exposure: harmful by inhalation (R20)
Total copper as Bordeaux mixture	Rat LC_{50} inhalation = 1.97 mg/L air/4 hour, nose-only exposure: harmful by inhalation (R20)
Total copper as tribasic copper sulphate	Adequate inhalable atmosphere technically not feasible – no classification was proposed
Total copper as copper (I) oxide	Rat LC_{50} inhalation = 2.92 mg/L air/4 hour, nose-only exposure: harmful by inhalation (R20)

LIST OF STUDIES TO BE GENERATED, STILL ONGOING OR AVAILABLE BUT NOT PEER REVIEWED

- The evidence submitted for the identity of the copper variants is not acceptable and further evidence is identified as a data gap. This should include elemental analysis by ICP-MS, if this technique has limitations then other methods should be utilised (relevant for all uses evaluated, data gap identified by the PRAPeR meeting of experts May 2008, proposed submission date unknown, refer to chapter 1)
- 5-batch data with an analytical closure of >98% has been identified as a data gap for all copper variants (relevant for all uses evaluated, data gap identified by the PRAPeR meeting of experts May 2008, proposed submission date unknown, refer to chapter 1)
- Details of the method of manufacture for Bordeaux mixtures and copper (I) oxide have been identified as a data gap (relevant for all uses of Bordeaux mixtures and copper (I) oxide evaluated, data gap identified by the PRAPeR meeting of experts May 2008, proposed submission date unknown, refer to chapter 1)
- A specific method for copper (I) in the “Nordox 75 WG” formulation has been identified as a data gap (relevant for all uses of “Nordox 75 WP” evaluated, data gap identified by the PRAPeR meeting of experts May 2008, proposed submission date unknown, refer to chapter 1)
- Conversion rate of copper (I) to copper (II) in the environment has been identified as a data gap (relevant for all uses of “Nordox 75 WP” evaluated, data gap identified by the PRAPeR meeting of experts May 2008, proposed submission date unknown, refer to chapter 1)
- A 2-year shelf-life study for “Nordox 75 WP” has been identified as a data gap (relevant for all uses for “Nordox 75 WP” evaluated, data gap identified by the PRAPeR meeting of experts May 2008, study submitted but not peer reviewed, refer to chapter 1).
- Attrition and dispersability for “Nordox 75 WP” have been identified as a data gap (relevant for all uses for “Nordox 75 WP” evaluated, data gap identified by the PRAPeR meeting of experts May 2008, study submitted but not peer reviewed, refer to chapter 1).
- A 2-year shelf-life study for “Macc 80 WP” has been identified as a data gap (relevant for all uses for “Macc 80 WP” evaluated, data gap identified by the PRAPeR meeting of experts May 2008, study submitted but not peer reviewed, refer to chapter 1).
- Particle size distribution for “Macc 80 WP” has been identified as a data gap (relevant for all uses for “Macc 80 WP” evaluated, data gap identified by the PRAPeR meeting of experts May 2008, study submitted but not peer reviewed, refer to chapter 1).
- A 2-year shelf-life study for “Cuprocaffaro WP” has been identified as a data gap (relevant for all uses for “Cuprocaffaro WP” evaluated, data gap identified by the PRAPeR meeting of experts May 2008, study submitted but not peer reviewed, refer to chapter 1).

- Particle size distribution "Cuprocaffaro WP" has been identified as a data gap (relevant for all uses for "Cuprocaffaro WP" evaluated, data gap identified by the PRAPeR meeting of experts May 2008, study submitted but not peer reviewed, refer to chapter 1).
- A 2-year shelf-life study for "Kocide 101" has been identified as a data gap (relevant for all uses for "Kocide 101" evaluated, data gap identified by the PRAPeR meeting of experts May 2008, study submitted but not peer reviewed, refer to chapter 1).
- Evidence that tribasic copper sulfate is stable in the "Cuproxat SC" in a 2-year shelf-life study (relevant for all uses of "Cuproxat SC", data gap identified by the PRAPeR meeting of experts May 2008, proposed submission date unknown, refer to chapter 1)
- Information on the maximum concentration levels of heavy metals in copper specification, considering the available toxicological data has been identified as a data gap (relevant for all representative uses evaluated; data gap identified at the PRAPeR 49 meeting of experts June 2008; no submission date proposed by the notifier; refer to point 2)
- Short term toxicity study by inhalation has been identified as a data gap (relevant for all representative uses evaluated; data gap identified at the PRAPeR 49 meeting of experts June 2008; no submission date proposed by the notifier; refer to point 2.3)
- Refinement of worker exposure risk assessment is required (relevant for some representative uses evaluated – grapes: program 1 and tomatoes with WP formulations; data gap identified after the PRAPeR meeting of experts upon re-calculation of worker exposure risk assessment; no submission date proposed by the notifier; refer to point 2.12)
- Further residue trials in accordance with the German use (defoliation) should be provided in order to support the proposed MRL (relevant representative uses in grapes in north Europe with defoliation practice; data gap identified at the PRAPeR meeting of experts, no submission date proposed by the notifier; refer to point 3.1.1).
- Data gap for accumulated PEC of copper in soil after several years of use has been identified. Worst case soluble fraction and bio-available fraction need to be estimated taking into consideration that bioavailability may differ in different organisms. Available monitoring data of copper residue in areas where it has been used for many years should be compared to background levels in areas without agricultural use of copper. The meeting noted that the applicant has provided information on an ongoing study that could eventually address part or the entire data gap once finalized (relevant for all representative uses evaluated; submission date proposed by the notifier: study ongoing; refer to point 4.1.2).
- Data gap has been identified for a higher tier estimation of PEC $_{SW/SED}$, including assessment of speciation into the sediment and accumulation after repeated applications (relevant for all representative uses evaluated; submission date proposed by the notifier: no date proposed; refer to point 4.2.1).
- Data gap has been identified for calculation of PEC_{GW} of copper, resulting from the agricultural use of copper salts as proposed in the GAP table of the representative uses. Necessary input data need to be derived from appropriate studies. Comprehensive evaluation

of monitoring data can also be provided to address the potential ground water contamination resulting from the agricultural use of copper salts (relevant for all representative uses evaluated; submission date proposed by the notifier: no date proposed; refer to points 4.1.3 and 4.2.2)

- The long-term risk to birds needs to be addressed further (relevant for the use in vine and the outdoor use in tomatoes; data gap identified in the PRAPeR 48 meeting of experts May 2008; no submission date proposed; refer to point 5.1.)
- The risk of secondary poisoning of earthworm-eating birds and mammals needs further refinement (relevant for the use in vine and the outdoor use in tomatoes; data gap identified in the PRAPeR 48 meeting of experts May 2008; no submission date proposed; refer to point 5.1.)
- A new refined acute and long-term risk assessment for mammals is needed (relevant for the use in vine and the outdoor use in tomatoes; data requirement identified by the rapporteur Member State and confirmed as a data gap in the PRAPeR 48 meeting of experts May 2008; no submission date proposed; refer to point 5.1.)
- The risk from bioaccumulation in aquatic organisms needs to be addressed (relevant for the use in vine and the outdoor use in tomatoes; data gap identified in the PRAPeR 48 meeting of experts May 2008; no submission date proposed; refer to point 5.2.)
- The risk to bees needs further refinement (relevant for all representative uses; data gap identified in the PRAPeR 48 meeting of experts May 2008; no submission date proposed; refer to point 5.3.)
- The long-term risk to earthworms needs to be addressed further (relevant for the use in vine and the outdoor use in tomatoes; data requirement identified by the rapporteur Member State and confirmed as a data gap in the PRAPeR 48 meeting of experts in May 2008; no submission date proposed; refer to point 5.5.)
- The risk to soil-dwelling macro-organisms from multi-annual application needs to be addressed (relevant for the use in vine and the outdoor use in tomatoes; data gap identified in the PRAPeR 48 meeting of experts May 2008; no submission date proposed; refer to point 5.6.)
- A new risk assessment for non-target plants taking into account accumulation of copper in the off-field area after several years of application is required. A more comprehensive summary of the literature information on the effects on plants is needed (relevant for the use in vine and the outdoor use in tomatoes; data gap identified in the PRAPeR 48 meeting of experts May 2008; no submission date proposed; refer to point 5.8.)

CONCLUSIONS AND RECOMMENDATIONS

Overall conclusions

This conclusion was reached on the basis of the evaluation of the representative uses as a fungicide/bactericide on grapes and tomatoes. Full details of the GAP can be found in the attached list of endpoints.

The representative formulated products for the evaluation were "Kocide 101" (copper hydroxide), a wettable powder formulation containing 500 g/kg of Cu, “Macc 80” (Bordeaux mixture), a wettable powder formulation containing 200 g/kg of Cu, “Cuprocaffaro WP” (copper oxychloride), a wettable powder formulation containing 500 g/kg of Cu, “Cuproxat SC” (tribasic copper sulfate), a suspension concentrate formulation containing 193 g/L of Cu and “Nordox 75 WG” (copper (I) oxide), a wettable granule formulation containing 750 g/kg Cu.

Only single methods for the determination of residues are available since a multi-residue-method like the German S19 or the Dutch MM1 is not applicable due to the nature of the residues.

Sufficient data relating to physical, chemical and technical properties are available to ensure that at least some quality control measurements of the plant protection product are possible. The methods of analysis for the technical materials and the formulations are not accepted at this time as the identity of the various variants of copper are in question. The specifications and batch data are not accepted. In addition to this, there are some missing physical and chemical properties as well as storage stability data for the variants of copper.

In the mammalian metabolism studies, bioequivalence was established for the five representative copper (I) and (II) variants with copper sulphate pentahydrate, with which most of the toxicological studies were conducted. As a micronutrient essential for life, copper follows a specific homeostatic regulation mechanism, which allows excess copper to be excreted mainly through the bile; once absorbed, copper is bound to proteins so that free copper is normally not found neither in the blood, nor in the cells.

Copper hydroxide is toxic by inhalation, harmful if swallowed and present a risk of serious damage to eyes. Bordeaux mixture is harmful by inhalation and presents a risk of serious damage to eyes. Copper oxychloride and copper (I) oxide are harmful by inhalation and if swallowed. Tribasic copper sulphate is harmful if swallowed. Target organs of excess copper after oral administration are the liver and the kidneys. A concern was raised over inhalation of copper as lung lesions found in operator exposure were reproducible in guinea pigs; a data gap was identified for a short term inhalation toxicity study. Genotoxicity was not of concern upon oral administration, however, there was insufficient evidence to exclude a genotoxic potential of copper after non-oral exposure, and a critical area of concern was raised after inhalation of copper (I) and (II) variants. No carcinogenic potential was attributed to copper neither in rats nor in humans. Copper did not produce adverse effects on fertility, reproductive parameters or on the development; no neurotoxicity was attributed to copper ingestion, either. Four categories of copper poisoning were identified in the literature, namely direct oral ingestion as suicide attempts, cases where food or drinking water had become contaminated with copper, cases where home-made Bordeaux mixture had resulted in lung disease, and a single case of long term administration of excess copper as a dietary supplement resulting in liver failure.

Based on the WHO values established for human copper intake, the ADI – or more appropriately designated as “upper limit for copper intake” - for copper (I) and (II) variants was 0.15 mg Cu/kg bw/day, the AOEL was 0.072 mg Cu/kg bw/day and no ARfD was allocated. Operator exposure calculated for field applications was below the AOEL only, if personal protective equipment was used; for greenhouse applications, estimated operator exposure was below the AOEL only, if a respirator equipment was added to the protective equipment. Unprotected bystander exposure was calculated to be below the AOEL for all proposed uses and all representative formulations. Estimates of worker exposure indicated that exposure to copper (I) and (II) variants may exceed the AOEL for workers wearing protective gloves, long-sleeved shirt and long trousers in some scenarios of application. Therefore, a study to refine worker risk assessment is required for those specific scenarios.

Data presented and evaluated on the uptake, translocation and nature of copper residues in plants consist mainly of a review of public scientific literature. To determine the magnitude of residues in the treated raw agricultural commodities, residue trials in grapes and tomatoes were submitted. Also data on the residue levels in processed tomato and grape products were made available, but only found valid and acceptable for grapes. The data allow for MRL proposals and for a consumer exposure assessment with regard to the notified representative uses.

As exposure to copper is not only due to residues from the use as a plant protection product, an aggregate exposure assessment was performed by the RMS, including in addition background levels of copper in food and drinking water, based on a recent French dietary survey. This aggregate estimate shows that, in particular for children, the overall dietary copper exposure is not negligible and approximates the established toxicological reference value. Additional potential sources of dietary copper intakes have not been considered. Moreover, the estimate is not representative for all European consumers and therefore situations may arise where the overall copper intake of some consumer groups exceeds the toxicological reference value.

The data presented in the dossier and summarized in the DAR on the fate and behaviour of copper in soil consist mainly of a review of public scientific literature. Although the information is qualitatively complete, it does not allow deriving quantitative parameters to perform a proper environmental risk assessment. Data gaps have been identified by the RMS for accumulated PEC soil, $PEC_{SW/SED}$ and PEC_{GW} values and for the experimental (laboratory, field or monitoring) data to asses them. The data gaps were confirmed by the peer review.

The risk to birds and mammals is considered to be low for the use in tomatoes in glasshouse. A potential high long-term risk to birds and a high acute and long-term risk to mammals cannot be excluded for the use in vines and the field use in tomatoes on the basis of the submitted information.

Copper is very toxic to aquatic organisms. An indoor-microcosm study was submitted to address the high risk to aquatic invertebrates. The experts suggested using a NOEC of 3.12 µg Cu (dissolved)/L together with a safety factor of 3-5 to account for uncertainties related to effects on chironomids and possible favourable exposure conditions in the microcosm (high pH). Information from public literature suggested a high potential of bioaccumulation of copper in some aquatic organisms. The potential risk of bioaccumulation in fish needs be addressed further. The risk assessment for aquatic organisms needs to be finalised once reliable PECsw/sed values are established for the outdoor uses of copper in tomatoes and vines. The risk to bees from oral exposure was assessed as high in the first-tier risk assessment and needs to be addressed further.

A high long-term risk to earthworms was indicated on the basis of the available information. A data gap was identified to address the long-term risk to earthworms. A final conclusion on the risk to soil-dwelling organisms is only possible after reliable PEC_{soil} values are established.

The assessment of the risk to non-target plants is based on information from public literature. It was not possible for the experts to draw a conclusion on the reliability of the studies. A more comprehensive summary of the literature information is needed and the accumulation of copper in the off-field area should be considered in the risk assessment.

Particular conditions proposed to be taken into account to manage the risk(s) identified

- Operator exposure estimates were below the AOEL only if personal protective equipment is worn for field applications, and if respiratory protective equipment is added to the personal protective equipment for the indoor use in greenhouses (refer to point 2.12).
- Worker exposure estimates were below the AOEL only if personal protective equipment is worn, as protective gloves, long-sleeved shirt and long trousers for some proposed application scenarios (refer to point 2.12).

Critical areas of concern

- The identity of the copper variants is not concluded on.
- Specifications for the copper variants have not been concluded on.
- Inhalation toxicity has not been addressed adequately (genotoxicity and short term exposure) in relation to occupational exposure.
- Worker exposure estimates were above the AOEL, even when personal protective equipment as long-sleeved shirt, long trousers and gloves are worn for some proposed application scenarios (for grapes: program 1 and tomatoes with WP formulations).

- The chronic consumer dietary risk assessment is provisional, considering mean residue levels from tomatoes and grapes, natural background levels in food and an average residue levels in drinking water of 0.5 mg/kg based on French consumption survey data. The ADI might be exceeded when additional sources of copper and/or the legally permitted maximum concentration of copper in drinking water of 2 mg/L are taken into account in dietary intake estimates for European consumers.
- No assessment of PEC soil, $PEC_{SW/SED}$ and PEC_{GW}. Environmental risk assessment may not be completed with the available information.
- The long-term risk assessment for birds needs further refinement
- The acute and long-term risk assessment for mammals needs to be supported by data/information.
- Dissolved copper is very toxic to aquatic organisms. The current risk assessment is not finalised.
- The risk to bees needs to be addressed further.
- A potential high long-term risk to earthworms is indicated which needs to be refined further.
- The risk assessment for soil-dwelling organisms is not finalised.

APPENDIX 1 – LIST OF ENDPOINTS FOR THE ACTIVE SUBSTANCE AND THE REPRESENTATIVE FORMULATION

(Abbreviations used in this list are explained in appendix 2)

Identity, Physical and Chemical Properties, Details of Uses, Further Information

Active substance (ISO Common Name) ‡	Copper (I), copper (II) variants (Not an ISO common name)
Function (*e.g.* fungicide)	Fungicide/Bactericide

Rapporteur Member State	France

Identity (Annex IIA, point 1)

Copper hydroxide

Chemical name (IUPAC)	Copper (II) hydroxide
Chemical name (CA)	Copper hydroxide
CIPAC No	44.305
CAS No	20427-59-2
EINECS No	243-815-9
FAO Specification (including year of publication)	FAO specification (1998)

Total copper content (minimum)	**Maximum heavy metals content** (expressed in g/kg as fraction of Copper content)		
% (w/w)	**Lead**	**Cadmium**	**Arsenic**
57.3	0.0005	0.0001	0.0001

Minimum purity of the active substance as manufactured (g/kg)	Open
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the Active substance as manufactured (g/kg)	Open

Appendix 1 – list of endpoints

Molecular formula	CuH_2O_2
Molecular mass	97.6 g/mol
Structural formula	$Cu(OH)_2$

Copper oxychloride

Chemical name (IUPAC)	Dicopper chloride trihydroxide
Chemical name (CA)	Copper chloride oxide hydrate or Copper chloride hydroxide
CIPAC No	44.602
CAS No	1332-65-6 or1332-40-7
EINECS No	215-572-9
FAO Specification (including year of publication)	FAO specification (1991)

Total copper content (minimum) % (w/w)	**Maximum heavy metals content** (expressed in g/kg as fraction of Copper content)				**Water %**
	Lead	**Cadmium**	**Arsenic**	**Water soluble copper**[c]	
55.0	0.0005	0.0001	0.0001	0.010	2.0

Minimum purity of the active substance as manufactured (g/kg)	Open
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the Active substance as manufactured (g/kg)	Open
Molecular formula	Open
Molecular mass	Open
Structural formula	Open

Bordeaux mixture

Chemical name (IUPAC)	Open

Appendix 1 – list of endpoints

Chemical name (CA)	Open
CIPAC No	44.604
CAS No	8011-63-0
EINECS No	Not listed
FAO Specification (including year of publication)	No FAO specification
Minimum purity of the active substance as manufactured (g/kg)	Open
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the Active substance as manufactured (g/kg)	Open
Molecular formula	Open
Molecular mass	Open
Structural formula	Open

Tribasic copper sulfate

Chemical name (IUPAC)	Open
Chemical name (CA)	Open
CIPAC No	44.306
CAS No	12527-76-3
EINECS No	Not listed
FAO Specification (including year of publication)	No FAO specification
Minimum purity of the active substance as manufactured (g/kg)	Open
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the Active substance as manufactured (g/kg)	Open
Molecular formula	Open
Molecular mass	Open
Structural formula	Open

Appendix 1 – list of endpoints

Copper (I) oxide

Chemical name (IUPAC)	copper (I) oxide
Chemical name (CA)	Copper (I) oxide
CIPAC No	44.603
CAS No	1317-39-1
EINECS No	215-270-7
FAO Specification (including year of publication)	FAO specification (1991)

Total copper content (minimum) % (w/w)	Maximum heavy metals content (expressed in g/kg as fraction of Copper content)					CuO %	Water %
	Lead	Cadmium	Arsenic	Water soluble copper	Metallic copper		
82.0	0.00050	0.00010	0.00010	0.025	0.05	0.10	1.5

Minimum purity of the active substance as manufactured (g/kg)	Open
Identity of relevant impurities (of toxicological, environmental and/or other significance) in the Active substance as manufactured (g/kg)	Open
Molecular formula	Cu_2O
Molecular mass	143.14 g/mol
Structural formula	Cu_2O

Appendix 1 – list of endpoints

Physical-chemical properties (Annex IIA, point 2)

Purity % given below is expressed as Copper

Melting point (state purity) ‡	Decomposition before melting point Copper hydroxide purity 60.1% Copper oxychloride purity 57.39% Bordeaux mixture purity 26.70% Tribasic copper sulfate purity 55.10% Copper (I) oxide purity 87.4%
Boiling point (state purity) ‡	No boiling point before decomposition
Temperature of decomposition (state purity)	229°C Copper hydroxide (purity 60.1%) 240°C Copper oxychloride (purity 57.39%) 110-190°C Bordeaux mixture (purity 26.70%) 360°C Tribasic copper sulfate (purity 55.10%) >332°C Copper (I) oxide (purity 87.4%)
Appearance (state purity) ‡	solid powder, blue odour weak ammonia likely Copper hydroxide (purity 60.1%) Light green, very fine, non-free flowing powder odourless Copper oxychloride (purity 57.39%) Light green, very fine, non-free flowing powder odourless Bordeaux mixture (purity 26.70%) Lumpy powder Bluish-green odourless Tribasic copper sulfate (purity 55.10%) Fine, easily compactable, orange powder odourless Copper (I) oxide (purity 87.4%)
Relative density (state purity) ‡	Copper hydroxide purity 60.1% : 3.717 ± 0.19 at 20°C Copper oxychloride purity 57.39% : 3.642 ± 0.008 at 20°C Bordeaux mixture purity 26.70% : 3.12 ± 0.00035 at 19.5°C Tribasic copper sulfate purity 55.10% : 3.90 ± 0.021 at 20.5°C Copper (I) oxide purity 87.4% : 5.87 ± 0.001 at 20.0°C
Surface tension	72.2 mN/m at 20°C at 1.1mg/L concentration Copper oxychloride (57.39%) 68.9 mN/m at 21°C at 1.43 x 10^{-3} g/L concentration Bordeaux mixture (26.7%) 72.2 mN/m at 20°C at < 2.9 x 10^{-3} g/L concentration Tribasic copper suphate (55.10%) Data confirmed as required by Praper 46 Copper (I) oxide and copper hydroxide : not required as the water solubility is less than 1 mg/kg
Vapour pressure (state temperature, state purity) ‡	not applicable
Henry's law constant ‡	not applicable

Appendix 1 – list of endpoints

Solubility in water (state temperature, state purity and pH) ‡ Copper hydroxide	At 20.0 ± 0.5°C (Purity not given) pH 8.1 salt $6.80x10^{-4}$g/L as Cu $4.43x10^{-4}$ pH 4 salt >39.8 g/L as Cu>25.9 pH 6.5 salt $5.06x10^{-4}$ g/L as Cu $3.29x10^{-4}$ pH 10 salt <<$2.50x10^{-4}$ g/L as Cu <$1.63x10^{-4}$
Solubility in water (state temperature, state purity and pH) ‡ Copper oxychloride	At 20.0 ± 0.5°C (Purity 57.39%) pH 3.1salt >101 g/L as Cu>60.1 pH 6.6 salt $1.19x10^{-3}$ g/L as Cu$7.08x10^{-4}$ pH 10.1salt ≤$5.25x10^{-4}$ g/L as Cu ≤$3.12x10^{-4}$
Solubility in water (state temperature, state purity and pH) ‡ Bordeaux Mixture	At 20.0 ± 0.5°C (Purity 26.70%) pH 2.9 salt >124 g/L as Cu >33.1 pH 6.8 salt $2.20x10^{-3}$ g/L as Cu$5.87x10^{-4}$ pH 9.8 salt ≤$1.1x10^{-3}$ g/L as Cu≤$2.94x10^{-4}$
Solubility in water (state temperature, state purity and pH) ‡ Tribasic copper sulfate	At 20.0 ± 0.5°C (Purity 55.10%) pH 5.6 salt 0.5 g/L as Cu 0.28 pH 6.2 salt < $3.42x10^{-3}$ g/L as Cu $1.88x10^{-3}$ pH 9.8 salt ≤$2.55x10^{-4}$ g/L as Cu ≤$1.41x10^{-4}$ Data confirmed as required by Praper 46
Solubility in water (state temperature, state purity and pH) ‡ Copper (I) oxide	At 20.0 ± 0.5°C (Purity 87.4%) pH 4 salt > 28.6 g/L as Cu > 25.4 pH 6.6 salt < $6.39x10^{-4}$ g/L as Cu $5.67x10^{-4}$ pH 9.8 salt ≤$5.39x10^{-4}$ g/L as Cu ≤$4.79x10^{-4}$ Data confirmed as required by Praper 46

Appendix 1 – list of endpoints

Solubility in organic solvents ‡ (state temperature, state purity) as Copper content	(µg/L) | Copper hydroxide 30.0 ± 0.1°C (60.1%) | Copper oxychloride 20.0 ± 0.5°C (57.39%) | Bordeaux mixture 20.0 ± 0.5°C (26.7%) | Tribasic Copper sulfate 20.0 ± 0.5°C (55.10%) — see table below. Copper (I) oxide below 14000 µg/L (20.0 ± 0.5°C, Purity 87.4%)
Partition co-efficient ‡ (state temperature, pH and purity)	log P_{ow} = 0.44 (Copper hydroxide (purity 60.1%))
Hydrolytic stability (DT_{50}) (state pH and temperature) ‡	Cu^{2+} ion being a mono-atomic inorganic charged species cannot exist in an un-solvated, un-associated state and cannot be transformed into related degradation products in solution. Hydrolytic processes will have no action on copper and therefore data are not presented.
Dissociation constant (state purity) ‡	not appropriate
UV/VIS absorption (max.) incl. ε ‡ (state purity, pH)	λ_{max} (nm)< 200nm (ε) (L. $M^{-1}.cm^{-1}$)=7007 (statement) λ_{max} (nm) 798nm (ε) (L. $M^{-1}.cm^{-1}$)=47.8 (statement)
Flammability ‡ (state purity)	Not highly flammable Theoretical assessment for Copper hydroxide, Copper Oxychloride, Tribasic copper sulphate and Copper (I) oxide Bordeaux mixture

(µg/L)	Copper hydroxide 30.0 ± 0.1°C (60.1%)	Copper oxychloride 20.0 ± 0.5°C (57.39%)	Bordeaux mixture 20.0 ± 0.5°C (26.7%)	Tribasic Copper sulfate 20.0 ± 0.5°C (55.10%)
heptane	7010			<1000
N hexane		<9800	<9800	
p xylene	15.7			<1000
1,2 dichloroethane	61			<1000
dichloromethane		<10000	<9800	
isopropyl alcohol	1640			
methanol		<8200	<9000	
acetone	5000	<8400	<8800	<1000
ethyl acetate	2570	<11000	<8400	<1000
Toluene		<11000	<9600	
n-octanol		<11000	<9600	<1000

Copper (I) oxide below 14000 µg/L (20.0 ± 0.5°C, Purity 87.4%)

Explosive properties ‡ (state purity)	Not explosive Theoretical assessment for Copper hydroxide, Copper Oxychloride, Tribasic copper sulphate and Copper (I) oxide Bordeaux mixture
Oxidising properties ‡ (state purity)	Not oxidising Theoretical assessment for Copper hydroxide, Copper Oxychloride, Tribasic copper sulphate and Copper (I) oxide Bordeaux mixture

Appendix 1 – list of endpoints

List of representative uses evaluated (Copper (I), copper (II) variants)

Crop and/or situation (a)	Member State or Country	Product Name	F G or I (b)	Pests or Group of pests controlled I	Formulation Type (d-f)	Formulation Conc. Of a.s. (i)	Application Method Kind (f-h)	Application Growth stage & season (j)	Application Number min max (k)	Application Interval between apps. (min)	Application rate per treatment kg a.s./hL min max	Application rate per treatment water (L/ha) min max	Application rate per treatment kg a.s./ha max	PHI (days) (l)	Remarks (m)
Grapes Prog. 1 (d)	N & S	Kocide 101	F	downy mildew	WP	500 g/kg	airblast sprayer	post-flowering to harvest (BBCH 71 to 89)	4	7	0.125 – 2.0	100 – 1600	2.0	21 (N) 21 (S)	
		Cuprocaffaro WP			WP	500 g/kg					0.125 – 2.0	100 – 1600	2.0		
		Bordeaux mixture MACC80			WP	200 g/kg					0.125 – 2.0	100 – 1600	2.0		
		Cuproxat SC			SC	190 g/L					0.09 – 1.5	100 – 1600	1.5		[1] [2]
		Nordox 75WG			WG	750 g/kg					0.09 – 1.5	100 – 1600	1.5		

Crop and/or situation (a)	Member State or Country	Product Name	F G or I (b)	Pests or Group of pests controlled I	Formulation Type (d-f)	Formulation Conc. Of a.s. (i)	Application Method Kind (f-h)	Application Growth stage & season (j)	Application Number min max (k)	Application Interval between apps. (min)	Application rate per treatment kg a.s./hL min max	Application rate per treatment water (L/ha) min max	Application rate per treatment kg a.s./ha max	PHI (days) (l)	Remarks (m)
Grapes Prog. 2 (d)	N & S	Kocide 101	F	bacterial necrosis	WP	500 g/kg	airblast sprayer	post-harvest and early spring (BBCH 99 to 11)	2	90	0.30	1000	3.0	N/A	- [2]
		Cuprocaffaro WP Bordeaux mixture			WP	500 g/kg					0.30	1000	3.0		
		MACC80			WP	200 g/kg					0.30	1000	3.0		
		Cuproxat SC			SC	190 g/L					0.20	1000	2.0		
		Nordox 75WG			WG	750 g/kg					0.30	1000	3.0		
Tomato (industrial and fresh)	S	Kocide 101	F + G	Bacteria and fungi	WP	500 g/kg	field crop sprayer	all stages	6	7	0.25	500	1.25	10 (industrial) 3 (fresh)	[1] [2]
		Cuprocaffaro WP Bordeaux mixture			WP	500 g/kg					0.25	500	1.25		
		MACC80			WP	200 g/kg					0.25	500	1.25		
		Cuproxat SC			SC	190 g/L					0.16	500	0.80		
		Nordox 75WG			WG	750 g/kg					0.225	500	1.125		

Appendix 1 – list of endpoints

Crop and/or situation (a)	Member State or Country	Product Name	F G or I (b)	Pests or Group of pests controlled I	Formulation		Application				Application rate per treatment			PHI (days) (l)	Remarks (m)
					Type (d-f)	Conc. Of a.s. (i)	Method Kind (f-h)	Growth stage & season (j)	Number min max (k)	Interval between apps. (min)	kg a.s./hL min max	water (L/ha) min max	kg a.s./ha max		

[1] Yellow shadowing: Worker exposure exceeds the AOEL even when the use of PPE is considered
[2] Identity of the variants and specifications are not concluded.

Remarks:

(a) For crops the EU and Codex classifications (both) should be used.
(b) Outdoor or field use (F), glasshouse application (G) or indoor application (I)
I e.g. biting and sucking insects, soil borne insects, foliar fungi, weeds
(d) e.g. wettable powder (WP),emulsifiable concentrate (EC), granule (GR)
(e) GIFAP Codes – GIFAP Technical Monograph No. 2, 1989
(f) All abbreviations must be explained
(g) Method, e.g. high volume spraying, low volume spraying, spreading, dusting, drench
(h) Kind, e.g. overall, broadcast, aerial spraying, row, individual plant, between the plants
(i) g/kg or g/l – purity expressed as the variants
(j) Growth stage at last treatment, including where relevant information on season at time of application
(k) The minimum and maximum number of applications possible under practical conditions must be given
(l) PHI – Pre-harvest interval
(m) Remarks may include: Extent of use/ economic importance/restrictions (e.g. feeding/grazing)/minimal intervals between applications. Indicate uses not yet authorised.

Appendix 1 – list of endpoints

Chapter 2.2: Methods of analysis

Analytical methods for the active substance (Annex IIA, point 4.1)

Technical as (analytical technique)	Open
Impurities in technical as (analytical technique)	Open
Plant protection product (analytical technique)	Open

Analytical methods for residues for active substance and relevant metabolites (Annex IIA, point 4.2)

Residue definitions for monitoring purposes

Food of plant origin		Total copper
Food of animal origin		-
Soil		Total copper
Water	surface	dissolved copper
	drinking/ground	dissolved copper
Air		Total copper

Monitoring/Enforcement methods

Food/feed of plant origin (analytical technique and LOQ for methods for monitoring purposes)	AAS (for total copper content) LOQ: 2 mg/kg tomatoes, 5 mg/kg for grapes
Food/feed of animal origin (analytical technique and LOQ for methods for monitoring purposes)	No method validated. No method required.
Soil (analytical technique and LOQ)	AAS LOQ 40 mg/kg (for total copper content)
Water (analytical technique and LOQ)	Method DIN38406 is available for surface water and drinking water with LOQ 0.1 µg/L
Air (analytical technique and LOQ)	AAS LOQ: 0.5 ng/m^3 (for total copper) ICP/OES LOQ: 0.3 ng/m^3 (for total copper)
Body fluids and tissues (analytical technique and LOQ)	ICP/OES LOQ 0.02 mg/L

Appendix 1 – list of endpoints

Classification and proposed labelling with regard to physical and chemical data (Annex IIA, point 10)

Copper hydroxide	None
Copper oxychloride	none
Bordeaux mixture	none
Tribasic copper sulfate	none
Copper (I) oxide	none

Appendix 1 – list of endpoints

Impact on Human and Animal Health

Absorption, distribution, excretion and metabolism in mammals (Annex IIA, point 5.1)

Rate and extent of oral absorption	36 % in human on a copper adequate diet 56 % (low copper diet) 12 % (high copper diet) Similar absorption in rats: 50%
Distribution	Widely distributed, the liver being the regulation organ; copper is bound to ceruloplasmin
Potential for accumulation	No potential for accumulation, except in cases of genetic disease or chronic administration of high dose (60 mg/person/day), where copper accumulates in the liver
Rate and extent of excretion	Rapidly excreted (> 90 %) within 48 hours. Terminal half/life in rat of 10.1 hours. Excretion via the bile. No entero-hepatic circulation occurs. Excretion mainly bound to metallothioneins of the intestinal brush border and lost in faeces. Minor amounts in urine and from skin and hair.
Metabolism in animals	Does not occur; copper is a monoatomic ion and cannot be metabolized
Toxicologically relevant compounds ‡ (animals and plants)	Parent compound
Toxicologically relevant compounds ‡ (environment)	Parent compound

Acute toxicity (Annex IIA, point 5.2)

Rat LD_{50} oral ‡	Copper Hydroxide: 489 – 1280 mg/kg bw	**R22**
	Copper Oxychloride: Rat: 950 – 1862 mg/kg bw Mouse: 299 mg/kg bw	**R22**
	Bordeaux mixture: > 2000 mg/kg bw	
	Tribasic copper sulphate: 300 – 500 mg/kg bw	**R22**
	Copper (I) oxide: 300 – 500 mg/kg bw	**R22**

Appendix 1 – list of endpoints

Rat LD_{50} dermal ‡	Copper Hydroxide, Copper oxychloride, Bordeaux mixture, Tribasic copper sulphate, Copper (I) oxide: > 2000 mg/kg bw	
Rat LC_{50} inhalation ‡	Copper Hydroxide: 0.50 mg/L air/4 h (whole body)	**R23**
	Copper Oxychloride: 2.83 mg/L air/4 h (nose only)	**R20**
	Bordeaux mixture: 1.97 mg/L air/4 h (whole body)	**R20**
	Tribasic copper sulphate: technically not feasible	
	Copper (I) oxide: 2.92 mg/L air/4 h (nose only)	**R20**
Skin irritation ‡	Slightly irritant	
Eye irritation ‡	Copper Hydroxide: severely irritant	**R41**
	Copper Oxychloride: slightly irritant	
	Bordeaux mixture: severely irritant	**R41**
	Tribasic copper sulphate: not irritant	
	Copper (I) oxide: slightly irritant	
Skin sensitisation ‡	Copper Hydroxide, Copper oxychloride, Bordeaux mixture, Tribasic copper sulphate, Copper (I) oxide: not sensitising (M & K)	

Short term toxicity (Annex IIA, point 5.3)

Target/critical effect	Kidney: Proteins droplets in epithelial cells of the proximal convoluted tubules in rats. Stomach: Hyperplasia and hyperkeratosis of the squamous mucosa of the limiting ridge separating forestomach and glandular stomach in rats and mice. Liver: inflammation in rats Blood: haematological changes (increase in HCT, HGB, platelets count and RBC) in rats.
Relevant oral NOAEL	90-day rat: 16 mg Cu/kg bw/day 90-day mouse: 97 mg Cu/kg bw/day 1-year dog: 15 mg Cu/kg bw/day (test substance: copper gluconate)

Appendix 1 – list of endpoints

Relevant dermal NOAEL	21-day rabbit: 1000 mg of copper hydroxide/kg bw/day equivalent to 500 mg Cu/kg bw/day
Relevant inhalation NOAEL	No data – data required

Genotoxicity ‡ (Annex IIA, point 5.4)

Copper is unlikely to present a human genotoxic risk after oral ingestion.

Equivocal findings *in vivo* studies using non oral route.

(concern in relation to inhalation exposure)

Long term toxicity and carcinogenicity (Annex IIA, point 5.5)

Target/critical effect	Rat: Liver: hypertrophied hyperchromatic parenchymal cells, necrosis and marked inflammatory reaction Kidney: changes on the proximal convoluted tubule	
Relevant NOAEL	2-year rat: 27 mg Cu/kg bw/day, administered as potassium sodium copper chlorophyllin Mouse study not available but not required	
Carcinogenicity	No carcinogenic potential in rats. No evidence of carcinogenic potential in humans after oral ingestion.	

Reproductive toxicity (Annex IIA, point 5.6)

Reproduction toxicity

Reproduction target/critical effect	Reduced spleen weight in parents and offspring No effect on reproduction parameters	
Relevant parental NOAEL	15.2 mg Cu/kg bw/day	
Relevant reproductive NOAEL	23 mg Cu/kg bw/day	
Relevant offspring NOAEL	15.2 mg Cu/kg bw/day	

Developmental toxicity

Developmental target/critical effect	Rat: no maternal and foetal findings up to the highest dose tested Rabbit and Mouse: foetotoxicity at maternal toxic doses	

Appendix 1 – list of endpoints

Relevant maternal NOAEL	Rat: 30 mg Cu/kg bw/day (test substance: copper gluconate) Rabbit: 6 mg Cu/kg bw/day Mouse: 285 mg Cu/kg bw/day	
Relevant developmental NOAEL	Rat : 30 mg Cu/kg bw/day (test substance: copper gluconate) Rabbit: 6 mg Cu/kg bw/day Mouse: 285 mg Cu/kg bw/day	

Neurotoxicity (Annex IIA, point 5.7)

Acute neurotoxicity ‡	No evidence for neurotoxicity – not required	
Repeated neurotoxicity ‡	No data – not required	
Delayed neurotoxicity ‡	No data – not required	

Other toxicological studies (Annex IIA, point 5.8)

Mechanism studies ‡	Guinea pigs exposed by inhalation to copper during 70 days or 6 months showed similar lung and liver lesions to those seen in humans with Vineyard Sprayer's Lung. A study in mice showed that copper can cause an inhibition of the immune response probably through an indirect mechanism involving zinc deficiency caused by excess copper.
Studies performed on metabolites or impurities ‡	No data – not required

Appendix 1 – list of endpoints

Medical data ‡ (Annex IIA, point 5.9)

	The evidence shows that European diets contain copper at between 1 and 2 mg Cu/person/day. Data on humans show that repeated long-term intakes greater than 30 mg/day are toxic, intakes between 10 and 30 mg/day are without ill-effect, and that intakes of up to 10 mg/day do not even challenge the homeostatic mechanisms. From more than 30 years of use the few adverse effects observed were clearly related to well known potential for slight to severe eye irritation. In case of physiological (genetic) dysfunction in human two diseases could occur in man namely Wilson's disease, and Menkes' disease which are well documented in the medical literature.

Summary (Annex IIA, point 5.10)	Value	Study	Safety factor
ADI	0.15 mg Cu/kg bw/day	WHO value of 0.15 mg Cu/kg bw/day for children (based on human data) supported by 1-year dog study	No SF for human data 100 regarding dog study
AOEL	0.072 mg Cu/kg bw/day	WHO value of 0.2 mg Cu/kg bw/day for adults (based on human data) supported by 1-year dog and 90-day rat studies	Oral absorption 36% for human data and 50% for animal data; No SF for human data; SF of 100 regarding animal data
ARfD	Not allocated – not necessary		
Drinking water limit	The current EU standard is 2 mg/L for the maximum concentration of copper in drinking water (EU Directive 98/83[4]).		

[4] European Commission (1998); Council Directive 1998/83/EC of 3 November 1998 on the quality of water intended for human consumption. Official Journal of the European Communities, 05.12.1998, L 330/32

Appendix 1 – list of endpoints

Dermal absorption ‡ (Annex IIIA, point 7.3)

5 representative formulations (Kocide 101, Macc 80 WP, Cuprocaffaro WP, Cuproxat SC, Nordox 75 WG)	10 % default value for the concentrate and the spray dilution

Appendix 1 – list of endpoints

Exposure scenarios (Annex IIIA, point 7.2)

Operator

Copper hydroxide, copper oxychloride and Bordeaux mixture

Grapes (up to 3.0 kg Cu/ha)

Model Type	No PPE	Gloves M+L & Application	Gloves M+L & Application & coverall	Coverall, broad-brimmed headwear and gloves M/L & application
German model	875%	559%	125%	**96.5%**
POEM	2627%	1037%	-	-

Tomatoes in open fields (1.25 kg Cu/ha)

Model Type	No PPE	Gloves M+L & Application	Gloves M+L & Application & coverall	Coverall, broad-brimmed headwear and gloves M/L & application
German model	434%	121%	**45.3%**	**43.8%**
POEM	3065%	1014%	-	-

Tomatoes in greenhouses	% of AOEL
Without PPE	521 %
With PPE (gloves, coverall and respiratory protective equipment)	89 %

(This scenario covers the exposure in greenhouses to all the other formulations below)

Tribasic copper sulphate

Grapes (up to 2.0 kg Cu/ha)

Model Type	No PPE	Gloves M+L	Gloves M+L & Application	Gloves M+L & Application & coverall
German model	446%	371%	349%	**60%**
POEM	524%	357%	232%	-

Tomatoes outdoor (0.8 kg Cu/ha)

Model Type	No PPE	Gloves M+L	Gloves M+L & Application	Gloves M+L & Application & coverall
German model	141%	**65.9%**	**54%**	**5.8%**
POEM	398%	168%	**37.7%**	-

Copper (I) oxide

Grapes (up to 3.0 kg Cu/ha)

Model Type	No PPE	Gloves M+L	Gloves M+L & Application	Gloves M+L & Application & coverall
German model	655%	561%	528%	**93.7%**
POEM	1372%	782%	594%	-

Tomatoes outdoor (1.125 kg Cu/ha)

Model Type	No PPE	Gloves M+L	Gloves M+L & Application	Gloves M+L & Application & coverall

Appendix 1 – list of endpoints

German model	184%	**96.0%**	**79.2%**	**11.3%**
POEM	1279%	542%	359%	-

Workers	Copper hydroxide, Copper oxychloride and Bordeaux mixture	Grapes, 2.0 kg Cu/ha, 4 applications Without PPE: With PPE (gloves, long sleeved shirt & long trousers) Grapes, 3.0 kg Cu/ha, 2 applications Without PPE With PPE (gloves, long sleeved shirt & long trousers) Tomatoes, 1.25 kg Cu/ha, 6 applications Without PPE With PPE (gloves, long sleeved shirt & long trousers)	% of AOEL 2222 % **111** % 1667 % 83.5 % 2083 % **104** %
	Tribasic copper sulphate	Grapes, 1.5 kg Cu/ha, 4 applications Without PPE: With PPE (gloves, long sleeved shirt & long trousers) Grapes, 2.0 kg Cu/ha, 2 applications Without PPE With PPE (gloves, long sleeved shirt & long trousers) Tomatoes, 0.8 kg Cu/ha, 6 applications Without PPE With PPE (gloves, long sleeved shirt & long trousers)	% of AOEL 1667 % 83.5 % 1111 % 55.5 % 1333 % 66.5 %
	Copper (I) oxide	Grapes, 1.5 kg Cu/ha, 4 applications Without PPE: With PPE (gloves, long sleeved shirt & long trousers) Grapes, 3.0 kg Cu/ha, 2 applications Without PPE With PPE (gloves, long sleeved shirt & long trousers) Tomatoes, 1.125 kg Cu/ha, 6 applications Without PPE With PPE (gloves, long sleeved shirt & long trousers)	% of AOEL 1667 % 83.5 % 1667 % 83.5 % 1875 % 93.8 %
Bystanders	Copper hydroxide, copper oxychloride, Bordeaux mixture and Copper (I) oxide	Worst case: 20.5% of AOEL	
	Tribasic copper sulphate	Worst case: 13.75% of AOEL	

Classification and proposed labelling with regard to toxicological data (Annex IIA, point 10)

RMS/peer review proposal

Appendix 1 – list of endpoints

Copper hydroxide	**T**	"Toxic"
	Xn, R22	"Harmful if swallowed"
	T, R23	"Toxic by inhalation"
	Xi, R41	"Risk of serious damage to the eye"
Copper oxychloride	**Xn**	"Harmful"
	Xn, R20/22	"Harmful by inhalation and if swallowed"
Bordeaux mixture	**Xn**	"Harmful"
	Xn, R20	"Harmful by inhalation"
	Xi, R41	"Risk of serious damage to the eye"
Tribasic Copper Sulphate	**Xn**	"Harmful"
	Xn, R22	"Harmful if swallowed"
Copper (I) oxide	**Xn**	"Harmful
	Xn, R20/22	"Harmful by inhalation and if swallowed"

Appendix 1 – list of endpoints

Metabolism in plants (Annex IIA, point 6.1 and 6.7, Annex IIIA, point 8.1 and 8.6)

Plant groups covered	No study, Not required
Rotational crops	Not required
Metabolism in rotational crops similar to metabolism in primary crops?	Not applicable
Processed commodities	Not required
Residue pattern in processed commodities similar to residue pattern in raw commodities?	Not applicable
Plant residue definition for monitoring	Total Copper
Plant residue definition for risk assessment	Total Copper
Conversion factor (monitoring to risk assessment)	None

Metabolism in livestock (Annex IIA, point 6.2 and 6.7, Annex IIIA, point 8.1 and 8.6)

Animals covered	No study, Not required
Time needed to reach a plateau concentration in milk and eggs	Not applicable
Animal residue definition for monitoring	Total Copper
Animal residue definition for risk assessment	Total Copper
Conversion factor (monitoring to risk assessment)	None
Metabolism in rat and ruminant similar (yes/no)	Not applicable
Fat soluble residue: (yes/no)	No

Residues in succeeding crops (Annex IIA, point 6.6, Annex IIIA, point 8.5)

Not applicable

Stability of residues (Annex IIA, point 6 introduction, Annex IIIA, point 8 Introduction)

Not applicable

Appendix 1 – list of endpoints

Residues from livestock feeding studies (Annex IIA, point 6.4, Annex IIIA, point 8.3)

	Ruminant:	Poultry:	Pig:
	Conditions of requirement of feeding studies		
Expected intakes by livestock ≥ 0.1 mg/kg diet (dry weight basis) (yes/no - If yes, specify the level)	Not required for notified use	Not required for notified use	Not required for notified use
Potential for accumulation (yes/no):	Not applicable	Not applicable	Not applicable
Metabolism studies indicate potential level of residues ≥ 0.01 mg/kg in edible tissues (yes/no)	Not applicable	Not applicable	Not applicable
	Feeding studies (Specify the feeding rate in cattle and poultry studies considered as relevant) Residue levels in matrices : Mean (max) mg/kg		
Muscle	n/a	n/a	n/a
Liver	n/a	n/a	n/a
Kidney	n/a	n/a	n/a
Fat	n/a	n/a	n/a
Milk	n/a		
Eggs		n/a	

Appendix 1 – list of endpoints

Summary of residues data according to the representative uses on raw agricultural commodities and feedingstuffs (Annex IIA, point 6.3, Annex IIIA, point 8.2)

Crop	Northern or Mediterranean Region, field or glasshouse, and any other useful information	Trials results relevant to the representative uses (a)	Recommendation/comments	MRL estimated from trials according to the representative use	HR (c)	STMR (b)
Table Grapes	South	2.2, 4.1, 4.6, 5.1, 6.2, 7.0, 7.1, 7.5, 7.6, 8.7,9.4, 11, 12		20	12	7.1
Wine Grapes	South	3 x<5, 5.2, 6.8, 6.9, 7.5, 9.9, 12, 20, 30, 45, 56		50	56	7.5
Wine Grapes	North	2.2, 4.1, 5.1, <5, 6.2, 7.6 7.1, 7.0, 8.7, 9.4, 11,			11	7.0
Tomato	South, Field and protected	1.9, 15 x<2, 6 x 2.0, 2 x 2.1, 5 x 2.2, 2x 2.3, 2x 2.4, 2.7, 3.7, 3.9		5	3.9	2

(a) Numbers of trials in which particular residue levels were reported *e.g.* 3 x <0.01, 1 x 0.01, 6 x 0.02, 1 x 0.04, 1 x 0.08, 2 x 0.1, 2 x 0.15, 1 x 0.17
(b) Supervised Trials Median Residue *i.e.* the median residue level estimated on the basis of supervised trials relating to the representative use
(c) Highest residue

Appendix 1 – list of endpoints

Consumer risk assessment (Annex IIA, point 6.9, Annex IIIA, point 8.8)

1: considering residues in crops of notified uses only:

ADI	0.15 mg/kg/day
TMDI (% ADI) according to WHO European diet	61.6% WHO European diet.
TMDI (% ADI) according to national (to be specified) diets	French adult: 245%, French toddler: 38%, French infant:22%
IEDI (WHO European Diet) (% ADI)	4.55% WHO European diet
NEDI (specify diet) (% ADI)	UK toddler 26% German child (BBA model) 7.4% French adult 10% French toddler 14%
Factors included in IEDI and NEDI	Besides the STMR processing factors for wine 0.19 and raisins 2.7 were used.

2: considering notified uses and average (background) levels of copper in food and drinking water for French consumers[5]

ADI	0.15 mg/kg/day
TMDI (% ADI) according to WHO European diet	not assessed
TMDI (% ADI) according to national (to be specified) diets	French adult : 317 %, French toddler: 155%, French infant: 160% (with EU drinking water limit of 2 mg/L)[6]
IEDI (WHO European Diet) (% ADI)	Cluster diet B: notified uses 14.7% Cluster diet B: 71 % from average (background) levels[2] and with French high copper content in water of 0.5 mg/L
NEDI (specify diet) (% ADI)	French adult 40%, French toddler 92%, French infant 103% (with French high copper content in water of 0.5 mg/L) French adult 26%, French toddler 86%, French infant 99% (with French average copper content in

[5] based on LEBLANC et al (2005): Dietary exposure estimates of 18 elements from the 1st French Total diet study; Food Add. Contam.22 (7): 624-641

[6] maximum concentration in drinking water according to Council directive 1998/83/EC, OJ 5.12.1998, L330/32

Appendix 1 – list of endpoints

	water of 0.05 mg/L)
Factors included in IEDI and NEDI	Besides the STMR processing factors for wine 0.19 and raisins 2.7 were used.

ARfD	None allocated
IESTI (% ARfD)	Not applicable
NESTI (% ARfD) according to national (to be specified) large portion consumption data	Not applicable
Factors included in IESTI and NESTI	Not applicable

Processing factors (Annex IIA, point 6.5, Annex IIIA, point 8.4)

Crop/ process/ processed product	Number of studies	Processing factors		Amount transferred (%) (Optional)
		Transfer factor	Yield factor	
grapes				
raisin	3	2.70		
grapes				
must	18	1.90		
juice	10	0.40		
wine	24	0.19		
wet pomace	7	2.80		

Proposed MRLs (Annex IIA, point 6.7, Annex IIIA, point 8.6)

Tomatoes7	5 mg/kg
Table grapes8	20 mg/kg
Wine grapes	50 mg/kg

When the MRL is proposed at the LOQ, this should be annotated by an asterisk after the figure.

[7] Field and protected crop S-EU
[8] S-EU

Appendix 1 – list of endpoints

Fate and Behaviour in the environment

Route of degradation (aerobic) in soil (Annex IIA, point 7.1.1.1.1)

Mineralization after 100 days	Not applicable to inorganic salts.

Distribution of copper in soils: study on 24 soils (supporting information)

Exchangeable % (Cu-Ca)	Mineral bound % (Cu-Aac)	Organic bound % (Cu-Pyr)	Oxide occluded % (Cu-Ox)	Residual % (Cu-Res)
0.1 – 0.2	0.1 – 2.8	13.3 – 46.4	2.5 – 36.0	23.5 – 76.6

Route of degradation in soil - Supplemental studies (Annex IIA, point 7.1.1.1.2)

Anaerobic degradation	
Mineralization after 100 days	Not applicable to inorganic salts.
Soil photolysis	Not applicable to inorganic salts.

Rate of degradation in soil (Annex IIA, point 7.1.1.2, Annex IIIA, point 9.1.1)

Laboratory studies

No degradation is expected. Transformation of the free soluble ion in different complexed species is expected according available published literature. However, no quantitative estimation of the rate of these processes is available. Ecotoxicological significance of availability of the different possible species is not known.

Field studies ‡ supporting information only

Soil type	Location	pH (mean)	Depth (cm)	Mobile copper by DTPA extraction (%)	Mobile copper by $CaCl_2$ extraction (%)
Vineyard	Italy	7.11	0–10	37.4	0.1
			10–20	38.2	0.1
			20–40	37.0	0.1
			40–60	32.8	0.1
			60-100	29.4	0.2

Appendix 1 – list of endpoints

Field studies ‡ supporting information only

Soil type	Location	pH (mean)	Depth (cm)	Mobile copper by DTPA extraction (%)	Mobile copper by $CaCl_2$ extraction (%)
Vineyard - Plain	Portugal	pH	Depth (cm)	Total copper (mg/kg)	Extractable copper (mg/kg)
Not ploughed		8.6	0-20	130.2	72.3
Ploughed, not fertilized		7.7	0-20	102.4	56.0
Ploughed and fertilized		8.2	0-20	120.8	66.8
-		8.6	20-50	106.9	55.3
-		8.4	50-100	74.4	32.6
-		8.4	100-135	23.4	2.6
Vineyard - Terrace	Portugal				
-		8.1	0-25	58.4	24.5
With roots, friable		8.2	25-45/50	45.2	16.3
No roots, firm		8.2	25-45/50	30.5	6.2
With roots, friable		8.2	45/50-100	38.7	9.4
No roots, firm		8.1	45/50-100	38.0	10.1

Appendix 1 – list of endpoints

Soil type	Location	pH	Depth (cm)	Mean copper content (mg/kg)	%[1]
Vineyard	Germany	n.d.	0 – 20	317	-
			20 – 40	159	50
			40 – 60	95	30
			60 – 80	59	19
			80 – 100	54	17
			100 – 120	45	14
			120 – 140	34	11
			140 – 160	15	5

n.d.: not determined
[1] Expressed as a percent of the 0 – 20 cm horizon result.

Soil adsorption/desorption (Annex IIA, point 7.1.2)

No valid study

Mobility in soil (Annex IIA, point 7.1.3, Annex IIIA, point 9.1.2)

Column leaching ‡	Eluation (mm): 300 mm Time period (d): 2 d
	Leachate: 1 % active substance in leachate ≈ 99 % total residues retained in top 6 cm
Aged residues leaching ‡	No study submitted
Lysimeter/ field leaching studies ‡	No valid study

Appendix 1 – list of endpoints

pH dependence	Soil pH values range from 4 to 8.5 in most soils. Over this pH range, Cu speciation in the soil solution is susceptible of considerable variation, although the total soluble Cu may not vary so much. The activity of the free Cu ion will steadily increase with decreasing pH for instance, while the contribution of complex species will decrease. Therfore, amount fo free copper ion is expected to be higher under acidic conditions.

PEC (soil) (Annex IIIA, point 9.1.3)

Parent Method of calculation	DT_{50} (d): not relevant Tier 1 estimation The PEC soils calculated do not cover accumulation of copper in soils following multiple applications and multi-annual application of copper pesticides.
Application data WP hydroxide, WP oxychloride, WP Bordeaux mixture	Crop: vines (downy mildew) Depth of soil layer: 5cm Soil bulk density: 1.5g/cm^3 % plant interception: 0 Number of applications: 4 Interval (d): 7 Application rate(s): 2000 g Cu/ha
Application data SC tribasic, WG oxide	Crop: vines (downy mildew) Depth of soil layer: 5cm Soil bulk density: 1.5g/cm^3 % plant interception: 0 Number of applications: 4 Interval (d): 7 Application rate(s): 1500 g Cu/ha

Appendix 1 – list of endpoints

Application data WP hydroxide, WP oxychloride, WP Bordeaux mixture, WG oxide	Crop: vines (bacterial necrosis) Depth of soil layer: 5cm Soil bulk density: 1.5g/cm^3 % plant interception: 0 Number of applications: 2 Interval (d): 90 Application rate(s): 3000 g Cu/ha
Application data SC tribasic	Crop: vines (bacterial necrosis) Depth of soil layer: 5cm Soil bulk density: 1.5g/cm^3 % plant interception: 0 Number of applications: 2 Interval (d): 90 Application rate(s): 2000 g Cu/ha
Application data WP hydroxide, WP oxychloride, WP Bordeaux mixture	Crop: tomato Depth of soil layer: 5cm Soil bulk density: 1.5g/cm^3 % plant interception: 0 Number of applications: 6 Interval (d): 7 Application rate(s): 1250 g Cu/ha
Application data SC tribasic	Crop: tomato Depth of soil layer: 5cm Soil bulk density: 1.5g/cm^3 % plant interception: 0 Number of applications: 6 Interval (d): 7 Application rate(s): 800 g Cu/ha
Application data WG oxide	Crop: tomato Depth of soil layer: 5cm Soil bulk density: 1.5g/cm^3 % plant interception: 0 Number of applications: 6 Interval (d): 7 Application rate(s): 1125 g Cu/ha

Appendix 1 – list of endpoints

$PEC_{(s)}$ (mg/kg)	Single application Max, initial	Single application Time weighted average	Multiple application Max, accumulation	Multiple application Time weighted average
Grape – Downy mildew				
	2.7		10.7	
	2.0			
Grape – Bacterial necrosis				
	4.0		8.0	
	2.67			
Grape – both uses				
	6.7		18.7	
Tomato				
	1.67		10.0	
	1.07			
	1.5			

Data gap outstanding for accumulations calculation and estimation of worst case soluble and bio-available fractions.

Route and rate of degradation in water (Annex IIA, point 7.2.1)

Hydrolytic degradation of the active substance and metabolites > 10 % ‡	Not relevant
Photolytic degradation of active substance and metabolites above 10 % ‡	Not relevant
Readily biodegradable ‡	Not relevant, substance not ready biodegradable

Degradation in water / sediment

Copper hydroxide WP	Distribution (eg max in water 60 % after 4 d. Max. sed 50 % after 375 d)									
Water / sediment system	pH water	pH sed	t. °C	DT_{50} whole sys.	St. (r^2	DT_{50} water	St. (r^2	DT_{50} sed	St. (r^2	Method of calculati

Appendix 1 – list of endpoints

	phase				)		)		)	on
Microcosm	7-10	nd	5-25	> 400 d	-	max: 30.5 d	-	> 400 d	-	Model Maker v.4

nd: not determined

PEC (surface water) (Annex IIIA, point 9.2.3)

No PECsw can be calculated due to the lack of validated model. FOCUS SW considered not appropriate for inorganic salts.
Data gap identified for higher tier estimation of PEC $_{SW/SED}$.

PEC (ground water) (Annex IIIA, point 9.2.1)

Not determined. FOCUS SW considered not appropriate for inorganic salts.

PEC$_{(gw)}$ From lysimeter / field studies
Not determined

Data gap identified to address potential ground water contamination by copper resulting form agricultural uses of copper salts.

Fate and behaviour in air (Annex IIA, point 7.2.2, Annex III, point 9.3)

Direct photolysis in air ‡	Not studied - no data requested
Quantum yield of direct phototransformation	-
Photochemical oxidative degradation in air ‡	-
Volatilisation ‡	Not relevant

PEC (air)

Method of calculation	none

PEC$_{(a)}$

Maximum concentration	negligible

Appendix 1 – list of endpoints

Residues requiring further assessment

Environmental occurring metabolite requiring further assessment by other disciplines (toxicology and ecotoxicology).	Soil: total copper Surface Water: dissolved copper Sediment: total copper Ground water: dissolved copper Air: none

Monitoring data, if available (Annex IIA, point 7.4)

Soil (indicate location and type of study)	-
Surface water (indicate location and type of study)	
Ground water (indicate location and type of study)	-
Air (indicate location and type of study)	-

Points pertinent to the classification and proposed labelling with regard to fate and behaviour data

Candidate for R53

Appendix 1 – list of endpoints

Effects on terrestrial vertebrates (Annex IIA, point 8.1, Annex IIIA, points 10.1 and 10.3)

Birds ‡				
Species	Test substance	Time scale	LD50 (mg Cu/kg bw)	
Colinus virginianus	Copper hydroxide	Acute	223	
Coturnix coturnix japonica	Copper hydroxide	Acute	556	
Colinus virginianus	Copper hydroxide WP	Acute	357	
Colinus virginianus	Copper oxychloride	Acute	511	
Coturnix coturnix japonica	**Copper oxychloride WP**	**Acute**	**173** [a]	
Colinus virginianus	Bordeaux mixture	Acute	> 616	
Colinus virginianus	Bordeaux mixture WP	Acute	> 439.9	
Colinus virginianus	Tribasic copper sulphate	Acute	616	
Colinus virginianus	Tribasic copper sulphate SC	Acute	> 72.4	
Coturnix coturnix japonica	Tribasic copper sulphate SC	Acute	221	
Coturnix coturnix japonica	Copper oxide	Acute	1 183	
Coturnix coturnix japonica	Copper oxide WG	Acute	650	
Species	Test substance	Time scale	LC50 (mg Cu/kg bw/day)	LD50 (mg Cu/kg feed)
Colinus virginianus	Copper oxychloride	Short-term	333	1939
Colinus virginianus	Bordeaux mixture	Short-term	> 334.1	> 1369
Species	Test substance	Time scale	NOEL (mg Cu/kg bw/day)	NOEC (mg Cu/kg feed)
Colinus virginianus	Copper hydroxide	Short-term	123.6 [b]	883 [c]
Anas platyrhynchos	Copper hydroxide	Short-term	215.6 [b]	1 053 [c]

Appendix 1 – list of endpoints

Colinus virginianus	Copper hydroxide	Short-term	135.1 [b]	963 [c]
Anas platyrhynchos	Copper hydroxide	Short-term	190.6 [b]	963 [c]
Colinus virginianus	Tribasic copper sulphate	Short-term	89.4 [b]	246 [c]
Anas platyrhynchos	Tribasic copper sulphate	Short-term	176.3 [b]	530 [c]
Colinus virginianus	**Copper oxide**	**Short-term**	**31.9** [ab]	**136** [ac]
Colinus virginianus	**Copper hydroxide**	**Long-term**	**5.05** [a]	**57.5** [a]
Anas platyrhynchos	Copper hydroxide	Long-term	7.05	57.5
Colinus virginianus	Copper hydroxide	Long-term	5.12	57.5
Anas platyrhynchos	Copper hydroxide	Long-term	50.3	288

a: data retained for the risk assessment
b: LD_{50} was not relevant because of food avoidance
c: LC_{50} was not relevant because of food avoidance

Mammals ‡			
Species	Test substance	Time scale	LD_{50} (mg Cu/kg bw)
Rat	Copper hydroxide	Acute	439
Rat	Copper hydroxide	Acute	736 (males) 679 (females)
Rat	Copper hydroxide	Acute	281
Rat	Copper hydroxide WP	Acute	417 (males) 458 (females)
Rat	Copper oxychloride	Acute	1 075
Mouse	Copper oxychloride	Acute	171
Rat	Copper oxychloride	Acute	807
Rat	Copper oxychloride	Acute	693 (males) 548 (females)
Rat	Copper oxychloride WP	Acute	1 180
Rat	Bordeaux mixture	Acute	642

Appendix 1 – list of endpoints

Rat	Bordeaux mixture	Acute	607
Rat	Bordeaux mixture WP	Acute	> 410
Rat	**Tribasic copper sulphate**	**Acute**	**162.6** [a] to 271
Rat	Tribasic copper sulphate SC	Acute	422 (males) 325 (females) 378 (males & females)
Rat	Copper oxide	Acute	261 to 435
Rat	Copper oxide WP	Acute	2 374
Species	Test substance	Time scale	NOEL (mg/kg bw/day)
Dog	Copper gluconate	Long-term	15
Rat	**Copper sulphate**	**Long-term**	**16** [a] (males) 17 (females)
Rat	Copper gluconate and copper sulphate	Long-term	27
Additional higher tier studies ‡			

a: data retained for the risk assessment

Toxicity/exposure ratios for terrestrial vertebrates (Annex IIIA, points 10.1 and 10.3)

Crop and application rate

Indicator species/Category	Crop	Time scale	ETE	TER	Annex VI Trigger
Tier 1 (Birds)					
Coturnix coturnix japonica (insectivorous bird)	Vine (1.5 – 3.0 kg/ha)	Acute	81.1–162.2	**2.4–1.1**	10
	Tomato (0.8 – 1.25 kg/ha)		432–67.6	**4.0–2.6**	
Colinus virginianus (insectivorous bird)	Vine (1.5 – 3.0 kg/ha)	Short-term	45.3–90.6	**0.7–0.4**	10
	Tomato (0.8 – 1.25 kg/ha)		24.1–37.8	**1.3–0.8**	
Colinus virginianus (insectivorous bird)	Vine (1.5 – 3.0 kg/ha)	Long-term	45.3–90.6	**0.11–0.06**	5
	Tomato (0.8 – 1.25 kg/ha)		24.1–37.8	**0.20–0.13**	

Appendix 1 – list of endpoints

Indicator species/Category	Crop	Time scale	ETE	TER	Annex VI Trigger
Earthworm-eating birds					
Copper hydroxide, Bordeaux mixture and copper oxychloride	Vine	Long-term	8.8	**0.57**	
	Tomato	Long-term	5.5	**0.92**	
Copper oxide	Vine	Long-term	7.9	**0.64**	
	Tomato	Long-term	5.0	-	
Tribasic copper sulphate	Vine	Long-term	6.1	**0.83**	
	Tomato	Long-term	3.5	**1.4**	
Tier 2 (Birds)					
Partridge	Vine (3.0 kg/ha)	Acute	12.7	**2.5**	10
Skylark	Vine (3.0 kg/ha)	Acute	6.5	**4.9**	
Starling	Vine (3.0 kg/ha)	Acute	1.3	25	
Group A	Vine (3.0 kg/ha)	Long-term	5.68	**0.9**	5
Group B	Vine (3.0 kg/ha)	Long-term	3.57	**1.4**	
	Tomato	Long-term	4.21	**1.2**	
Group C	Vine (3.0 kg/ha)	Long-term	6.57	**0.8**	
	Tomato (1.25 kg/ha)	Long-term	2.90	**1.7**	
Group D	Tomato (1.25 kg/ha)	Long-term	2.24	**2.3**	
Group E	Vine (3.0 kg/ha)	Long-term	2.24	**2.2**	
	Tomato (1.25 kg/ha)	Long-term	2.63	**1.9**	
Tier 1 (Mammals)					
Rat (herbivorous mammal)	Vine (1.5 – 3.0 kg/ha)	Acute	177.3-354.6	**0.9–0.5**	10
	Tomato (0.8 – 1.25 kg/ha)		94.6-147.8	**1.7–1.1**	
Rat (herbivorous mammal)	Vine (1.5 – 3.0 kg/ha)	Long-term	95.9–191.7	**0.17–0.08**	5

Appendix 1 – list of endpoints

Indicator species/Category	Crop	Time scale	ETE	TER	Annex VI Trigger
	Tomato (0.8 – 1.25 kg/lha)		51.1–79.9	**0.31–0.20**	
Earthworm-eating mammals					
Copper hydroxide, Bordeaux mixture and copper oxychloride	Vine	Long-term	11.2	**1.3**	5
	Tomato	Long-term	7.0	**2.1**	
Copper oxide	Vine	Long-term	10.1	**1.5**	
	Tomato	Long-term	6.3	**2.4**	
Tribasic copper sulphate	Vine	Long-term	7.9	**1.9**	
	Tomato	Long-term	4.5	**3.3**	
Tier 2 (Mammals)					
Vole	Vine (copper hydroxide)	Acute	145.8	**1.9**	10
	Vine (copper oxychloride)		145.8	**1.2**	
	Vine (Bordeaux mixture)		145.8	**4.2**	
	Vine (tribasic copper sulphate)		145.8	**1.1**	
	Vine (copper oxide)		145.8	**1.8**	

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

Group	Test substance	Time-scale (Test type)	End point	Toxicity [a] (mg/L)
Laboratory tests ‡				
Fish				
O. mykiss	Copper hydroxide WP	96 hr (flow-through)	Mortality, EC_{50}	0.0165 total (mm) **0.0080** dissolved (mm)
O. mykiss	Copper oxychloride	96 hr (flow-through)	Mortality, EC_{50}	> 43.8 total (mm) > 0.106 dissolved

Appendix 1 – list of endpoints

Group	Test substance	Time-scale (Test type)	End point	Toxicity [a] (mg/L)
				(mm)
O. mykiss	Copper oxychloride	96 hr (semi-static)	Mortality, EC_{50}	0.052 dissolved (mm)
O. mykiss	Copper oxychloride WP	96 hr (flow-through)	Mortality, EC_{50}	0.78 total (mm) 0.0109 dissolved (mm)
O. mykiss	Bordeaux mixture	96 hr (semi-static)	Mortality, EC_{50}	> 21.39 total (mm) > 0.125 dissolved (mm)
O. mykiss	Bordeaux mixture	96 hr (semi-static)	Mortality, EC_{50}	0.086 dissolved (mm)
O. mykiss	Bordeaux mixture WP	96 hr (semi-static)	Mortality, EC_{50}	0.052 total (mm)
O. mykiss	Tribasic copper sulphate SC	96 hr (static)	Mortality, EC_{50}	13.18 total (mm)
C. carpio	Tribasic copper sulphate SC	96 hr (flow-through)	Mortality, EC_{50}	> 19.3 total (mm)
O. mykiss	Copper oxide	96 hr (flow-through)	Mortality, EC_{50}	0.207 total (mm) 0.0344 dissolved (mm)
O. mykiss	Copper oxide WP	96 hr (flow-through)	Mortality, EC_{50}	0.047 total (mm) 0.0106 dissolved (mm)
C. carpio	Copper oxide WG	96 hr (semi-static)	Mortality, EC_{50}	4.37 total (nom)
O. mykiss	Copper hydroxide WP	ELS – 92 d	Growth NOEC	0.0155 total (nom) 0.0017 dissolved (nom)
O. mykiss	Tribasic copper sulphate SC	21 d(flow-through)	Growth NOEC	0.97 total (nom)
O. mykiss	*Copper Hydroxide WP (with sediment)*	96 hr (static)	Mortality, EC_{50}	0.54 total (mm) 0.18 dissolved (mm)
D. rerio	Copper hydroxide	48 hr (static)	Mortality, NOEC	3.2 total (nom)

9 the method used in these tests is not validated and is known to have a bias. The fish egg membrane is difficult to be crossed over by some molecules. The most sensitive stage is actually after hatching. The results can therefore not be used in the risk assessment

Appendix 1 – list of endpoints

Group	Test substance	Time-scale (Test type)	End point	Toxicity [a] (mg/L)
	Copper oxychloride	48 hr (static)	Mortality, NOEC	18.0 total (nom)
	Bordeaux mixture	48 hr (static)	Mortality, NOEC	22.5 total (nom)
	Tribasic copper sulphate	48 hr (static)	Mortality, NOEC	76.8 total (nom)
	Copper oxide	48 hr (static)	Mortality, NOEC	1.06 total (nom)
Aquatic invertebrate				
D. magna	Copper hydroxide	48 h (static)	Mortality, EC_{50}	0.038 total (mm) 0.0266 dissolved (mm)
D. magna	Copper oxychloride	48 h (static)	Mortality, EC_{50}	0.29 total (nom)
D. magna	Bordeaux mixture	48 h (static)	Mortality, EC_{50}	1.87 total (mm)
D. magna	Copper oxide	48 h (static)	Mortality, EC_{50}	0.45 total (nom)
D. magna	Copper oxychloride	21 d (semi-static)	Reproduction, NOEC	0.0076 total (nom)
D. magna	Copper oxychloride	21 d (semi-static)	Reproduction, NOEC	0.059 total (nom)
D. magna	Tribasic copper sulphate SC	21 d (semi-static)	Reproduction, NOEC	0.057 total (mm)
D. magna (21-d studies with sediment)	Copper hydroxide WP	21 d (semi-static)	Mortality, EC_{50}	0.024 total (mm)
			Reproduction,	0.0299 total (mm)
	Copper hydroxide SC	21 d (semi-static)	Mortality, EC_{50}	0.0109 total (mm)
			Reproduction,	0.027 total (mm)
	Copper oxychloride WP	21 d (semi-static)	Mortality, EC_{50}	0.0298 total (mm)
			Reproduction,	0.0461 total (mm)
	Bordeaux mixture WP	21 d (semi-static)	Mortality, EC_{50}	0.0198 total (mm)
			Reproduction,	0.0378 total (mm)
	Tribasic copper sulphate SC	21 d (semi-static)	Mortality, EC_{50}	0.0167 total (mm)
			Reproduction,	0.0334 total (mm)
	Copper oxide WP	21 d (semi-static)	Mortality, EC_{50}	0.0113 total (mm)
			Reproduction, NOEC	0.0122 total (mm)
Sediment dwelling organisms				

Appendix 1 – list of endpoints

Group	Test substance	Time-scale (Test type)	End point	Toxicity [a] (mg/L)
Chironomus riparius	Tribasic copper sulphate	28 d (static)	NOEC	0.50 total (nom) water spiked test
Algae				
S. capricornutum	Copper hydroxide WP	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.00939 total (nom) 0.02229 total (nom)
S. subspicatus	Copper oxychloride	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	52.3 total (mm) 197.9 total (mm)
S. capricornutum	Copper oxychloride WP	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.033 total (mm) 0.066 total (mm)
S. capricornutum	Bordeaux mixture	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.011 total (mm) 0.041 total (mm)
P. subcapitata	Bordeaux mixture WP	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50} Biomass: E_bC_{50} Growth rate: E_rC_{50}	1.73 total (mm) 13.06 total (mm) 0.15 dissolved (mm) 0.75 dissolved (mm)
P. subcapitata	Tribasic copper sulphate SC	72 h (static)	Biomass: E_bC_{50}	> 12.3 total (mm)
P. subcapitata	Copper oxide WP	72 h (static)	Biomass: E_bC_{50} Growth rate: E_rC_{50} Biomass: E_bC_{50} Growth rate: E_rC_{50}	0.147 total (mm) 0.299 total (mm) 0.045 dissolved (mm) 0.133 dissolved (mm)
Microcosm or mesocosm tests				
Indoor microcosm study	**Copper hydroxide WP**	**6 applications at 10-d interval**	**NOEC**	0.012 total (nom) **0.00312 dissolved**[b]

a: based on mean measured concentrations (mm) or nominal (nom) (which are used when measured concentrations are ≥ 80 % of the nominal ones)
b: data retained for the risk assessment with a safety factor between 3 and 5 (according to the PRAPeR meeting 48, May 2008)

Appendix 1 – list of endpoints

Toxicity/exposure ratios for the most sensitive aquatic organisms (Annex IIIA, point 10.2)

No risk assessment can be conducted due to the lack of valid PEC values.

Bioconcentration	
	Active substance
$logP_{O/W}$	0.44
Bioconcentration factor (BCF)[1] ‡	Data gap identified in PRAPeR 48
Annex VI Trigger for the bioconcentration factor	-
Clearance time (days) (CT_{50})	-
(CT_{90})	-
Level and nature of residues (%) in organisms after the 14 day depuration phase	-

[1] only required if log $P_{O/W}$ >3.

Effects on honeybees (Annex IIA, point 8.3.1, Annex IIIA, point 10.4)

Test substance	Acute oral toxicity (LD_{50} µg/bee)	Acute contact toxicity (LD_{50} µg/bee)
Copper hydroxide technical	-	44.46
Copper hydroxide WP	49.0	> 57.0
Copper oxychloride	**12.1** [a]	**44.3** [a]
Bordeaux mixture WP	23.3	> 25.2
Tribasic copper sulphate SC	40.0	> 23.5
Copper oxide technical	-	> 22.0
Copper oxide WG	> 116.0	-
Copper oxide WP	-	> 82.5
Field or semi-field tests: Two outdoor cages were performed. No significant effects		

a: data retained for the risk assessment

Hazard quotients for honey bees (Annex IIIA, point 10.4)

Crop and application rate

Test substance	Route	Hazard quotient	Annex VI Trigger

Appendix 1 – list of endpoints

Vines (mildew) – 2 kg Cu/ha			
Copper hydroxide	Oral	40.8	50
Copper oxychloride	Oral	**165**	50
Bordeaux mixture	Oral	**85.8**	50
Vines (mildew) – 1.5 kg Cu/ha			
Tribasic copper sulphate	Oral	37.5	50
Copper oxide	Oral	< 12.9	50
Vines (mildew) – 2 kg Cu/ha			
Copper hydroxide	Contact	45.0	50
Copper oxychloride	Contact	45.1	50
Bordeaux mixture	Contact	**< 79.4**	50
Vines (mildew) – 1.5 kg Cu/ha			
Tribasic copper sulphate	Contact	**< 63.8**	50
Copper oxide	Contact	< 18.2	50

Appendix 1 – list of endpoints

Effects on other arthropod species (Annex IIA, point 8.3.2, Annex IIIA, point 10.5)

Laboratory tests with standard sensitive species

Species	Test Substance	End point	Effect (LR_{50} kgCu/ha)
Aphidius rhopalosiphi	Copper hydroxide WP	Mortality	0.05
	Bordeaux Mixture	Mortality	> 14.7
	Tribasic copper sulphate	Mortality Parasitisation	> 0.0101 > 0.1344
	Copper oxide	Mortality	39.2
	Copper hydroxide	Mortality	> 14.88
Typhlodromus pyri	Copper oxychloride	Mortality	> 14.89
	Bordeaux Mixture	Mortality	> 13.2
	Tribasic copper sulphate	Mortality	> 0.08
	Copper oxide	Mortality	> 26.1

Crop and application rate

Test substance	Species	Effect (LR_{50} kgCu/ha)	HQ in-field	HQ off-field[1]	Trigger
Copper hydroxide					
Vines (downy mildew) – 2 kgCu/ha	*A. rhopalosiphi*	0.05	**108**	0.725	2
	T. pyri	14.88	< 0.36	< 0.002	2
Vines (bacterial necrosis) – 3 kgCu/ha	*A. rhopalosiphi*	0.05	**102**	0.258	2
	T. pyri	14.88	< 0.34	< 0.001	2
Tomatoes – 1.25 kgCu/ha	*A. rhopalosiphi*	0.05	**80**	0.513	2
	T. pyri	14.88	< 0.27	< 0.002	2
Copper oxychloride					
Vines (downy mildew) – 2 kgCu/ha	*A. rhopalosiphi*	3.97	< 1.36	< 0.009	2
	T. pyri	14.89	< 0.36	< 0.002	2
Vines (bacterial necrosis) – 3 kgCu/ha	*A. rhopalosiphi*	3.97	< 1.28	< 0.003	2
	T. pyri	14.89	< 0.34	< 0.001	2
Tomatoes – 1.25 kgCu/ha	*A. rhopalosiphi*	3.97	< 1.01	< 0.006	2
	T. pyri	14.89	< 0.27	< 0.002	2

Appendix 1 – list of endpoints

Test substance	Species	Effect (LR_{50} kgCu/ha)	HQ in-field	HQ off-field[1]	Trigger
Bordeaux Mixture					
Vines (downy mildew) – 2 kgCu/ha	*A. rhopalosiphi*	14.7	< 0.37	< 0.002	2
	T. pyri	13.2	< 0.41	< 0.003	2
Vines (bacterial necrosis) – 3 kgCu/ha	*A. rhopalosiphi*	14.7	< 0.35	< 0.001	2
	T. pyri	13.2	< 0.39	< 0.001	2
Tomatoes – 1.25 kgCu/ha	*A. rhopalosiphi*	14.7	< 0.27	< 0.002	2
	T. pyri	13.2	< 0.30	< 0.002	2
Tribasic copper sulphate					
Vines (downy mildew) – 2 kgCu/ha	*A. rhopalosiphi*	0.1344	**< 30**	< 0.202	2
	T. pyri	0.08	**< 51**	< 0.340	2
Vines (bacterial necrosis) – 3 kgCu/ha	*A. rhopalosiphi*	0.1344	**< 25**	< 0.064	2
	T. pyri	0.08	**< 43**	< 0.108	2
Tomatoes – 1.25 kgCu/ha	*A. rhopalosiphi*	0.1344	**< 19**	< 0.122	2
	T. pyri	0.08	**< 32**	< 0.205	2
Copper oxide					
Vines (downy mildew) – 2 kgCu/ha	*A. rhopalosiphi*	39.2	0.10	0.001	2
	T. pyri	26.1	< 0.16	< 0.001	2
Vines (bacterial necrosis) – 3 kgCu/ha	*A. rhopalosiphi*	39.2	0.13	0.0003	2
	T. pyri	26.1	0.20	< 0.0005	2
Tomatoes – 1.25 kgCu/ha	*A. rhopalosiphi*	39.2	0.09	0.001	2
	T. pyri	26.1	< 0.14	< 0.001	2

[1] distance assumed to calculate the drift rate: 3 m

Further laboratory and extended laboratory studies ‡

Species	Life stage	Test substance, substrate and duration	Dose (kg Cu/ha)	End point	% effect	Trigger value
T. cacoeciae	adults	Copper hydroxide WP	0.59	parasitisation	6.4	50 %
T. cacoeciae	adults	Copper oxychloride WP	2.02	parasitisation	- 42.9	50 %
D. rapae	adults	Copper hydroxide WP	0.59	mortality parasitisation	14.8 60.0	50 %
P. cupreus	adults	Copper hydroxide WP	0.59	mortality predation	0 8.0	50 %

Appendix 1 – list of endpoints

Species	Life stage	Test substance, substrate and duration	Dose (kg Cu/ha)	End point	% effect	Trigger value
P. amentata	adults	Tribasic copper sulphate SC	0.0202 0.2688	mortality predation	3.95 4.39	50 %
C. carnea	larvae	Copper hydroxide WP	0.56	mortality fecundity	55.6 71.1	50 %
C. 7-punctata	larvae	Copper oxychloride WP	0.58	mortality fecundity	17.5 - 149	50 %
C. 7-punctata	larvae	Tribasic copper sulphate SC	0.0067 0.1344	mortality fecundity	20.88 43.8	50 %
A. rhopalosiphi	adults	Copper hydroxide WP	1.25 2.00	mortality	**54.5** **66.9**	50 %
A. rhopalosiphi	adults	Copper oxychloride WP	1.0 3.97 1.0 3.97	mortality parasitisation	0 0 - 22.38 10.89	50 %
A. rhopalosiphi	adults	Tribasic copper sulphate	0.00154 0.00768 0.0384 0.192 0.960 0.00154 0.00768 0.0384 0.192 0.960	mortality parasitisation	0.0 2.5 2.5 5.0 2.5 - 29.8 - 72.6 - 40.4 - 13.8 30.5	50 %
T. pyri	protonymphs	Tribasic copper sulphate SC	0.015 0.06 0.25 1.01 4.032 0.015 0.06 0.25 1.01 4.032	mortality fecundity	1.8 3.5 13.9 3.5 0.0 - 7.3 - 17.1 - 11.0 12.2 31.7	50 %

Appendix 1 – list of endpoints

Species	Life stage	Test substance, substrate and duration	Dose (kg Cu/ha)	End point	% effect	Trigger value
C. carnea	larvae	Copper oxychloride WP	0.5 1 2 4 8 0.5 1 2 4 8	mortality fecundity	4.8 21.4 11.9 23.8 40.5 1.7 16.7 7.9 15.3 6.7	50 %

Field or semi-field tests
Not required

Effects on earthworms, other soil macro-organisms and soil micro-organisms (Annex IIA points 8.4 and 8.5. Annex IIIA, points, 10.6 and 10.7)

Test organism	Test substance	Time scale	End point
Earthworms			
			LC_{50} mg Cu/kg d.w.soil
Eisenia foetida	Copper hydroxide WP	Acute 14 days	> 677.3
Eisenia foetida	Copper oxychloride WP	Acute 14 days	> 489.6
Eisenia foetida	Bordeaux mixture WP	Acute 14 days	> 195.5
Eisenia foetida	Tribasic copper sulphate SC	Acute 14 days	> 155
Eisenia foetida	**Copper oxide WP**	**Acute 14 days**	**> 862** [a]
			NOEC mg Cu/kg d.w.soil
Eisenia foetida	**Copper oxychloride**	**Chronic 8 weeks**	**< 15** [a]
Other soil macro-organisms			

Appendix 1 – list of endpoints

Test organism	Test substance	Time scale	End point
Porcellio scaber	Copper chloride	Chronic 8 weeks	LC_{50} = 1 117
Platynothrus peltifer	Copper nitrate	Survival Reproduction	NOEL = 2 000 NOEL = 630
Oribatid mites (7 species)	Copper sulphate	Survival 6 weeks Reproduction 6 weeks	NOEC = 200 NOEC < 200
Plectus acuminatus	Copper chloride	Chronic 21d	EC_{50} = 162 NOEC = 32
Collembola			
			Endpoint mg Cu/kg d.w.soil (mg a.s/ha)
Folsomia candida	Copper nitrate	Reproduction	EC_{50} = 700 EC_{50} = 710 EC_{50} = 1,480
Folsomia fimetaria	Copper chloride	Reproduction 21d Growth 21d	EC_{10} = 38 EC_{10} = 509 to 845
Folsomia fimetaria	Copper chloride	Reproduction	EC_{10} = 337
Field studies			
Nematode species	Copper sulphate	Abundance	reduced at 250 kg Cu/ha
Soil micro-organisms			
Nitrogen mineralisation	Copper hydroxide WP		no effect at day 62 at 12.5 kg Cu/ha
	Copper oxychloride WP		no effect at day 28 at 12.4 kg Cu/ha
	Copper oxychloride WP		no effect at day 28 at 18.1 kg Cu/ha
	Bordeaux mixture WP		no effect at day 28 at 20.0 kg Cu/ha
	Tribasic copper sulphate SC		no effect at day 28 at 11.6 kg Cu/ha
	Copper oxide WP		no effect at day 28 at 15.0 kg Cu/ha
Carbon mineralisation	Copper hydroxide WP		no effect at day 62 at 12.5 kg Cu/ha

Appendix 1 – list of endpoints

Test organism	Test substance	Time scale	End point
	Copper oxychloride WP		no effect at day 28 at 12.4 kg Cu/ha
	Copper oxychloride WP		no effect at day 28 at 18.1 kg Cu/ha
	Bordeaux mixture WP		no effect at day 28 at 20.0 kg Cu/ha
	Tribasic copper sulphate SC		no effect at day 28 at 11.6 kg Cu/ha
	Copper oxide WP		no effect at day 28 at 15.0 kg Cu/ha
Field studies			
A multi-field site study was carried out in three sites in France. Up to four months after treatment with Copper Hydroxide WP (8 x 2 kg Cu/ha and 48 kg Cu/ha) there were no effects on the CO_2 evolution and nitrogen mineralization. There was no either evidence of significant effects on evolved CO_2 and nitrogen nitrification after a 28-day incubation in the presence of ground vine leaves, based on soils contaminated with Copper Hydroxide WP at 16 kg and 48 kg Cu/ha.			

a: data retained for the risk assessment

Toxicity/exposure ratios for soil organisms

Crop and application rate

Test organism	Crop and application rate	Time scale	Soil PEC	TER	Trigger
Earthworms					
Eisenia foetida	Vines (14 kgCu/ha/year)	Acute	18.7	> 46.1	10
Eisenia foetida	Tomatoes (7.5 kgCu/ha/year)	Acute	10.0	> 86.2	10
Eisenia foetida	Vines (14 kgCu/ha/year)	Chronic	18.7	**< 0.8**	5
Eisenia foetida	Tomatoes (7.5 kgCu/ha/year)	Chronic	10.0	**< 1.5**	5

Effects on non target plants (Annex IIA, point 8.6, Annex IIIA, point 10.8)

A data gap was suggested in the meeting of experts (PRAPeR 48) to address the risk to non-target plants for several years of application and accumulation of copper in the off-field area..

Appendix 1 – list of endpoints

Effects on biological methods for sewage treatment (Annex IIA 8.7)

Test type/organism	end point
Activated sludge	EC50 = 43 mg Cu/L
Activated sludge	EC50 = 269 mg Cu/L
Activated sludge	EC50 = 337 mg Cu/L
Activated sludge	EC50 > 15.5 mg Cu/L
Activated sludge	EC50 = 157 mg Cu/L
Pseudomonas sp	no study submitted

Ecotoxicologically relevant compounds (consider parent and all relevant metabolites requiring further assessment from the fate section)

Compartment	
soil	Total copper
water	Dissolved copper
sediment	Total copper
groundwater	Dissolved copper

Classification and proposed labelling with regard to ecotoxicological data (Annex IIA, point 10 and Annex IIIA, point 12.3)

	RMS/peer review proposal
Active substance	N, R50-53 (all copper salts)

	RMS/peer review proposal
Preparation	N, R50-53 (all copper preparations)

APPENDIX 2 – ABBREVIATIONS USED IN THE LIST OF ENDPOINTS

AAS	atomic absorption spectrophotometry
ADI	acceptable daily intake
AOEL	acceptable operator exposure level
ARfD	acute reference dose
a.s.	active substance
BCF	bioconcentration factor
bw	body weight
CA	Chemical Abstract
CAS	Chemical Abstract Service
CIPAC	Collaborative International Pesticide Analytical Council Limited
d	day
DAR	draft assessment report
DM	dry matter
DNA	deoxyribonucleic acid
DT_{50}	period required for 50 percent dissipation (define method of estimation)
DT_{90}	period required for 90 percent dissipation (define method of estimation)
ε	decadic molar extinction coefficient
EC_{50}	effective concentration
EEC	European Economic Community
EINECS	European Inventory of Existing Commercial Chemical Substances
ELINKS	European List of New Chemical Substances
EMDI	estimated maximum daily intake
ER50	emergence rate, median
EU	European Union
FAO	Food and Agriculture Organisation of the United Nations
FOCUS	Forum for the Co-ordination of Pesticide Fate Models and their Use
GAP	good agricultural practice
GCPF	Global Crop Protection Federation (formerly known as GIFAP)
GLP	good laboratory practice
GS	growth stage
h	hour(s)
ha	hectare
hL	hectolitre
HPLC	high pressure liquid chromatography or high performance liquid chromatography
HQ	hazard quotients

Appendix 2 – abbreviations used in the list of endpoints

ICP-OES	inductively coupled plasma optical emission spectrometry
ISO	International Organisation for Standardisation
IUPAC	International Union of Pure and Applied Chemistry
K_{oc}	organic carbon adsorption coefficient
L	litre
LC_{50}	lethal concentration, median
LD_{50}	lethal dose, median; dosis letalis media
LOAEL	lowest observable adverse effect level
LOD	limit of detection
LOEC	lowest observable effect concentration
LOQ	limit of quantification (determination)
µg	microgram
mN	milli-Newton
MRL	maximum residue limit or level
MS	mass spectrometry
NESTI	national estimated short term intake
NIR	near-infrared-(spectroscopy)
nm	nanometer
NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
PD	proportion of different food types
PEC	predicted environmental concentration
PEC_A	predicted environmental concentration in air
PEC_S	predicted environmental concentration in soil
PEC_{SW}	predicted environmental concentration in surface water
PEC_{GW}	predicted environmental concentration in ground water
PHI	pre-harvest interval
pK_a	negative logarithm (to the base 10) of the dissociation constant
PPE	personal protective equipment
ppm	parts per million (10^{-6})
ppp	plant protection product
PT	proportion of diet obtained in the treated area
r^2	coefficient of determination
RPE	respiratory protective equipment
SCF	Scientific Committee on Food
STMR	supervised trials median residue
TER	toxicity exposure ratio

Appendix 2 – abbreviations used in the list of endpoints

TMDI	theoretical maximum daily intake
UV	ultraviolet
WHO	World Health Organisation
WG	water dispersible granule
WP	wettable powder
yr	year

APPENDIX 3 – USED COMPOUND CODE(S)

None.