Ministero della Salute

DIREZIONE GENERALE PER L'IGIENE E LA SICUREZZA DEGLI ALIMENTI
E LA NUTRIZIONE
Uff. VII - PRODOTTI FITOSANITARI

Copper: guidance for the assessment following EFSA conclusions

E-fate evaluation

Soil

Reviewer evaluation
Based on a simple first tier approach, PEC_{soil} calculations for copper following application of PPP were generally provided by the Applicants, considering a soil bulk density of 1.5 g cm^{-3} and a soil layer depth of 5 cm (PEC_{soil} initial). For PEC_{soil} long-term calculations a soil layer depth of 20 cm was considered only for field crops.
The following application scenarios were considered:

- n. 6 applications to vines with an application rate of 1000 g a.s./h;
- n. 5 applications to pome and stone fruit (early applns) at 1500 g a.s./ha;
- n. 6 applications to pome fruit (late applns) at 750 g a.s./ha;
- n. 5 applications to citrus fruit and olives at 1500 g a.s./ha;
- n. 6 applications to vegetables and strawberries at 1000 g a.s./ha;
- n. 6 applications to potatoes at 1000 g a.s./ha.

No crop interception was considered.

New information about PEC_{soil} calculations is available in the EFSA conclusions (*EFSA Journal 2013*;11(6):3235), where the Meeting of Experts agreed that natural background levels of copper need to be taken into account. Indeed, it was proposed that a preliminary PECsoil calculation can be considered based on the maximum application rate over a 5 cm soil layer for a period of 20 years, also considering an average background level of copper in agricultural soils in EU of 32 mg Cu/kg.
Therefore, new PEC_{soil} values were re-calculated by the Reviewer, in accordance with EFSA conclusion 2013. The results are reported below.

Crop	**n. of appl.**	**A.R. (g a.s./ha)**	**Amount reaching soil (g a.s./ha)**	**$PEC_{soil,init}$ (mg/kg) - 1 year**	**PEC_{soil} (mg/kg) 20 years**	
				Soil layer 5 cm	**Soil layer 5 cm**	**Soil layer 5 cm (+background*)**
Vines	8	1000	8000	10.6	213	245

Pome & stone fruit (early appl), also including nuts	5	1500	7500	10	200	232
Pome fruit & stone fruit (late appl)	3	1500	4500	6	120	152
Citrus fruit & olives, also including cypress	6	1500	9000	12	240	272
Vegetables & strawberries	6	1000	6000	8	160	192
Potatoes	6	1000	6000	8	160	192

*Natural background level (average 32 mg Cu/kg)

Groundwater

Although copper is considered as weakly mobile in soil, in the above referred EFSA conclusions a data gap for a groundwater exposure assessment of copper resulting from the agricultural use was identified. However, a modelling software is not yet available for predicting PEC_{GW} of inorganic substances such as copper.
Reviewer, pragmatically, asked the EU notifier for copper compounds (EUCuTF, European Copper Task Force) to provide results from available groundwater monitoring studies to confirm the absence of risk of groundwater contamination following the application of copper.

Surface water

Notifier approach
$PEC_{sw/sed}$ calculations for the active substance copper following application of copper compounds were generally provided by the Applicants considering spray-drift rates derived from FOCUS drift calculator and assuming a standard EU water body of 1 m width, 30 cm depth and 100 m length. Single application scenario was considered as a realistic worst-case for the calculation of PEC_{sw} values. On the contrary, multiple applications were considered for PEC_{sed} values. A correction factor of 3 was applied to PEC_{sw} in order to guarantee the conversion from total copper loading to dissolved copper loading. Standard Step 3 drift rate were used along with those for 5, 10 and 20 m no-spray buffers. The Applicant also considered the estimation of the input via run-off and drainflow by using the IDMM, *i.e*. Intermediate Dynamic Model for Metals.

Reviewer approach
In the EFSA conclusion (EFSA Journal 2013;11(6):3235) the IDMM model has not been considered valid, since it was not possible to conclude on the suitability of the use of the IDMM model in the context of the PPP registration at the EU level.
Although the Reviewer is aware of the potential usefulness of the IDMM model for the calculation of $PEC_{sw/sed}$ of metals, yet an in-depth assessment of the model would be required, in order to consider it fully acceptable by all sources.

Regarding the use of the FOCUS drift calculator, the Reviewer does not agree with the choice of the Applicants of using a single application as worst case scenario in the calculation of the PEC_{sw} via drift, giving the reason of a very rapid dissipation of copper from surface water to sediment with a DT_{50} << 1 d. On this last point, indeed, the Reviewer has to highlight that an approved water-DT_{50} value of 30.5 d was derived from the microcosm study of Schäfers (2000), as reported in the DAR 2007, Vol. 3, B.8.

Since in the EFSA document, maximum initial PEC values from $FOCUS_{sw}$ Step 2 were used in the aquatic risk assessment, new $PEC_{sw/sed}$ values were re-calculated by the Reviewer using FOCUS Steps 1&2 (see table below).

Crop	**Steps 1-2**	**PEC_{sw} (µg/L)**		**PEC_{sed} (µg/kg)**	
		Actual	**TWA**	**Actual**	**TWA**
Vines	Step 1	224.04	15.83	21500	21500

	Step 2	26.76*	2.82	4190	4190
Pome & stone fruit (early), also including nuts	Step 1	739.26	29.37	24100	24000
	Step 2	145.99*	10.67	11700	11700
Pome & stone fruit (late)	Step 1	241.48	12.08	13000	12900
	Step 2	78.63*	4.08*	2230	2220
Citrus fruit, olives, cypress	Step 1	482.96	24.15	25900	25800
	Step 2	78.63*	4.32	4720	4710
Vegetables & strawberries	Step 1	62.65	8.98	15400	15300
	Step 2	9.20*	2.57	5610	5600
Potatoes	Step 1	62.65	8.98	15400	15300
	Step 2	9.20*	2.45	5310	5300

* values referred to single application

However, the lower tier risk assessment proposed with FOCUS Steps 1&2 may not be adequate to demonstrate a safe use for the aquatic environment.
Consequently, a different approach still based on FOCUS Step1&2 model for the exposure assessment in surface water is here proposed by the Reviewer, which considers the contribution both of spray-drift and runoff in addition to the one already calculated by the model itself.

Basically, calculations were performed on a excel spreadsheet file, and they were based on the same Step2 equations, as described in FOCUS Steps1&2 software. However, also <u>spray drift loadings</u> estimated with FOCUS drift calculator were taken into account, as well as 90th percentile worst case values for efficiencies of <u>10 m and 20 m vegetated buffer zones</u> in reducing the loading of pesticide transported in the aqueous and sediment phases of runoff (as reported in SANCO/10422/2005, version 2.0, September 2007).
Lastly, use of drift reducing spray nozzles was also considered, which allowed a further 50% of drift reduction. **It is opinion of the reviewer that also spray drift reduction of 75% and 90% could be used**.
The Reviewer acknowledges that this procedure is not entirely suitable for metals, since many processes relevant for inorganic compounds are not considered. However, in the Reviewer's opinion, this assessment is rather conservative, since based on Step2 considerations, but at the same time it allows a kind of refinement, since run-off and drift mitigation measures along with nozzle spray drift reduction techniques are considered. Therefore, currently it seems a quite good compromise for the definition of the exposure assessment, until an adequate method for calculating PEC_{sw-sed} of inorganic compounds as active ingredients of PPP will not be fully developed and agreed on, where also all relevant processes such as drift, runoff, drainage, erosion will be considered at the same stage.

Another refinement could be the consideration of a **further reduction of a factor of 3** to take into account the dissolved copper vs. the total copper. This last value is derived from the microcosm study and suggested also by the EUCuTF. Nevertheless, this value is quite questionable, since it is very variable among different studies.

An example of $PEC_{sw/sed}$ values calculated by the Reviewer are reported in the table below.

Crop	Drift rates (%)			Runoff	PEC_{sw} (µg/L)	PEC_{sed} (µg/kg)	Further 50% nozzle reduction	
	Buffer (m)	Single	Multiple	Veg. buffer strip (m)			Final PEC_{sw} (µg/L)	Final PEC_{sed} (µg/kg)
Vines	10	1.1329	0.8521	10	3.77*	617.18	**1.89***	**308.59**
	20	0.3974	0.2954	20	1.32*	208.70	**0.66***	**104.35**
Pome & stone fruit (early), nuts	10	11.39	8.08	10	56.95*	2613.84	**28.48***	**1306.92**
	20	2.6039	1.9784	20	13.00*	741.81	**6.50***	**370.91**
Pome & stone fruit (late)	10	3.3569	2.5232	10	16.8*	430.87	**8.40***	**215.44**
	20	1.0359	0.7290	20	5.20*	131.60	**2.60***	**65.80**
Citrus, olives, cypress	10	3.3569	2.2530	10	16.80*	902.11	**8.40***	**451.06**
	20	1.0359	0.6296	20	5.20*	274.79	**2.60***	**137.40**
Vegetables & strawberries	10	0.2771	0.1607	10	1.10	834.39	**0.55**	**417.20**
	20	0.1440	0.0830	20	0.55	283.80	**0.28**	**141.90**
Potatoes	10	0.2771	0.1607	10	1.04	789.35	**0.52**	**394.68**
	20	0.1440	0.0830	20	0.52	268.71	**0.26**	**134.36**

* values referred to single application.

Ecotox evaluation

Earthworms

Copper risk assessment to earthworms relies substantially on a long-term field study (Klein, 2011) carried out in two different sites in Germany. The study was evaluated by a panel of three independent experts (copper compounds DAR, Volume 3 B-9, Addendum 4). Their conclusion confirms that a NOEC could be established at 8 kg/ha. The reviewer fully agrees with the evaluation of the independent panel and support the setting of a **NOEC at 8 kg/ha** for this particular study.
Since the bioavailability of copper is strongly dependent on physical-chemical characteristics of soil, the extrapolation of this specific study to all possible scenarios must be carefully considered. The reviewer supports the introduction of an **assessment factor of 2** for risk assessment procedures. **This would lead to a Regulatory Acceptable Concentration (or, in this case a Regulatory Acceptable Application Rate) of 4 kg/ha**.
Further refinements are required to address this point.

Birds and mammals

Some studies presented by the EUCuTF in the Confirmatory Data, and considered acceptable by EFSA, clearly showed that some mouse populations are able to regulate the body concentration of copper trough homeostatic mechanisms also when exposed to high metal levels. In general, the studies provided by EUCuTF show absence of adverse effects up to the application rates of 4.5 kg Cu/ha. Reviewer tends to agree with the conclusion of the absence of long-term risk for mammals, but stresses once again the role that evolutionary mechanisms may have played within specific populations.
In table below the proposed endpoints for bird and mammal section

Toxicity of Copper to birds			
Test species	**Time scale**	**Test substance**	**Agreed endpoints** **(EFSA Scientific Report (2008) 187,1-101) ***
Coturnix coturnix japonica	Acute	Copper oxychloride WP	**LD_{50} = 173 mg Cu/kg bw**
Colinus virginianus	Acute	Bordeaux mixture	LD_{50} > 616 mg Cu/kg bw
Colinus virginianus	Acute	Bordeaux mixture WP	LD_{50} > 439.9 mg Cu/kg bw
Colinus virginianus	Short-term	Copper oxide	**NOEL = 31.9 mg Cu/kg bw/day ****
Colinus virginianus	Long-term	Copper hydroxide	**NOEL = 5.05 mg Cu/kg bw/day**
Toxicity of Copper to mammals			
Rat	Acute	Bordeaux mixture	LD_{50} = 642 mg Cu/kg bw
Rat	Acute	Bordeaux mixture	LD_{50} = 607 mg Cu/kg bw
Rat	Acute	Tribasic copper sulphate	**LD_{50} = 162.6** to 271 **mg Cu/kg bw**
Rat	Long-term	Copper sulphate	**NOEL = 16 mg Cu/kg bw/day (males)** NOEL = 17 mg Cu/kg bw/day (females)

* values in bold proposed for the risk assessment
** LD_{50} not relevant due to food avoidance

No specific information is given on potential bioaccumulation of copper in earthworms. While several studies (e.g. Hobbelen & Van Gestel, 2007) show that increased internal concentration in earthworms body does not cause significant effects on their own performances (until very high values), it has not be explored how this potential bioaccumulation may affect dietary exposure of birds. Also, among the three species considered in the abovementioned study, none feed specifically on earthworms.
Further refinements are required to address this point.

Bees

A standard tunnel test was carried out and submitted to address the risk to honey bees. No effects on mortality, flight intensity, behaviour, condition of the colonies and development of bee brood were observed. Since the study did not cover the highest application rate foreseen in the GAP table, EFSA identified a data gap (EFSA, 2013). However:

1. As pointed out by the EUCuTF (2013), doses higher than the tested one are only applied against necrosis in winter or early spring before flowering. An exposure to bees from this applications is therefore highly unlikely and considered negligible.
2. Copper has a long history of use in agriculture and past application rates were sometimes much higher than those foreseen for this particular authorisation process. Unlike other animal species, domestic bees' health has always been monitored due to the high economic importance of the colonies in agriculture. Italy is not aware of any reported problem to bees caused by the use of copper in agriculture.

In conclusion, reviewer opinion is that risk to bees due to the use of copper as active ingredients in agriculture is acceptable.

Freshwater organisms

A huge amount of data on effects determined by copper in aquatic organisms is available in the literature. Particularly, during the registration procedure of copper compounds as pesticide active substances, several single-species tests on fish, invertebrates, and algae were presented. Also, a microcosm study was carried out and considered acceptable during the EU review. The NOEC of this microcosm study was set at 4.8 µg/L expressed as initial dissolved Cu. Further, the experts agreed that for risk assessment procedures, a safety factor between 3 and 5 should be applied to this endpoint. In addition, the endpoint derived from the microcosm study was not considered suitable to estimate risk for fish. This has been already highlighted in the RMS (France) comments included in the DAR addendum 3 - Confirmatory data (August 2012).
Reviewer in principle agrees with the idea that separate endpoints for fish should be considered, mainly because no fish were present in the microcosm study. However, as illustrated below, we believe that in this case the approach normally used for pesticides risk assessment is not appropriate.
In the table below, critical endpoints, assessment factors and resulting RACs, obtained by following standard procedures according to EFSA conclusions, are summarised.

Species	Time scale	Critical endpoint (µg/L)	AF	RAC (µg/L)
Fish	Acute LC_{50}	8.0	100	**0.08**
Fish	Chronic NOEC	1.7	10	0.17
Invertebrate, Algae	NOEC microcosm	4.8	3-5	1.6-0.96

Thus, following normal procedures, the lowest value of 0.08 µg/L should be selected as overall RAC. It should be highlighted that this concentration (expressed as total copper) is 11 times lower than the median natural background concentrations of copper in surface waters according to the data reported in the VRAR and considered acceptable by the SCHER. Further, from monitoring data it can be stated that water collected from at least 90% of relatively pristine sites in Europe presents concentrations higher than the RAC.
It is reviewer opinion that the use of large assessment factors is not a suitable approach for natural compound such as copper, because it leads to unrealistic concentrations, as it has just been shown.
In addition, as clearly specified in the SCHER opinion on the VRAR, environmental factors (e.g. hardness, pH, and dissolved organic carbon) play a major role in determining copper toxicity on aquatic organisms. Biotic Ligand Models (BLMs) have the potential to take into account the bioavailability of metals and the influence of physical-chemical parameters on the relative toxicity.
In the VRAR, BLMs have been developed for algae, invertebrates and fish using a great amount of ecotoxicological data. Then, 7 scenarios representing different conditions of European natural water bodies have been selected in order to cover a wide range of physical-chemical conditions. The BLM has been applied to the different scenarios in order to derive site-specific SSD curves based on chronic NOEC values. Finally, HC_5 values specific for the different scenarios were calculated.
Italy opinion is that the use of this approach is valid and that the work already done is extremely valuable.

Therefore, it is proposed to take into account the lower 95% confidence limit of the lowest HC_5 calculated among the selected scenarios (River Otter in the United Kingdom). The relevant concentration value is 4.4 μg/L, expressed as total copper concentration.
It is also proposed that this value should be taken as it is for risk assessment procedures, without applying any safety factors, taking into account that:

- Inter-species sensitivity as well as inter-laboratory variability has been fairly covered by considering a large number of ecotoxicological studies (139), including data on 27 different species from 9 different taxonomic groups. Further, a side evaluation on amphibians (7 species, not included in the statistical analysis) showed that this taxon has low relative sensitivity to copper.
- The long-term effects due to copper exposure have been covered by considering chronic toxicity tests only.
- A great source of uncertainty, regarding the extrapolation of toxicity data from the laboratory to the field, was addressed by the use of BLM.
- The uncertainty regarding the statistical elaboration has been fully addressed in the VRAR, with the conclusion that the approach used is robust in determining the HC_5.
- NOEC is a very conservative endpoint *per se,* and the approach proposed here takes the lower 95% confidence limit (statistical worst-case) of the lowest HC_5 (environmental worst case among European possible scenarios).

In conclusion, reviewer supports the establishment of a RAC at 4.4 μg/L, for risk assessment procedures.

Sediment dwelling organisms

Data available for sensitivity on sediment dwelling organisms are scarce compared to freshwater organisms. During the registration process of copper compounds as pesticide active substances, only one study on *Chironomus riparius* was presented, and the endpoint was expressed in terms of water concentration (mg/L). However, the derivation of an endpoint for sediments on the basis of a water concentration is questionable in the case of copper.
In the VRAR, the assessment of effects of copper on benthic organisms was performed by using a tiered approach: Tier 1 used the equilibrium partitioning (EP) method; Tier 2 was based on the available sediment toxicity data; Tier 3 took the available mesocosm and semi field studies into account.
The SCHER challenged some aspects of the proposed approaches, particularly the use of the EP approach. Moreover, the statistical and ecological significance of the SSD approach, based on a small number of species, was judged as quite weak. However, the different approaches converged on very similar results, so that the HC_5 value (=1741 mg Cu/kg OC, corresponding to 87 mg Cu/kg dry weight for a sediment with 5% O.C.) derived from the SSD approach (log-normal distribution), was considered enough conservative by the SCHER.
Reviewer does not intend to express a strong position on this particular assessment, as data are not sufficiently clear. **However, for the registration of plant protection products containing copper compounds, it seems fair to apply the same criteria used for freshwater organisms. Thus, considering the lower 90% confidence limit of the proposed HC_5, the relevant value is 1112 mg Cu/kg OC, corresponding to 55.6 mg Cu/kg dry weight for a sediment with 5% O.C.**

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