3.2.9	Control animals	Yes
3.3	**Administration/ Exposure**	Oral
3.3.1	Duration of exposure before mating	Not specified
3.3.2	Duration of exposure in general	(i) day 46 to day 21 post-partum (ii) day 1 to 60 of the study
3.3.3	Type	Not specified
3.3.4	Concentration	(i) 0, 3, 30 mg/kg bw/day (ii) 3 mg/kg bw/day (males); 0 or 3 mg/kg bw/day (females) (iii) 0 mg/kg bw/day
3.3.5	Vehicle	Not stated
3.3.6	Concentration in vehicle	Not stated
3.3.7	Total volume applied	Not stated
3.3.8	Controls	Not specified
3.4	**Examinations**	
3.4.1	Clinical signs	Not stated
3.4.2	Body weight	Not stated
3.4.3	Food consumption	Not stated
3.4.4	Oestrus cycle	Not stated
3.4.5	Sperm parameters	Not stated
3.4.6	Offspring	sex and weight of pups stillbirths live births presence of gross anomalies
3.4.7	Other examinations	percentage of pregnancies, number and distribution of embryos in each uterine horn, presence of empty implantation sites and number of resorption sites, abnormal uterine conditions that may have contributed to embryonic death, length of gestation, litter size
3.5	**Further remarks**	The results cited in the reference are based on the following report, which is not publicly available: de la Iglesia, F.W. et al. (1973): Fertility study of W10219A (Copper gluconate) in male and female albino Wistar rats, Warner-Lambert, Sheridan, Canada, 250-0061). The extrapolation from copper gluconate to copper hydroxide is considered not be restricted in any way, since the moiety of interest is the copper ion itself, which may be expected to be released from both compounds during passage of the GI tract after oral uptake. Despite the somewhat limited bioavailability for poorly soluble copper compounds, the extrapolation from the readily bioavailable copper gluconate will only lead to a more conservative but nevertheless valid assessment.

		4 RESULTS
4.1	**Effects**	Parameters studied included percentage of pregnancies, number and distribution of embryos in each uterine horn, presence of empty implantation sites and number of resorption sites, abnormal uterine conditions that may have contributed to embryonic death, length of gestation, litter size, number stillborn/number live born, gross anomalies in the offspring and pup sex and weight. There were no significant differences between treated and control groups in any of the parameters studied. Under the conditions of the study it was concluded that copper gluconate did not affect the fertility potential of either male or female rats.
		5 APPLICANT'S SUMMARY AND CONCLUSION
5.1	**Materials and methods**	The effect of orally administered copper gluconate on fertility was studied using male and female Wistar rats.
5.2	**Results and discussion**	There were no significant differences between treated and control groups in any of the parameters studied.
5.3	**Conclusion**	Under the conditions of the study it was concluded that copper gluconate did not affect the fertility potential of either male or female rats.
5.3.1	Reliability	0
		Not assignable, since only a short summary in secondary literature is available.
5.3.2	Deficiencies	Yes
		Insufficient reporting

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE (*)
Date	06/12/2004
Materials and Methods	Agree with applicant's version
Results and discussion	Agree with applicant's version
Conclusion	Agree with applicant's version keeping in mind that reliability of this study is 0
Reliability	0
Acceptability	Acceptable
Remarks	
	COMMENTS FROM ...
Date	
Materials and Methods	
Results and discussion	
Conclusion	
Reliability	
Acceptability	

Remarks	

Section A6.8.2 Two generation reproduction study

Annex Point IIA6.8.2 **Supportive data**

The following data were already submitted in the context of an application for inclusion of the active substance Copper hydroxide in Annex I of Directive 91/414/EEC. Since these data are not considered to represent key studies, they are cited below as supportive data only:

A6.8.2/03

Report: Auerlich, R.J., Ringer, R.K., Bleavins, M.R. and Napolitano, A. (1982). Effects of supplemental dietary copper on growth, reproductive performance and kit survival of standard dark mink and the acute toxicity of copper to mink. Dept of Animal Science, Michigan State University. (Part Mink Farmer's Research Foundation and Heger Co). *Journal of Animal Science*, **55**, 337-343.

Guideline: Not stated.

- No
-

This study was initiated following early kit (kitten – post-weaning animal) losses in commercial mink farms. It was proposed that copper supplementation might reduce the losses. The study was performed to see if there were beneficial or adverse effects of copper dietary supplementation in farmed mink. As part of the same investigation, an LD_{50} study was performed. Copper sulphate pentahydrate was administered in the diet to groups of 12 male and 12 female standard natural dark mink kits (i.e. phenotype wild-type) at dietary levels of 0, 25, 50, 100 and 200 ppm copper (Cu). In the pre-mating phase, animals were housed individually in standard industrial farm cages. During the mating phase animals were housed in standard industrial breeder cages with nesting box attached. Body weights were recorded once every two weeks for the first two months and then monthly thereafter. Feed and water were provided ad libitum. Eight males from each group were killed after five months treatment. At the scheduled interim kill of the males, blood samples were obtained for plasma Cu analysis and for haemoglobin and haematocrit determinations. Livers were weighed and samples were taken for Cu, Zn and Fe analysis by spectrophotometry and for histopathological examination. Fur quality was evaluated by arranging the pelts from the males according to colour and assigning numerical scores of 1 to 5; the darkest 20% having a score of 5, the next darkest 20%, 4 etc. After approximately 8 months treatment the females were serially mated with the males (1m:1f) during a three-week period. Mating was confirmed by the presence of sperm in vaginal smears. Kits were counted and weighed on the day of birth and at 4 weeks of age. At the end of the study blood samples were collected from the remaining animals for haemoglobin and haematocrit determinations. Statistical analyses were performed.

Table A6.8.2- 4 Body weights at selected weeks

Week	Bodyweight (g) at dose level (ppm)				
	0	25	50	100	200
Males					
Start	709	676	701	625	650
8	1525	1425	1438	1351	1374
20	1897	1828	1831	1693	1753
Females					
Start	517	563	545	536	534
8	909	937	947	947	965
20	1074	994	1068	1065	1058

Findings: **Findings:**
Body weights: There was no effect on adult body weight gains (refer to Table A6.8.2–2).

Findings: Haematology and clinical chemistry parameters: There were no differences from controls in haemoglobin or haematocrit parameters, but slight elevations were seen in plasma Cu in treated male animals at low dose levels at 5 months. The authors conclude that these values are within normal limits for most species. However, the plasma Cu levels were consistently higher in treated males, although they were not strictly dose-related. The group size was only 3 or 4 individuals, so that the data should be interpreted with caution. However, plasma copper levels were consistently higher in mink at relatively low levels of dietary inclusion, compared to the marked stability in plasma copper levels at high levels of dietary inclusion in rats, indicating that mink may be more susceptible to copper than other species.

Table A6.8.2- 5 Mean haemoglobin, haematocrit and plasma Cu levels

Parameter	Dose level (ppm)				
	0	25	50	100	200
Males after 5 months treatment					
Haemoglobin (g/dL)	22.5	22.5	21.7	22.0	22.4
Haematocrit (%)	56.8	55.8	54.3	55.8	54.6
Plasma Cu (µg/dL)	54.4	78.6	73.2	61.8	65.6
Males after 12 months treatment					
Haemoglobin (g/dL)	22.0	21.0	21.2	20.8	22.4
Haematocrit (%)	51.7	52.5	54.4	53.9	54.3
Females after 12 months treatment					
Haemoglobin (g/dL)	20.9	21.0	21.0	22.1	20.8
Haematocrit (%)	49.5	52.5	52.0	54.9*	52.4

* $P < 0.05$

Plasma copper not reported at 12 months

Pelt colour: The average fur colour scores were increased for the animals at the higher dose levels suggesting that higher levels of supplemental copper may have a beneficial effect of intensifying the hair colour of mink. These data are based on a limited number of observations.

Table A6.8.2- 6 Mean pelt colour scores

Parameter	Dose level (ppm)				
	0	25	50	100	200
Males after 5 months treatment					
Number of animals	7	8	8	8	8
Mean pelt colour score	3.0	2.2	2.9	3.5	3.6

Liver weight, analysis and histopathology: There were no differences from controls in relative liver weights of males at the 5-month interim kill. Deposition of copper in the liver was not observed microscopically (Uzman's stain) but atomic absorption spectrophotometry showed that the concentrations of copper in the liver were greater than the controls. As with plasma copper levels, this indicates that the mink is unusually sensitive to copper in the diet.

Table A6.8.2- 7 Mean liver weight and mean concentrations of Cu, Zn and Fe

Parameter	Dose level (ppm)				
	0	25	50	100	200
Males after 5 months treatment					
Number of animals	7	8	8	8	8
Liver/body weight ratio %	2.69	2.61	2.76	2.85	2.56
Concentration in liver (ppm):					
Cu	293	340	411	364	479*
Zn	507	504	488	516	530
Fe	1197	1121	1263	1303	1267

* $P < 0.05$

Litter data: Pregnancy rate was not adversely affected by treatment. The number of pregnant animals was similar to controls at 200 and 50 ppm, and slightly lower at 25 and 100 ppm. Gestation period and kit weight at birth were not adversely affected by treatment but there was greater kit mortality during the nursing period and reduced litter mass at weaning at 100 and 200 ppm copper, suggesting that maternal supplemental copper had an adverse effect on kit growth during the lactation period.

Table A6.8.2- 8 Reproductive and litter data

Parameter	Dose level (ppm)				
	0	25	50	100	200
Number of females mated	12	11	12	12	12
Number of females littered	11	6	12	8	10
Mean days of gestation	47.2	46.7	49.6	49.4	46.7
Number of kits born:					
Alive	69	33	64	50	57
Dead	8	5	6	4	6
Mean per female	7.0	6.3	5.8	6.8	6.3
% kit mortality birth to 4 weeks	12	9	19	38	32
Mean kit weight (g):					
Birth	8.8	9.7	9.4	8.5	8.3
At 4 weeks	136.9	143.0	133.3	116.4*	143.3
Litter mass (g)[a]	704.6	666.5	582.3	474.8	580.5

[a] mean kit body weight gain between birth and 4 weeks x mean number of kits raised per lactating female

* $P<0.05$

Conclusions:
Shorter term copper supplementation had no significant effects on adult mink body weight gains or on haemoglobin or haematocrit concentrations. Plasma and liver copper concentrations were increased in treated mink. Darker fur was observed in pelted males at the higher dose levels. Reproductive performance of mink was not adversely affected although greater kit mortality and reduced kit weight were observed at 100 ppm copper and above. A NOEL for reproductive performance was 50 ppm. The NOEL for copper plasma and liver levels was <25 ppm, the lowest dose tested.

Section A6.9 Annex Point IIIA VI.1	Neurotoxicity study	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [X]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	The performance of a neurotoxicity study is considered to be not required since no indications of neurotoxic properties are known for Copper hydroxide.	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	17/01/2005	
Evaluation of applicant's justification	Agree with applicant's summary	
Conclusion	Agree with applicant's summary. But some Cu accumulation in brain was observed in some studies. The performance of a specific neurotoxicity study is not required because some data exists from human diseases and can be used for this end-point.	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.10 Annex Point IIIA VI.7	Mechanistic study – any studies necessary to clarify effects reported in toxicity studies	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [X]**	
Limited exposure [ ]	**Other justification [ ]**	
Detailed justification:	The performance of studies of the mechanisms of toxicity is considered to be not required since no non-genotoxic mechanisms for carcinogenicity, no species specific effects, and no adverse effects on reproduction, immunotoxicity or hormone related effects are known for copper.	X
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	17/01/2005	
Evaluation of applicant's justification	We cannot agree with the applicant's version because there is some effects concerning mutagenicity and reproductive toxicity. These effects highly depends on the route of exposure and are not expected if Cu is administered by oral route. It could be some concerns if exposure by inhalation route is not negligible. However, no mechanistic studies would be required, even if this route of exposure could occur.	
Conclusion	No mechanistic study is required.	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.11 Annex Point IIIA	Studies on other routes of administration (parenteral routes)	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [X]**	
Detailed justification:	According to the additional data requirements for active substances the performance of studies on other routes of administration is only required if such data already exist, which is not the case for copper.	

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	17/01/2005
Evaluation of applicant's justification	Agree with applicant's justification
Conclusion	Acceptable
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.1
Annex Point IIA6.9.1

Section 6.12.1 Medical surveillance data on manufacturing plant personnel

		Official use only
	6 REFERENCE	
6.1 Reference	[redacted] (2004): Statement on exposure of workers to copper salts Dated: 22 March 2004. Doc.No. 00620B-IIA-6121	
	7 APPLICANT'S SUMMARY AND CONCLUSION	
	In an over 12 years period there has not been observed chronically toxic damage to health at the production workplaces for copper hydroxide and basic copper carbonate. In exceptional cases temporary symptoms such as fever, similar to metal fume fever, have occured as a result of inhaling significant quantities of copper salts. These symptoms disappear relatively quickly without any lasting adverse effects.	

Evaluation by Competent Authorities	
	Use separate "evaluation boxes" to provide transparency as to the comments and views submitted
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	17/01/2005
Materials and Methods	No other data. No information on the number of workers examined over 12 years, on the type of examination performed, etc.
Results and discussion	This is only a letter from the occupational physician of Spiess Urania. According to the TGD, the applicant should provide "detailed information on the design of the programme and exposure to the active substance and other chemicals"
Conclusion	Not suitable for risk assessment.
Remarks	
	COMMENTS FROM ... *(specify)*
Date	*Give date of comments submitted*
Materials and Methods	*Discuss if deviating from view of rapporteur member state*
Results and discussion	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.2 **Direct observation, e.g. clinical cases, poisoning incidents if available**

Annex Point IIA6.9.2

The following data were already submitted in the context of an application for inclusion of the active substance in Annex I of Directive 91/414/EEC. Since these data are not considered to represent key studies, they are given below in summarised format only:

Abstract

The are four general categories of copper poisoning in the literature: direct oral ingestion of large amounts of salts (usually cupric sulphate $CuSO_4$, referred to throughout as copper sulphate), 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.

Summary of clinical cases and poisoning incidents

There are four general categories of copper poisoning: direct oral ingestion of copper salts, 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. Detailed descriptions of symptoms and treatment are given in other sections. Diagnosis of poisoning and Expected effects of poisoning, and summaries of food and drinking water contamination are also presented in other sections.

Copper has been used in suicide attempts. Most of these have involved copper sulphate pentahydrate. Intoxication is associated with emesis, superficial or deep ulcerations of the gastric and intestinal mucosa. Liver histopathology revealed dilatation of central veins, varying degrees of liver cell necrosis and bile thrombi. In kidneys there was congestion of glomeruli swelling or necrosis of tubular cells and haemoglobin casts. These findings are similar to those seen in animal studies. Elevated serum copper levels are only seen in moderate to severe cases of intoxication. Unfortunately, as the amount of copper taken in these suicide attempts is never quantified accurately, it is impossible to use the data from these cases to define a NOEL/LOEL for elevated serum copper in humans.

In a case of self-administration, a 26-year-old Irishman took 30 mg Cu/day for two years (apparently without ill effect), then increased the dose to 60 mg Cu/day in the third year and suffered liver failure. This indicated that long-term repeat daily dose of 60 mg/day is toxic, but that 30 mg/day was not toxic. While the case serves to warn of the dangers of excessive self-administration, it also is an indication that the upper level of the homeostatic control mechanism in humans is far higher than those suggested by some regulatory bodies.

Relatively low concentrations of free copper in water induce nausea in humans. In an international trial, 179 individuals were given water containing copper sulphate at 0, 2, 4, 6 or 8 mg Cu/L in a 200 mL bolus of water (equivalent to a dose of 0, 0.4, 0.8, 1.2 and 1.6 mg Cu). Subjects were monitored for nausea and other symptoms. The NOAEL for nausea was 4 mg Cu/L. However, this represents a taste effect of a soluble copper salt in water. Copper sulphate is a gastric irritant, and the nausea is probably associated with irritation of the stomach. Natural levels of copper in food include 6 mg/kg (= ppm) for shrimp and liver, 10 mg/kg for mushrooms, and 27 mg/kg for dark (bitter) chocolate. Consumption of 200 g of shrimp or liver in a meal, or 160 g of mushrooms, or 50 g of dark chocolate (which would each provide the same amount of bound copper as was administered in drinking water in the drinking water nausea study) would not be expected to induce nausea, therefore the conclusion from this study should not be used in any dietary assessment for copper present in food.

Studies with patch testing of copper as sulphate and as metal revealed only one case in 2660 of an independent allergy to copper (in a subject who worked with copper metal), although a small number of subjects that were sensitised to nickel also showed sensitivity to copper. Copper is not regarded as an allergen.

The condition known as Vineyard Sprayer's Lung (VSL) has been reported in several papers, mostly from Portugal, but also from the former Yugoslavia. The condition is characterised by lung lesions with a focal distribution corresponding to three distinct patterns; a varying number of alveoli filled with desquamated macrophages, granulomas in the alveoli septa and fibro-hyaline nodules which appear to be the scars of the

granulomas. Hepatic changes included proliferation and diffuse swelling of Kupffer's cells and the formation of well defined histiocytic or sarcoid-type granulomas all with inclusions of copper. These lesions were always found near the portal tracts. The identification of copper within the lesions characterised the nature of these granulomas. Copper deposits were never found in hepatocytes. The papers describe the preparation on-site of Bordeaux Mixture, as a copper sulphate solution neutralised with hydrated lime, and primitive application techniques at higher rates than those used in modern agriculture, where Bordeaux Mixture is formulated under controlled conditions in dedicated factories, and applied using modern machinery by workers wearing appropriate protective equipment. Most of the published findings date from the 1970s and 1980s. Some of the papers were compromised because the authors did not adequately describe the smoking habits of the subjects, only noting that certain subjects were heavy smokers. The Yugoslav paper surveyed smoking and non-smoking rural workers, including those which did and those which did not use home-made Bordeaux mixture, and found that there were indications of adverse effects in users of Bordeaux Mixture that were exacerbated by smoking.

Bordeaux Mixture is a highly complex mineral mixture. If the reaction of the lime and copper sulphate is not strictly controlled, the resulting mixture may not be sufficiently neutralised, and may contain significant amounts of plaster and gypsum, in a form that if inhaled, may result in lung disease. One paper also notes that similar liver lesions to those in VSL have been recorded in workers exposed to other pathogenic dusts (cement, cork, fur, mica and wood), where the inhaled dust has been transported, presumably by macrophages, to the liver. While the effects of prolonged use of home-made Bordeaux mixture without any protective measures are beyond doubt, the condition is not relevant to modern agriculture.

Reference A6.12.2/01: Chowdhury, A.K.R., Ghosh, S. and Pal, D. (1961). Acute copper sulphate poisoning. J. Indian M.A., **36(8)**, 330- 336.

Copper sulphate is ingested for suicidal purposes. Study lists signs and symptoms. Unfortunately, it is rarely possible to ascertain the quantity of copper ingested. The paper follows twenty cases of acute copper sulphate poisoning. Blood and urine samples were taken after hospital admission. Erythrocyte fragility was assessed. Liver function tests (serum proteins, thymol turbidity tests, serum alkaline phosphatase, bilirubin) were performed, and serum copper level assessed.

Of the twenty cases, 6 were mild, 9 moderate and 5 severe. The following symptoms were recorded:

Mild cases: metallic taste in the mouth, slight pain and tenderness over the epigastric region, nausea.

Moderate cases: in addition to the above, retrosternal burning sensation, vomiting, tachycardia, low blood pressure, tender liver, scanty urine with albumin and sometimes blood.

Severe cases: all of the above signs and symptoms, but more acute; severe tenderness, persistent tachycardia, falling blood pressure, bluish/greenish loose stools often with blood, urine with blood, albumin and sometimes sugar. Jaundice developed, and patients became restless, apathetic, or became stuporose and developed muscular weakness. No deaths were recorded.

Haemolysis was noted in 10 of the 14 moderate/severe cases, serum bilirubin slightly elevated, total protein reduced, with reversal of albumin : globulin ratio. Albumin and red blood cells were present in urine, and glycosurea in the more severe cases. Port-wine urine was observed in the most severe case. Serum copper was elevated in most cases. Control levels were stated as 130 µg.%. Serum copper was not presented for all cases, but most values ranged from 150 to 280.

BAL (dimercaprol) therapy was stated to be useful in the more severe cases, and the authors claimed that BAL therapy plus transfusion saved the life of one of the more severe cases.

Conclusions: Signs and symptoms following ingestion of single large doses of copper sulphate, in suicide attempts, were recorded. Elevated serum copper in moderate and severe cases was the only diagnostic clinical chemistry test.

Reference A6.12.2/02: Chuttani, H.K., Gupta, P.S., Gulati, S. and Gupta, D.N. (1965). Acute copper sulfate poisoning. Dept of Medicine and Pathology, Maulana Azad Medical College, New Delhi. American Journal of Medicine, Vol 39, 849-854.

A study was performed on 53 subjects, with an age range of 14 to 60 years; 48 having been admitted to hospital and seven deaths (of 48) from acute copper sulphate poisoning. There was no reliable information on the amount of copper sulphate ingested but apparently varied from approximately 1 to 100 g. The paper notes that copper sulphate is relatively common as a suicide agent among the lower income groups in India. Regular progress notes were maintained for each patient. Vomit was tested for the presence of copper sulphate. Blood was analysed for haemoglobin, red and white blood cell counts, blood urea, serum bilirubin, zinc sulphate turbidity, alkaline phosphatase, SGOT and prothrombin time. Urine samples were analysed for urinobilinogen and haemoglobin. Plasma copper, serum copper and whole blood copper were estimated. A liver biopsy was performed in thirty-three patients and a kidney biopsy in four. Autopsy material was available in nine cases.

Metallic taste, nausea, vomiting and burning in the epigastrium were the main symptoms, with all patients being affected. Diarrhoea, jaundice, haemoglobinuria and /or haematuria, and anuria occurred in approximately 25% of patients, and oligouria, hypotension, coma and melaena in small numbers of patients. The cause of gastrointestinal injury was presumed to be injury of the mucosa by copper sulphate. The gastric mucosa of the patient that died showed superficial and deep erosions. The small intestine showed areas of haemorrhage, and the liver showed severe histological changes.

In severe cases, deep jaundice appeared on the second or third day following administration of copper sulphate.. The liver was large and tender, and liver function test showed gross derangement. Histology of biopsy or autopsy samples showed dilatation of central veins, varying degrees of centrilobular necrosis, bile thrombi and biliary stasis. Patients showing oliguria or anuria had normal blood pressure, such that hypotension could not have been the cause of the suppression of urine. Kidney biopsy showed swelling or necrosis of the tubular cells in two patients. Autopsy of patients who died showed kidneys swollen and congested, with histology revealing congestion of glomeruli, necrosis and denudation of tubular cells, and in some cases, haemoglobin casts. Coma occurred in four patients, and the authors considered it to be due to uraemia resulting from renal damage; there were no indications of a direct effect on the brain. Deaths occurring within 24 hours were due to shock, and those occurring later appeared to be due to hepatic and/or renal complications. Mean values for serum ionic copper were approximately seven times greater than normal in patients with poisoning (see Table Reference A6.12.2-1).

Table Reference A6.12.2-1 Copper content of blood after copper poisoning

Cases	Copper (µg/100 ml)		Serum ionic copper (µg/100 ml)
	Total serum	Whole blood	
Normal	151.6	217	21.8
$CuSO_4$ Poisoning: Mild – gastrointestinal symptoms only	294.2	287	-
Severe – jaundice, renal manifestations or shock, plus gastrointestinal	334.4	798	-
Assay within 12 hours of ingestion – severe cases	-	-	257.2
Assay after 12 hours of ingestion – severe cases	-	-	23.4

There was no correlation between degree of symptoms and individual serum or whole blood copper levels, but more severe cases showed highest levels. It is also noted that even in severe cases the serum levels were near normal 12 or more hours after ingestion, indicating the efficiency of homeostatic mechanisms even in extreme cases of intoxication..

Conclusions: Copper intoxication following oral administration, as sulphate in suicide attempts, is associated with emesis, superficial or deep ulcerations of the gastric and intestinal mucosa. Liver histopathology revealed dilatation of central veins, varying degrees of liver cell necrosis and bile thrombi. In kidneys there was congestion of glomeruli swelling or necrosis of tubular cells and haemoglobin casts. These findings are similar to those seen in animal studies.

Reference A6.12.2/03: Walsh, F.M., Bayley, M. and Pearson, B.J. (1977). Acute copper intoxication. Pathophysiology and therapy with a case report. Am J. Dis. Child, **131**, 149 – 151.

Case history of an 18-month-old boy admitted to hospital one hour after drinking a solution containing 3 g cupric sulphate (being used by an older sibling in chemistry experiments).

Spontaneous vomiting prior to hospital admission. Gastric lavage with milk used as demulcent until there was no blue colour in the aspirate. Child became progressively obtunded, but no changes to respiratory or cardiac status. Treatment with dimercaprol (BAL) intra muscular 2.5 g/kg every four hours, was begun five hours after ingestion. Edetic acid, 12.5 g/kg was added with the second dose of dimercaprol. Initial urinalysis results were normal, but serum copper was 1,650 µg/100 ml (normal for this age quoted as 110 – 170 µg/100 ml, threshold for toxicity stated to be 540 µg/100 ml). Twenty-four hours after admission, the child was fully alert, and serum copper level had decreased to 230 µg/100 ml, and decreased over the next three weeks to 200 µg/100 ml. A two-hour urine sample contained 50 µg/100 ml (normal range quoted as 5 – 25 µg/100 ml). Urinary copper values rose to a maximum of 280 – 300 µg/100 ml between the second and third week. On the second hospital day, acute haemolytic anaemia developed, and glucose-6-phosphate dehydrogenase activity was decreased to 75 units/10^9 cells (normal range quoted as 250 – 500 units /10^9 cells), although SGPT and SGOT levels were normal. Hematuria, glycosuria, cylinduria and proteinuria were noted, indicative of renal tubular damage. The child was given two RBC transfusions over the next five days because of continued haemolysis. After five days, Hb level stabilised, urine returned to normal and the child appeared clinically well. Dimercaprol and edetic acid were discontinued and penicillamine (used in the treatment of Wilson's disease) 250 mg/day was begun and continued at home for one month. At examination after one year there were no adverse effects.

Ingestion of a large amount of copper sulphate showed signs consistent with other incidents, and was treated successfully. Indications of temporary renal damage were consistent with those seen in rat toxicity studies.

Reference A6.12.2/04: Mittal, S.R. (1972). Oxyhaemoglobinuria following copper sulphate poisoning: a case report and review of the literature. Forens.Sci. **1** 245-248.

Case report of male human admitted to hospital after ingesting 175 g copper sulphate. BAL was given, but there was only sufficient for four injections.

Patient showed typical signs of acute copper sulphate ingestion. After six days, he developed red-coloured urine, and analysis revealed oxyhaemoglobin. The authors consider that the haemolysis (seen in other cases) combined with renal damage, allowed the passage of oxyhaemoglobin, which is not normally seen in urine.

Conclusions: Ingestion of copper sulphate was associated with haemolysis and renal damage, allowed the passage of oxyhaemoglobin, which is not normally seen in urine.

Reference A6.12.2/05: O'Donohue, J.W., Reid, M.A., Varghese, A., Portmann, B. and Williams, R. (1993). Micronodular cirrhosis and acute liver failure due to chronic copper self-intoxication. European Journal of Gastroenterology & Hepatology **5**:561-562.

A 26-year old Irishman presented to Coleraine hospital, Co. Londonderry, with a 6-week history of malaise, jaundice and abdominal swelling. Three years previously he had started to take 30 mg copper (purchased by mail order, Nature's Best, Tunbridge Wells, UK) after reading about trace metal deficiency in a health magazine. The recommended daily dose was 3 mg. During the third year, he increased the dose to 60 mg/day (twenty times the recommended dose). Six weeks after admission to hospital, the patient was transferred to King's College Hospital, London, and given a liver transplant, from which he made a good postoperative recovery.

On initial examination, the patient was thin, jaundiced, with moderate ascites, splenomegaly, and with Kayser-Fleischer rings and sunflower cataracts visible on slit-lamp examination. Serum copper was 22.6 mmol/L (normal range quoted as 12.6 – 26.7 mmol/L), serum ceruloplasmin was 0.24 mmol/L (normal range quoted as 0.21 – 0.49 mmol/L), alkaline phosphate 257 IU/L (normal <90 IU/L), aspartate amino transferase 401 IU/L (normal quoted as <40 IU/L), γ-glutamyl-transpeptidase 356 IU/L (normal quoted as <50 IU/L). Prothrombin time 23s (control 14s). Twenty-four hour urinary copper excretion was 204 µmol (normal quoted as <1.2 µmol/day). Histology of the explanted liver was indistinguishable form that seen in ICC and Wilson's disease. Mean liver copper was 3230 µg/g dry weight (normal quoted as 20 – 50 µg/g). Postoperative copper urine content declined to near normal. The patient's parents and sisters revealed normal 24-hour urinary copper excretion.

Conclusions: This was the first recorded case of cirrhosis and acute liver failure due to copper overdose. Investigation of the patient's immediate family revealed normal copper metabolism, and absence of sub-clinical Wilson's disease, such that the authors conclude that the effects seen were due to self-administration of excess copper as a dietary supplement. It is worthy of note that no ill effects were recorded even after two years at 30 mg/day, ten times the recommended supplementary intake (which would have been in addition to the normal food intake of 1 – 2 mg/day), and that liver failure only occurred after a third year at twenty times the recommended supplementary intake. While the case serves to warn of the dangers of excessive self-administration, it also is an indication that the upper level of the homeostatic control mechanism in humans is far higher than those suggested by some regulatory bodies.

Reference A6.12.2/06: Araya, M., McGoldrick, M.C., Klevay, L.M., Strain, J.J., Robson, P., Nielsen, F., Olivares, M., Pizarro, F., Johnson, L-A. and Poirier, K. (2001). Determination of an acute no-observed adverse effect level (NOAEL) for copper in water. Regulatory Toxicology and Pharmacology **34**, 137-145.

A prospective, double-blind controlled study was designed to determine the acute, no-observed adverse effect level (NOAEL) of nausea in an apparently healthy population of 179 individuals from 3 international centres who were given water containing copper sulphate at 0, 2, 4, 6 or 8 mg Cu/L in 200ml bolus. Final total copper dose was 0, 0.4, 0.8, 1.2 and 1.6 mg). Treatment was once weekly over five weeks. Symptoms of nausea, abdominal pain, vomiting or diarrhoea were screened for 24 hours

Nausea was the most frequently reported effect, and was reported within 15 minutes of ingestion. From the total of 179 individuals, treated at 0, 2, 4, 6 or 8 mg Cu/L, the incidence of subjects responding positively to one or more of the GI symptoms was 8, 9, 14, 25 and 44. There was a clear dose response, with statistically significant increase at 6 and 8 mg Cu/L.

Conclusions: The acute NOAEL for nausea for copper sulphate in water was 4 mg Cu/L, and the LOEL was 6 mg Cu/L. This is not a NOEL for dietary intake of copper bound within foodstuffs. Copper sulphate is a gastric irritant, and the nausea is probably associated with irritation of the stomach. Linder (op.cit) quotes levels in food of 6 mg/kg (=ppm) for shrimp and liver, 10 mg/kg for mushrooms, and 27 mg/kg for dark (bitter) chocolate. Consumption of 200 g of shrimp or liver in a meal, or 160 g of mushrooms, or 50 g of dark chocolate (which would each provide the same amount of bound copper as was administered in drinking water in the drinking water nausea study) would not be expected to induce nausea, therefore the conclusion from this study should not be used in any dietary assessment for copper present in food.

Reference A6.12.2/07: Pimentel, J.C. and Marques, F. (1969). 'Vineyard sprayer's lung': a new occupational disease. I.A.N.T. (Dept of Pathology and Thoracic Surgery of Sanatorio D. Carlos I) and Institute of Pathology, University of Lisbon. Thorax, 24, 678-688.

Case reports of two male rural workers, whose main occupations were spraying vineyards using 'home-made' Bordeaux Mixture (solution of copper sulphate neutralised with hydrated lime) and/or cleaning the tartar from wine presses, admitted to the Thoracic Surgery Centre for investigation. In both cases tuberculosis had been diagnosed some months previously and had been treated. In one case there was improvement but not complete clearing and as his sputum was persistently negative for tubercle bacilli surgical lung biopsy was proposed. Similarly in the other case after improvement with treatment the symptoms reappeared on his return to work and lung biopsy was performed. The paper notes that the Bordeaux Mixture used to be applied to vines up to 14 times a season. The preparation of Bordeaux Mixture on the farm, from copper sulphate and lime is not relevant to the purchase of factory-prepared materials, as the home-made preparation is imprecisely neutralised, leading to excess of either copper sulphate or lime in the preparation. The home-made preparation was also applied by relatively primitive methods, e.g. by hand using a rush broom, or manual sprayers. Such practices should not be taken into account when assessing the application of modern commercial formulations with modern machinery at the significantly lower application rates (approx. 8 kg/Ha compared to >24 kg/Ha historically). The paper also describes an inhalation study in guinea pigs. This study is described in Section 5.8.2.

In Case 1, lung lesions had a focal distribution and corresponded to three distinct patterns; a varying number of alveoli filled with desquamated macrophages, granulomas in the alveoli septa and fibro-hyaline nodules which seemed to be the scars of the granulomas. Copper was found in the granular material contained in the intra-alveolar macrophages. Similar findings were present in Case 2. In a separate experimental study using guinea pigs (see Point IIA, 5.8.2/08), similar findings were reproduced.

Conclusions: This investigation showed the need for protective measures for workers while spraying and that lung biopsy was required for the correct identification of this type of condition. The fact that the condition has not been reported in the recent literature indicates that the condition was primarily associated with uncontrolled use of 'home-made' product without any protective measures, and that modern application techniques for copper products are not associated with the condition. It does highlight the need for respiratory protection.

Reference A6.12.2/08: Pimentel, J.C. and Menezes, A.P. (1975). Liver granulomas containing copper in vineyard sprayer's lung. Dept of Pathology of Sanatorio D. Carlos I and Institute of Pathology, University of Lisbon. American Review of Respiratory Disease, Volume III, 1975, 189-195.

Three cases were examined, one an alcoholic and all were rural workers involved with spraying vineyards using Bordeaux Mixture, a copper sulphate solution neutralised with hydrated lime (referred to in this summary as 'home-made' Bordeaux mixture). All had characteristic pulmonary lesions described previously for vineyard sprayers using 'home-made' Bordeaux Mixture (Reference A6.12.2/01). Livers were examined histopathologically either at necropsy or from percutaneous biopsy material. Various staining techniques for the sections were used, including histochemically for copper. The sections were also viewed using ordinary and polarised light.

In all cases hepatic changes were found consisting of proliferation and diffuse swelling of Kupffer's cells and the formation of well defined histiocytic or sarcoid-type granulomas all with inclusions of copper. These lesions were always found near the portal tracts. The identification of copper within the lesions characterises the nature of these granulomas. The lesions were different from those observed in conditions such as primary biliary cirrhosis in which copper deposits can be found in hepatocytes; granulomas containing copper are never found. In the present condition, copper deposits were never found in the hepatocytes.

Conclusions: The occupational exposure to 'home-made' Bordeaux Mixture, the characteristic pulmonary lesions of vineyard sprayer's lung and the presence of copper in the liver of these patients define this new variety of hepatic granulomatosis.

Reference A6.12.2/09: Pimentel, J.C. and Menezes, A.P. (1977). Liver disease in vineyard sprayers. Dept of Pathology of Sanatorio D. Carlos I and Institute of Pathology, University of Lisbon. *Gastroenterology*, **72**, 275-283.

The livers of 30 rural workers who sprayed vineyards with Bordeaux Mixture (solution of copper sulphate with hydrated lime) for periods that varied from 3 to 45 years were studied. The paper states that spraying was carried out from 15 to 100 days per year, and 600 litres of mixture were sprayed each day by each worker. As has been observed previously, these practices from more than 25 years ago, using home-made Bordeaux mixture and primitive application techniques and significantly higher application rates should not be used in a risk assessment of factory-produced copper plant protection products, applied using modern engineering equipment and protective clothing, at modern (lower) application rates. The spleens of four of cases were also examined. All cases with other possible causes of liver damage, such as hepatitis, alcoholism etc were excluded. Several stains were used for sections including those for histochemical localisation of copper. Various light forms including conventional, polarised, phase contrast and interference microscopy were used. Normal livers were used as controls. The paper also describes an inhalation study in guinea pigs. This study is described in Section 5.8.2

The pathological findings were varied and included diffuse and focal swelling and proliferation of Kupffer cells, (diagnostic, and present in all cases), histiocytic and sarcoid-like granulomata (7 cases) fibrosis of variable degree in the perisinusoidal, portal and subcapsular areas (8 cases), accompanied by atypical proliferation of the sinusoidal lining cells, one case of liver angiosarcoma, micronodular cirrhosis (3 cases) and idiopathic portal hypertension (2 cases). Abundant deposits of copper were revealed, by histochemical techniques, within pulmonary and hepatic lesions. These cases were characterised by long-term exposure. The single case of angiosarcoma was in a man who had sprayed vineyards with 'copper sulphate' from the age of 18 to 53 (35 years). The average exposure in the cases of fibrosis was 29 years, and the two cases of cirrhosis followed exposure for 28 and 30 years.

Conclusions: The presence of abundant deposits of copper within the liver suggest a relationship between the occupational exposure and liver disease. This is explored further in following summaries.

Reference A6.12.2/10: Villar, T.G. (1974). Vineyard Sprayer's Lung. American review of Respiratory Disease, **110**, 545-555.

Description of 15 consecutive patients admitted to Lisbon University Hospital, and review of earlier papers (cited above). Patients were 35 to 76 years of age, average 54 years. Patients had all been exposed to Bordeaux Mixture. The periods of exposure were not stated for all subjects, but some had been exposed for over 20 years. Most had used 'manual pulverizers carried on their backs', although one subject had used a rush broom. Seven of the patients smoked, one had been exposed to pigeon droppings and another to wood dust. Lung x-rays, biopsies, autopsies (where deceased) and histopathology were performed.

The initial diagnosis was Vineyards Sprayer's Lung (VSL) in three cases, pigeon fancier's lung in one case, tuberculosis in five cases, and pulmonary granulomatosis in two cases. In all cases, VSL was subsequently noted. The paper noted that in some cases, the condition remained clinically 'silent' until a bronchiopulmonary bacterial or viral infection , or exposure to some other dust triggered further progression of the disease. It is interesting that the authors made an association between lung cancer and VSL, both in the Abstract (describing it as 'remarkable') and in several places in the paper, ignoring the relationship between lung cancer and cigarette smoking. The paper contained no information as to which of the patients had smoked, only that seven of the fifteen had smoked.

Fifteen patients suffering from VSL were in some cases initially misdiagnosed, but all followed chronic exposure to Bordeaux Mixture. The authors noted that three patients also showed lung cancer, and that seven patients had smoked cigarettes, although the paper gave no information as to the smoking habits of the patients with lung cancer, preferring to emphasise a 'remarkable incidence' of lung cancer in patients with VSL.

Reference A6.12.2/11: Villar, T.G. and Nogueira, T. (1980). Radiology and Respiratory Function in Vineyard Sprayer's Lung. *Bronchopneumologie* **30(1)**: 61-67.

Study cites a review of 20,000 autopsies of (presumably Portuguese) rural workers. Vineyard Sprayer's Lung (VSL) was identified in 832 cases (retrospectively), corresponding to 4% of all autopsies and 20% of those with respiratory symptoms. The paper cites 33 patients admitted to Lisbon University Hospital. There is no information in the paper to determine if some of these patients had been described previously in an earlier paper (Reference A6.12.2/04). It is worthy of note that the description of the single female in this study matches closely the single female in the previous study, and it is reasonable to assume that the fifteen cases in the earlier paper have been included in this paper. Where possible, lung function tests were performed, as were biopsies, autopsies, and histopathology.

The age range of the patients was 35 to 76 years, average 53 years. Twenty-four percent were stated to be medium to heavy smokers (8 of the 33 cases), although number of non-smokers was not stated. The single female in the study was stated to have sprayed vines from the ages of 10 to 14, and to have suffered pneumonia at the age of 50, during which she developed diffuse progressive fibrosis. She then presented with lung disease and was diagnosed with VSL. There were seven cases of lung cancer. The paper is seriously compromised in that there are no data to correlate smoking, which is known to be associated with lung cancer, and exposure to Bordeaux Mixture and VSL.

Conclusions: The author repeats an earlier conclusion that VSL is associated with high incidence of lung cancer, but ignores any possible association with cigarette smoking.

Reference A6.12.2/12: Plamenac, P. Santic, Z., Nikulin, A. and Serdarevic, H. (1985). Cytologic changes of the respiratory tract in vineyard spraying workers. *Eur. J. Respir. Dis.* **67**, 50-55.

Study of workers in the former Yugoslavia (Listica, Herzegovina) using 'home-made' Bordeaux Mixture prepared by neutralising copper sulphate solution with lime. Unlike previous studies in Portugal, the study also recorded the smoking habits of the workers examined. The author performed some particularly stomach-churning sputum analyses in workers professionally exposed to regular inhalation of Bordeaux Mixture, who at the time of investigation showed no sign of pulmonary or any other disease. Sputum specimens were obtained from 52 exposed rural workers and 51 unexposed rural workers, from the same region who did not work in vineyards and did not come into contact with

copper. These acted as controls. Sputum samples were obtained by morning cough on three consecutive days. Only expectorated material containing pulmonary macrophages was accepted as sputum. Sputa samples were fixed in 75% alcohol, embedded in paraffin and sections stained with H & E. These were then tested for iron (Turnbull stain)and for copper with rubeanic acid and benzidine.

Smokers produced sputa containing abnormal columnar cells in all cases. Macrophages containing copper granules in the cytoplasm were found in 64% of workers engaged in vineyard spraying, compared to none in the control group. Sputum specimens were evaluated for eosinophils, respiratory spirals, respiratory cell atypia and squamous metaplasia. Abnormal findings were more frequent in smokers than non-smokers. Atypical squamous metaplasia was observed in 29% of smokers who were vineyard workers, but only in 5% of cases in the non-smoking vineyard sprayers. There was enhanced expectoration of sputum in a high percentage of vineyard sprayers and in smoking controls, indicating that exposure to copper and cigarette smoke affects the respiratory epithelium.

Conclusions: Exposure to (home-made) Bordeaux Mixture in vineyard spaying affects the sputum. Smoking appears to exacerbate the effects.

Reference A6.12.2/13: Menzes, A.P., and Pimentel, J.C. (1996). Liver Pathology in pulmonary diseases of inhalatory origin. Am. Rev. Respir. Dis. **113(4)**:106 (abstract only).

Abstract only. Summarises changes seen in liver of patients with Vineyard Sprayer's Lung, and notes that similar liver lesions have been recorded in the livers of workers exposed to other pathogenic dusts (cement, cork, fur, mica and wood).

The foreign material could be identified within the lesions, using appropriate histological and histochemical techniques. It would appear that inhaled particulates can be transported to the liver, and can cause liver changes.

Conclusions: The authors conclude that the identification of foreign materials stored by the liver can be an important diagnostic tool in inhalatory disease.

	Evaluation by Competent Authorities
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	17/01/2005
Evaluation of applicant's justification	We agree that these studies are not key studies, but give some indication about the possible toxic properties of copper.
Conclusion	For acute toxicity by oral route, if no NOEAL can be derived for the data reported, typical symptoms can be observed including generally: gastrointestinal irritation, hemolysis and renal injury. For inhalation route, the available studies demonstrated that Bordeau mixture is responsible of a specific lung pathology, certainly due to copper (according to the authors). This pathology could be explained by the local action of copper in the lung. For this dossier, if no or negligible inhalation exposure is expected (as stated by the applicant), no further investigation would be needed. But if inhalation exposure could occur, these properties should be studied.
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A 6.12.3 Health records, both from industry and any other available sources

Annex Point IIA 6.9.3

	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [X]	**Technically not feasible [ ]** **Scientifically unjustified [X]**	
Limited exposure [ ]	**Other justification [X]**	
Detailed justification:	According to subchapter 6.12.3 of the TNsG on data requirements, health records both from industry and any other available sources should be submitted. However, it is noted here that under AIII 6.12.1, information on medical surveillance of manufacturing plant personnel is given, and in AIII 6.12.2, 6.12.4 and 6.12.6, detailed information on cases of human exposure, and on epidemiological studies has been given. The applicant is therefore of the opinion that the submission of any further information is neither required, nor possible beyond the data provided under the points listed above, since any health issues related to the occupational use of the active substance, and any other human exposure issue has comprehensively been addressed thereby.	
Undertaking of intended data submission [ ]		

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	17/01/2005
Evaluation of applicant's justification	There is no information available to support this data point. Agree with applicant's justification
Conclusion	Acceptable
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.4 Epidemiological studies on the general population

Annex Point IIA6.9.4

The following data were already submitted in the context of an application for inclusion of the active substance in Annex I of Directive 91/414/EEC. Since these data are not considered to represent key studies, they are given below in summarised format only:

Summary of general population exposure.

Contamination of food by copper has occurred in the past where 'untinned' cooking vessels have been used to prepare food, and copper metal has been dissolved by and in the food. This was the case in Indian Childhood Cirrhosis (ICC), where cow's milk was boiled in copper pans before being fed to infants. There are also cases in the literature where copper is used to pipe water within the home, where either the water is particularly acidic (e.g. pH<6.5), or in a small number of cases where the houses concerned were at the termination of a water main, and the dwell-time within the pipes was excessive. There are also cases from the US State of Massachusetts where whole cities were exposed to drinking water concentrations of over 8 mg/L without obvious ill-effects.

There is no evidence for adverse effects of oral exposure through customary diets world-wide (which includes countries where copper is used in agriculture) for any adverse effects of copper on pregnancy, parturition, lactation or growth and development in the human. There is evidence of toxicity particularly to neonates repeatedly exposed to milk heated in copper vessels, or exposure to acid fruit stewed in copper vessels.

Incidence of illness/injury from copper-containing pesticides in California was less than 1% of the total number of reported illness/injury cases in 1987.

There have been no reported cases where ill-health has resulted from diets where food crops has been treated with copper as a plant protection product, despite its extensive use (particularly in Mediterranean countries of Europe) for over one hundred years.

Reference A6.12.4/01: Ralph, A. and McArdle, H. (2001). Copper metabolism and copper requirements in the pregnant mother, her fetus, and children. International Copper Association New York, N.Y.USA. (ISBN 0-943642-12-12).

Guidelines: Not relevant – summary of literature

GLP: No

Publication is a review of data on copper metabolism and toxicity during pregnancy and lactation, with emphasis on the human.

The review emphasises the importance of copper as an essential micronutrient to all aerobic life forms, including humans. It includes a review of the homeostatic mechanisms by which copper balance is maintained at whole body, organ and cellular levels. A review of the metabolism of copper is presented in Section 5.1 of the dossier, and will not be further discussed here. This review concentrates on deficiencies to the mother, foetus and offspring, but also discusses toxicity. Copper accumulation in humans takes place mostly during periods of growth, in the womb, during childhood and adolescence. The requirement for copper is greater during these periods, and it is logical to assume that as the need is greater, then not only is deficiency more likely, but also that toxicity is less likely. This is important, because traditional risk assessments assume that the foetus, the neonate and adolescent are more vulnerable than the adult, and may need higher safety factors in assessing risk. With copper, the nutritional demands are greater, and the opposite is the case, and therefore limits set for adults should be considered conservative for the pregnant female, foetus, neonate and adolescent. Copper is required for infant growth, host defence mechanisms, red and white cell maturation, bone strength, connective tissue integrity, iron transport, cholesterol mechanism and brain development. Copper deficiency is associated with growth retardation, anaemia, skin lesions, impaired immunity, intestinal atrophy, impaired cardiac function, reproductive disturbance, neurological defects and skeletal lesions. Copper is essential for normal

physiological function; cellular respiration, free radical defence, synthesis of melanin, connective tissue, iron metabolism, regulation of gene expression, and normal function of the heart and immune system.

The review considers the following aspects:

Fertilisation; copper metal is known to interrupt implantation and development of the blastocyst when present in the uterus as an intra-uterine contraceptive device (IUD), but once implantation has taken place, IUDs do not show adverse effects on maintenance of pregnancy.

Pregnancy. Maternal serum copper levels and ceruloplasmin levels rise steadily throughout pregnancy, and fall significantly at parturition. The concentration in the mother is higher than in the foetus, which establishes a concentration gradient from the mother to the foetus. The rise in plasma concentration may be due to either enhanced uptake from food or decreased biliary excretion. It is induced by oestrogen. Various studies have shown that copper requirements of pregnant humans are up to one third greater than non-pregnant human females. Copper and ceruloplasmin are present in amniotic fluid, but uptake from amniotic fluid by the foetus is small. The placenta has been shown to take copper from the maternal blood as both ceruloplasmin and by lower-weight complexes (albumin, histidine), but that delivery by ceruloplasmin is more efficient. Ceruloplasmin is not itself passed across the placenta, but ceruloplasmin and histidine may deliver copper to the placental cells via specific cell surface receptors. The placenta has a regulatory role on the transfer of copper from mother to baby, as infant serum concentrations of copper do not correlate with those of the mother. This has been demonstrated in both human and rat. Women with Wilson's disease can give birth to healthy babies if the condition is well managed (zinc sulphate therapy). Pregnant women with untreated Wilson's disease tend to have spontaneous abortions. Of 26 pregnancies in 19 women, studied by Brewer (2000), 24 new-borns were normal, one had a heart defect (corrected by surgery) and another showed anencephaly. Anencephaly has also been associated with very low maternal copper serum levels, and there have been two reported cases of anencephaly where an IUD was used.

Foetal development: copper accumulates in the placental layers and is transferred to the foetus by an active process driven by foetal needs; it is thought to be incorporated in the foetal liver into foetally synthesised ceruloplasmin. Copper is present in the foetal circulation in ceruloplasmin, albumin, α-fetoprotein, transcuprein and low molecular weight ligands. The human foetus accumulates copper at a rate of 50 µg/kg/day during the latter half of pregnancy, and 50% of it is stored as metallothionein in the liver. The ratio of copper in the liver of newborn infants to adults is 15:4. **There are no reports of adverse effects of acute toxicity of copper in human pregnancy.** Foetal copper accumulation occurs in the third trimester, and premature and low-weight babies are at risk of copper deficiency. Studies indicate that the capacity of pre-term infants to utilise copper from the diet is limited; most of the ingested copper is present in the stool, indicating either ineffective absorption or limited ability to retain and store copper.

Parturition. Serum maternal plasma level returns to normal in the human within two to five weeks. The timing of the return to normal may be influenced by the duration of breast-feeding.

Lactation. Ceruloplasmin occurs in the milk of humans and other mammals, concentrations being higher in the early stages of lactation. Approximately 20-25% of copper in human milk is present as ceruloplasmin. Breast-feeding supplies up to 60 µg/kg/day, and is approximately 24% bioavailable. Maternal copper blood levels are under hormonal control (e.g. oestrogen, see above), but alterations in maternal copper intake through dietary supplementation, or elevated blood levels through other factors, such as severe infections, and even Wilson's disease, do not alter copper content of breast milk. It is likely that there are homeostatic mechanisms that regulate mammary gland uptake of copper and its secretion in milk, but these have not been explained. In human breast milk, approximately 75% of the copper is in the whey, bound to soluble albumin or low molecular weight ligands. Another 15-20% is in lipids, bound to the outer fat globule membrane, and about 5% is in insoluble form, possibly bound to casein. Differences in composition of other milks (cow, soy) affect the bioavailability to the human baby. Absorption and retention rates from formula milks are very low, although toxicity has been observed where infants have been given substantial amounts of cow's milk boiled in untinned copper vessels. Awareness of the disease in India [Indian Childhood Cirrhosis] and Austria [Idiopathic Copper Toxicosis] has resulted in use of other containers, and the incidence has fallen. Human milk, unsurprisingly, contains the most bioavailable copper for the human baby. Healthy infants fed exclusively on cow's milk for 6 months became copper deficient, but the condition reversed on weaning to solid foods.

Growth and development. Neonatal humans have high concentrations of copper in the liver and low concentrations of serum copper and ceruloplasmin. Newborn humans also show high concentrations of metallothionein that decrease after birth. Copper in the new-born's liver appears to provide much of the copper requirements of the infant while it is breast-fed, until weaning at 4-6 months. However, milk must provide a significant contribution, as mice showing 'toxic milk mutation' die if they are kept on mother's milk, because the

mother cannot secrete the normal amounts of copper into the milk, and the pups die of copper deficiency. Premature birth restricts the hepatic storage of copper (as the mother's supply via the placenta is no longer available), and milk formulae for premature infants contains additional copper to compensate for this. Low copper levels at this time may have neurological implications during the critical period of brain growth. Excess copper in drinking water at concentrations of approximately 8 mg/L showed chronic toxicity in adults but not in children under 6 years of age. As the infant grows, levels of ceruloplasmin increase. Studies in rats show that copper absorption is high during the neonatal period, but decreases by weaning, as more is retained in the intestinal mucosa. With increasing postnatal age, more is transported to the liver and less is bound to the intestine. There is evidence in rats that during lactation, intestinal copper absorption occurs by diffusion and solvent drag, and only after weaning does a saturable (adult, see Section 5.1) copper transport system become evident. Children require higher levels of copper in the diet than adults, especially during periods of rapid growth. Girls aged 6-10 were fed on diets of copper ranging from 1.1 to 3.8 mg/day. At intakes under 2 mg/day, copper balance was negative. A positive copper balance was achieved on a vegetarian diet with a copper intake of over 2.8 mg/day. It was suggested that an intake of 1.3 mg/day was sufficient for equilibrium, but that 2.5 mg/day was necessary for growth. Serum of normal children reaches a peak of 1.57 mg/L between 6 and 11 years and falls to 1.1 mg/L in adults between 22 and 75 years.

Intake: the review found no evidence of copper toxicity from customary dietary intake, unless the food had been accidentally contaminated with copper during preparation e.g. acid fruit such as apples, were stewed in a copper vessel, or there was repeated ingestion of milk heated in copper vessels. A study of three cities in the US state of Massachusetts showed no incidence of ill-health in adults or children under 6 years of age, despite drinking water concentrations of over 8 mg/L. Most dietary intakes are below the 10-12 mg/adult/day set by international organisations. This is discussed in detail in Section 5.1, and summarised in 5.10.

Conclusions: There is no evidence for adverse effects of oral exposure through customary diets worldwide (which includes countries where copper is used in agriculture) for any adverse effects of copper on pregnancy, parturition, lactation or growth and development in the human. There is evidence of toxicity particularly to neonates repeatedly exposed to milk heated in copper vessels, or exposure to acid fruit stewed in copper vessels.

Reference A6.12.4/02: Dassel de Vergara, J., Zietz, B. Schneider H.B. and Dunkelberg, H. (1999). Determination of the extent of excessive copper concentrations in the tap-water of households with copper pipes and an assessment of possible health hazards for infants. Eur. J. Med. Res. **4**:475-482

Study of water samples from 956 households with drinking water delivered in copper pipes, and the state of health of infants in these houses was monitored. Study prompted by concerns for possible copper toxicity because of increasing use of copper piping in German households, together with knowledge of Indian Childhood Cirrhosis (ICC) and Non-Indian Childhood Cirrhosis (NICC). ICC is a disease resulting from excess copper in infants fed cow's milk boiled in copper vessels. The disease has been eliminated by not using copper vessels. NICC is a similar disease described in Germany where infants were fed formula milk made from well water, where the source water pH was < 6.5, and the house water pipes were copper. The well water did not comply with German quality regulations. The disease was eliminated by improving the quality of water used. This paper contains several references to ICC and NICC that are not relevant to the agrochemical use of copper, and are not explored further in this dossier. It also contains references to studies with drinking water.

Households with infants under the age of 12 months, with copper piping, were investigated. A 'stagnation' sample of cold tap water after overnight stagnation, and a random daytime sample were obtained from each family. Data on the infants, such as state of health, breast-feeding and intake of other foods were also recorded. Water samples were analysed using atomic absorption technique. Where copper values of >0.5 mg/L were found, a further two composite water samples were taken. If these indicated a level of 0.8 mg/L or greater, the family was placed into one of two groups: those where the infants were breast-fed for at least 12 weeks and who were given less than 200 ml of tap water per day during that time, and those who were breast-fed no longer than 12 weeks, or who were given more than 200 ml tap water per day during the first 12 months. Infants in the latter group were examined by a paediatrician. The examination included blood sample and examination of the liver by palpation and ultrasound. Blood samples were analysed for serum copper, ceruloplasmin, immunoglobulins (IgG, IgM, IgA), transaminases (GOT, GPT), GGT, total bilirubin and CRP.

Of the initial 1000 families, 44 withdrew or moved. Of the 956 households sampled, 836 (87.4%) had stagnation samples with less than 0.5 mg/L copper. A total of 83 households had stagnation samples of 0.5 mg/L or greater, and of these, 37 households were of 0.8 mg/L or more. Stagnation samples were not collected from 37 households. The highest copper concentration in the high exposure group was 2 mg/L. Of the 12 infants in the non-breast-fed or >200 ml tap water/day category, eight were examined. Only one infant showed abnormal serum copper, at 220 µg/dl (normal range for this age 103-168 µg/dl). Composite samples from the house were 0.5 and 0.8 mg/L. The infant had been breast-fed for only one week, and for 4 months had been given formula milk, prepared with 1000 ml per day. On being notified of the high copper content of the water, the parents had stopped using tap water to prepare the milk, and at 11 months a second check showed a normal serum copper value of 146 µg/dl (normal range for that age 133-179 µg/dl). At no time had this infant, or any of the others on the study suffered vomiting diarrhoea or any other characteristic symptoms of copper poisoning.

Conclusions: The authors conclude that it is unlikely that there is a health hazard from postnatal intake of copper in tap water with values between 0.8 and 2 mg/L.

Reference A6.12.4/03: Maddy, K.T, Edmiston, S. and Richmond, D. (1990). Illness, injuries and deaths from pesticide exposures in California 1949-1988. CDPA, Sacramento, USA. Reviews of Environmental Contamination and Toxicology, **114**, 58-122.

California is a significant agricultural state, with 79,000 farms covering 13 million hectares in 1989. Records of pesticide-related injuries have been maintained since the 'early to mid 1900's'. This is an extensive paper, concentrating on the year 1987, but giving background from 1950, dealing with accidental and deliberate deaths resulting from pesticide use and abuse, and injuries, including skin, eye and other illnesses to workers applying pesticides, and to workers in crops after application of pesticides. Workers are categorised as applicators, aerial, ground (tractor), hand-held, and people mixing (diluting) pesticides and loading them into spray tanks, with exposure being to concentrate, or residues. Aerial application also involved 'flaggers' (workers holding flags to allow spray pilots to orient their aircraft to spray the crops correctly). Other categories include workers at pesticide formulation plants.

There were no deaths or homicides associated with the use or abuse of copper-containing pesticides. In 1950, out of a total of 293 pesticide-related injuries, there were three injuries resulting from copper sulphate use, two were skin injuries, and one was unspecified systemic. In 1987, there were 1754 cases of occupational illness/injury determined as being related to pesticide exposure in California, out of a working population of some 12,000,000 people. Of these a total of 14 (0.8% of the numbers of illness/injury)) were attributed to copper-containing pesticides: one skin injury to a ground applicator, two systemic injuries (unspecified) and one eye injury to hand-held applicators, and one systemic, two eye and one skin injury to 'unspecified' applicators. There was one skin and eye injury resulting from coincidental exposure, and one skin injury to a worker post-application. There were two skin injuries to copper 8-quinolate from handling crops (presumably post-harvest), and one systemic injury to a flagger from copper sulphate, and one eye injury to a mixer/loader, also from copper sulphate.

Conclusions: Overall conclusion of the report is that illness and injury from pesticides is of a low incidence. No data concerning amounts of copper used compared to other active substances were presented, but from the low incidence of cases, the risks to workers from copper-containing products is considered very low.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	17/01/2005
Evaluation of applicant's justification	Agree with applicant's version
Conclusion	Agree with applicant's version
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.5 Diagnosis of poisoning including specific signs of poisoning and clinical tests

Annex Point IIA6.9.5

The following data were already submitted in the context of an application for inclusion of the active substance in Annex I of Directive 91/414/EEC. Since these data are not considered to represent key studies, they are given below in summarised format only:

No such data exists specifically for the active substance covered by this dossier.. Data for copper sulphate are cited. Copper sulphate is water-soluble, unlike the active substance here. However, it is reasonable to assume that if sufficient quantities of a biocidal product are consumed to overwhelm the body's homeostatic mechanisms, the resulting toxicity will present similar signs and symptoms to those of copper sulphate. Biocidal products containing copper are unlikely to cause acute toxicity except in the case of deliberate ingestion. Copper salts are emetic and highly coloured, and the patient rarely loses consciousness, so that the clinician is usually informed of the nature of the intoxicant. Analysis of the vomitus, or the gastric lavage can confirm copper intoxication, as can serum copper elevation (where present), however, there is no single diagnostic test for copper intoxication. The following represent a summary of diagnostic information from the medical literature (see also section 5.9.6, Expected effects of poisoning):

Mild cases: metallic taste in the mouth, slight pain and tenderness over the epigastric region, nausea.

Moderate cases: in addition to the above, retrosternal/epigastric burning sensation, vomiting, tachycardia, low blood pressure, tender liver, scanty urine with albumin and sometimes blood.

Severe cases: all of the above signs and symptoms, but more acute; severe tenderness, persistent tachycardia, falling blood pressure, diarrhoea, bluish/greenish loose stools often with blood, urine with blood, haemoglobinuria, haematuria, oligouria, anuria, albumin in urine and glucosuria. Jaundice, restlessness, apathy, stupor, muscular weakness, coma and death.

In moderate and severe cases, haemolysis and haemolytic anaemia, serum bilirubin slightly elevated, total protein reduced, with reversal of albumin : globulin ratio. Albumin and red blood cells present in urine, and glycosurea in the more severe cases. Port-wine urine (haematouria) observed in the most severe cases. Serum copper elevated, but not in proportion to dose. Liver enlarged and tender, and liver function test show gross derangement. Patients showing oliguria or anuria have normal blood pressure. Kidney biopsy may show swelling or necrosis of the tubular cells. Where coma occurs it is probably due to uraemia resulting from renal damage; rather than a direct effect on the brain. Deaths occurring within 24 hours were due to shock, and those occurring later appeared to be due to hepatic and/or renal complications.

Long term oral exposure to excess dietary supplement of copper (single case) was associated with malaise, jaundice and abdominal swelling, moderate ascites, splenomegaly, and with Kayser-Fleischer rings and sunflower cataracts visible on slit-lamp examination. Copper urinary excretion abnormally high, elevated enzyme levels (alkaline phosphate, aspartate amino transferase, γ-glutamyl-transpeptidase). Copper liver histopathology indistinguishable from Wilson's disease and ICC.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	17/01/2005
Evaluation of applicant's justification	Agree with applicant's summary
Conclusion	Agree with applicant's summary
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.6 Sensitisation/ allergenicity observations

Annex Point IIA6.9.6

The following data were already submitted in the context of an application for inclusion of the active substance in Annex I of Directive 91/414/EEC. Since these data are not considered to represent key studies, they are given below in summarised format only:

Reference A6.12.6/01: Wöhrl, S., Hemmer, W., Focke, M., Götz, M. and Jarisch, R. (2001). Copper Allergy revisited. J. Am. Acad. Dermatol.**45:**863-70.

Study including copper sulphate in routine patch testing for allergies for 2 ½ years. Review contrasts copper, 'believed to be a rare cause of contact dermatitis', to common metal allergens, such as nickel, cobalt, palladium and chromium. A database comprising 2660 patients (2037 female, 623 male, mean age 39.5 years, range 2 to 91) was compiled. Routine patch testing was performed, with a standard series of 34 allergens, and including copper sulphate 2% in petrolatum (pet), nickel sulphate, 5% in pet, palladium chloride 1% pet and cobalt chloride 1% pet, as well as thimerosal 0.05% pet as reference allergen. Patients with a response to copper (excluding children and adults living at a distance from the hospital) were enrolled on a follow-up study in which they were re-tested with copper sulphate in pet at 5%, 2%, 0.6% and 0.2%. and in aqueous solution at 1%, 0.5% and 0.05%. metallic copper foil was tested as 6 mm discs. Plasters were applied to each patients back for 48 hours, and scoring performed at 48 and 72 hours.

Positive test results for copper were firmly associated with nickel hypersensitivity. Of 2660 results, 94 (3.53%) were positive for copper. Nickel and palladium were much more common (21% and 5.90%, respectively). Of the 26 patients available for the second phase, only 10 (38%) were judged positive to copper on re-testing. Of these 8 had a positive nickel test, and one a positive cobalt test. The sole patient with a positive copper result independent of other metal sensitivity was an electrician, constantly exposed to copper metal in wiring. He suffered from chronic eczema on his fingertips, and was the only case of an exclusive copper sensitization in the 2660 patients of the study group.

Conclusions: Cases of allergy to copper are extremely rare in humans, and copper is not considered a sensitiser.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	17/01/2005
Evaluation of applicant's justification	Agree with applicant's summary
Conclusion	Agree with applicant's summary. But it should be stated that if exclusive copper sensitisation is very rare in human, crossed sensitisation with Ni or other metallic compounds is more often observed.
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.7 Specific treatment in case of an accident or poisoning: first aid measures, antidotes and medical treatment

Annex Point IIA6.9.7

The following data were already submitted in the context of an application for inclusion of the active substance in Annex I of Directive 91/414/EEC. Since these data are not considered to represent key studies, they are given below in summarised format only:

Following ingestion, gastric lavage with milk used as demulcent until there is no colour in the aspirate. Treatment with dimercaprol (BAL) 2.5 g/kg and edetic acid, 2.5 g/kg intra muscular every four hours.

Where these are not available, administer egg white orally (albumin binds copper).

Where there is haemolytic anaemia, whole blood or RBC transfusions have been successful.

After acute phase recovery, discontinue dimercaprol/edetic acid and replace with oral penicillamine, as for treatment of Wilson's disease.

Monitor blood for liver enzyme function, red blood cell integrity and serum copper levels.

Monitor urine for copper levels, enzymes, albumin, sugar and haemoglobin.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	18/12/2006
Evaluation of applicant's justification	Agree with applicant's version.
Conclusion	Acceptable
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.12.8 Prognosis following poisoning

Annex Point IIA 6.9.8

The following data were already submitted in the context of an application for inclusion of the active substance in Annex I of Directive 91/414/EEC. Since these data are not considered to represent key studies, they are given below in summarised format only:

No data specifically exist on the active substance covered n this dossier. Data for copper sulphate are cited. Copper sulphate is water-soluble, unlike the five forms. However, it is reasonable to assume that if sufficient quantities of a biocidal product are consumed to overwhelm the body's homeostatic mechanisms, the resulting toxicity will present similar signs and symptoms to those of copper sulphate. The biocidal product is unlikely to cause acute toxicity except in the case of deliberate ingestion. Copper salts are emetic and highly coloured, and the patient rarely loses consciousness, so that the clinician is usually informed of the nature of the intoxicant. Analysis of the vomitus, or the gastric lavage can confirm copper intoxication, as can serum copper elevation (where present), however, there is no single diagnostic test for copper intoxication. The following represent a summary of diagnostic information from the medical literature (see also section 5.9.6, Expected effects of poisoning):

Mild cases: metallic taste in the mouth, slight pain and tenderness over the epigastric region, nausea.

Moderate cases: in addition to the above, retrosternal/epigastric burning sensation, vomiting, tachycardia, low blood pressure, tender liver, scanty urine with albumin and sometimes blood.

Severe cases: all of the above signs and symptoms, but more acute; severe tenderness, persistent tachycardia, falling blood pressure, diarrhoea, bluish/greenish loose stools often with blood, urine with blood, haemoglobinuria, haematuria, oligouria, anuria, albumin in urine and glucosuria. Jaundice, restlessness, apathy, stupor, muscular weakness, coma and death.

In moderate and severe cases, haemolysis and haemolytic anaemia, serum bilirubin slightly elevated, total protein reduced, with reversal of albumin : globulin ratio. Albumin and red blood cells present in urine, and glycosurea in the more severe cases. Port-wine urine (haematouria) observed in the most severe cases. Serum copper elevated, but not in proportion to dose. Liver enlarged and tender, and liver function test show gross derangement. Patients showing oliguria or anuria have normal blood pressure. Kidney biopsy may show swelling or necrosis of the tubular cells. Where coma occurs it is probably due to uraemia resulting from renal damage; rather than a direct effect on the brain. Deaths occurring within 24 hours were due to shock, and those occurring later appeared to be due to hepatic and/or renal complications.

Long term oral exposure to excess dietary supplement of copper (single case) was associated with malaise, jaundice and abdominal swelling, moderate ascites, splenomegaly, and with Kayser-Fleischer rings and sunflower cataracts visible on slit-lamp examination. Copper urinary excretion abnormally high, elevated enzyme levels (alkaline phosphate, aspartate amino transferase, γ-glutamyl-transpeptidase). Copper liver histopathology indistinguishable from Wilson's disease and ICC.

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	18/12/2006
Evaluation of applicant's justification	Agree with applicant's version.
Conclusion	Acceptable
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.13 Annex Point IIIA VI.2	Toxic effects on livestock and pets	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [X]	**Other justification [ ]**	
Detailed justification:	Information on toxic effects on livestock and pets is considered not to be relevant since a release of the active substance from treated wood used in animal housings (indoor use) can be excluded by the application technique. Copper salts are applied to construction wood only by vacuum pressure treatment or dipping (professional application; no superficial application, e.g. via brushing or spraying, at the site of use).	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	February 2007	
Evaluation of applicant's justification	Agree with the applicant version	
Conclusion	Applicant justification	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.14 Annex Point IIIA XI.2	Other tests related to the exposure of humans	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [X]**	
Detailed justification:	Information on further toxicity tests related to the exposure of humans is considered not to be relevant since information is required only on the toxicity of degradation products, by-products, or reaction products which are not formed by Copper Hydroxide.	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	01/2005	
Evaluation of applicant's justification	Agree with applicant's justification.	
Conclusion	Acceptable	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.15 Annex Point IIIA VI.4	**Food and feedingstuffs** **Sections A6.15.1 – A6.15.6**	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [X]**	
Detailed justification:	Information on the active substance Copper hydroxide in relation to residues on food and feedingstuff is considered not to be required since additional data requirements of sections A6.15.1 – A6.15.6 do not provide for the submission of data in this context for PT08.	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	01/2005	
Evaluation of applicant's justification	Agree with applicant's justification.	
Conclusion	Acceptable	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		

Section A6.16 Annex Point IIIA VI.3.5	Any other tests related to the exposure of the active substance to humans, in its proposed biocidal products, that are considered necessary, may be required	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	Technically not feasible [ ] Scientifically unjustified [ ]	
Limited exposure [ ]	Other justification [X]	
Detailed justification:	No information is submitted to this section point because no requirement for other tests related to the exposure of the a.s. to humans is foreseeable.	

Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE
Date	01/2006
Evaluation of applicant's justification	Agree with applicant's justification.
Conclusion	Acceptable
Remarks	
	COMMENTS FROM OTHER MEMBER STATE *(specify)*
Date	*Give date of comments submitted*
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*
Conclusion	*Discuss if deviating from view of rapporteur member state*
Remarks	

Section A6.17 Annex Point IIIA VI.6	If the active substance is to be used in products for action against plants ...	
	JUSTIFICATION FOR NON-SUBMISSION OF DATA	Official use only
Other existing data [ ]	**Technically not feasible [ ]** **Scientifically unjustified [ ]**	
Limited exposure [ ]	**Other justification [X]**	
Detailed justification:	No information to this additional data requirement is considered to be relevant since no use of the active substance against plants is envisaged.	
	Evaluation by Competent Authorities	
	EVALUATION BY RAPPORTEUR MEMBER STATE	
Date	01/2005	
Evaluation of applicant's justification	Agree with applicant's justification.	
Conclusion	Acceptable	
Remarks		
	COMMENTS FROM OTHER MEMBER STATE *(specify)*	
Date	*Give date of comments submitted*	
Evaluation of applicant's justification	*Discuss if deviating from view of rapporteur member state*	
Conclusion	*Discuss if deviating from view of rapporteur member state*	
Remarks		