Comments on "Technical guide on metals and alloys used as food contact"

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1. Executive summary

The Council of Europe (CoE) has developed guidelines on materials in contact with foodstuffs (February 2002).

These technical guidelines on metals and alloys used as food contact materials are currently being revised and the CoE proposal includes Specific Release Limits (SRL) for a range of metals in contact with food materials. For copper, the first draft revision included a SRL of 5 mg Cu/kg food, consistent with the SRL set for releases from plastic materials.

The second draft recommended a SRL of 1 mg Cu/kg food for adults. The third and latest draft specified a copper SRL of 1 mg Cu/kg food for children. Please note that the second and third draft proposals include an exemption for "traditional materials".

The European copper industry, represented by the European Copper Institute, does not agree with the conclusions for copper in the second and third draft proposals. The conclusion in the latest draft version is:

> *"Based on the assessments of the SCF (2003) and EFSA (2006), the upper limit of 1 mg/day should be applied in order to protect children as a vulnerable sub-population. Since this value was derived by extrapolation from an adult upper limit where no adverse effects were detected, an allocation factor is not regarded as necessary. Consequently, assuming that a person of 60 kg body weight consumes 1 kg of foodstuffs per day that is packaged and/or prepared with food contact materials made from metals and alloys, the SRL for copper is set at 1 mg/kg."*

As already mentioned in earlier comments to the CoE proposals, new scientific information has become available and peer-reviewed since the SCF (2003) and EFSA (2006) assessments.

The new information leads to the derivation of a safe upper limit (UL) of 0.16 mg/kg body weight (bw)/day (corresponding to 10 mg/day for an adult of 60kg) and Specific Release Limits (SRL) for respectively adults and children:

- **The Specific Release Limit (SRL) value of 5 mg Cu/kg food, proposed for plastics, is adequate to protect the general adult population (60 kg).**
- **A SRL of 2.6 mg Cu/kg food is derived for children (1-3 yr). This SRL value could be considered <u>if</u> translation of an upper limit from adults to children is consistently used for all food contact materials. Such SRL for children is however not consistently derived for all materials.**

The exemption for "traditional materials" is still needed.

The rational for the proposal is outlined below.

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2. Rationale for the human upper limit value of 0.16 mg Cu/kg body weight/day

The human upper limit value of 0.16 mg/kg body weight/day is obtained from the peer reviewed Existing Substances Regulation (ESR) copper risk assessment report.

A copper risk assessment report was drafted by the University of Birmingham and reviewed by the Italian Istituto Superiore di Sanita (2002-2005). The revised Voluntary Risk Assessment (VRA) report (2005 version) was submitted to the European Commission (EC) and discussed at the Technical Committee for New and Existing Substances (TC NES): TC NES II 05, TC NES I 06, TC NES II 06, and TC NES IV 07. The copper RA report (2008 version) was finally evaluated by EC Scientific Committee for Health and Environmental Risk (SCHER) and a SCHER opinion adopted in July 2008. The final copper VRA report (2008), as well as the TCNES and SCHER opinions, is available from the European Chemicals Agency website:
http://echa.europa.eu/chem_data/transit_measures/vrar_en.asp

The copper Voluntary Risk Assessment (VRA) report (2008) is based on reports from international experts (e.g. IPCS (1098), IOM (2001), SCF (2003), WHO (2004)), broad literature searches as well as the development of new data (e.g. 2-generation rat feeding study (Mylchreest, 2005)).

All this information was used to derive a human No Observed Adverse Effect Level (NOAEL) of 0. 16 mg Cu/kg body weight/day (corresponding to 10 mg Cu/day/60kg). Since human data demonstrated the absence of effects, the human NOAEL can be considered as an Upper Limit value.

A summary of the key studies used is provided below:

2.1 A human NOAEL of 10 mg Cu/day (60kg) was derived from animal data and application of conservative Uncertainty Factors

Two high quality animal repeated dose studies (oral intake of a soluble copper compound) allowed to derive an animal NOAEL:

a. A rat NOAEL of 16 mg Cu/kg body weight/day (sub-chronic 90 days rat toxicity study with soluble copper sulphate added to the diet - Hebert et.al, 1993).
b. A chronic NOAEL of 15-27 mg Cu/kg body weight/day was obtained from a 2-generation rat reproductive toxicity study with soluble copper sulphate added to the diet (Mylchreest, 2005). No age-related sensitivity was observed from the study. In this study the NOAEL for reproductive toxicity, was higher than the highest dose tested (> 24 mg Cu/kg bw/day).

The animal NOAEL (15-27 mg/kg bw) from Mylchreest (2005) therefore confirmed the animal NOAEL (16 mg/kg bw) from Hebert et al., 1993. After applying an Uncertainty Factor (UF) of 100, a human NOAEL of 0.16 mg Cu/kg/day is derived, corresponding to 10mg/day for an adult (60 kg).

To conclude, the extrapolation of the rat NOAEL (16 mg/kg bw/day) to a human NOAEL (AF 100) of 0.16 mg/kg bw/day is a conservative extrapolation, including an uncertainty factor for "variability within the normal population".

The 2-generation study (Mylchreest, 2005) further demonstrated the absence of age-related effects and therefore the human NOAEL of 0.16 mg/kg bw/day is applicable to adults and children. For an adult of 60 kg, a NOAEL of 10 mg/day is derived.

2.2. Human data demonstrates the absence of adverse effects up to 10 mg Cu/day

Three human studies are highly relevant to the derivation of the human upper limit:

a. The human data from Pratt et al. (1985) (7 individuals, one dose, no dose-response) indicated an absence of effects associated with repeated oral intake of 10 mg Cu/day for 12 weeks as a supplement in adults (total copper intake estimated as 11-12 mg /day) (study used in copper EFSA 2006).
b. Turnlund et al., (1990 and 1991) demonstrated homeostasis up to 7.5 mg Cu/day (used in EFSA, 2006).
c. The absence of effects at copper supplementation of 8 mg/day (total estimated intake of 9-10 mg Cu/day) was demonstrated for the treatment of mild Alzheimer Disease (AD) during a phase 2 clinical trial (68 individuals, 12 months copper administration)(Kessler et al., 2008a and 2008b).

To conclude, human studies support the absence of effects up to 10 mg Cu/day/person.

Comment: The use of an additional uncertainty factor of 2 on the human threshold value of 10 mg/day derived by Pratt et al (1985) as proposed in SCF (2003) was discussed at TCNES during the copper VRA discussions and it was concluded that considering the weight of evidence from animal and human data, such factor was not necessary.

2.3. The human upper limit of 10 mg/day is consistent with several independent reviews

In addition to the VRA reviews (Istituto Superiore di Sanita, TCNES and SCHER), other independent national and international commissions concluded on an adult UL of 10 mg/day and absence of particular sensitivity of children with normal copper homeostasis:

a. IOM 2001 concluded on a tolerable upper copper intake limit of 10 mg/day.
b. WHO drinking water guideline 2004 further considered adult and children data and concluded: "*Based on the studies by Araya et al. (2001, 2003), Olivares et al. (1998, 2001), Pizarro et al. (1999, 2001) and Zeitz et al. (2003), the guideline value of 2 mg/L is no longer provisional. It should permit consumption of 2 or 3 liters of water per day, use of a nutritional supplement and copper from foods without exceeding the tolerable upper intake level of 10 mg/day (IOM, 2001) or eliciting an adverse gastrointestinal response*."
   - The WHO drinking water guideline includes the study of Olivares et al. (1998), who demonstrated the absence of effects in children (3-12 months) that were copper fortified formula-fed (2 mg Cu/L) versus breast-fed infants.
   - Retrospective investigation of Scheinberg and Sternlieb (1994) as well as Zeitz et al. (2003) demonstrated the absence of effects on children (0-5 years) up to respectively 6 and 8 mg Cu/L.
c. WHO drinking water guideline 2008 confirmed the human upper limit of 10 mg Cu /day and drinking water standard of 2 mg/L.
d. The UL of 10 mg/day is equal to the one derived by the UK Expert Group on Vitamins and Minerals.

To conclude an upper limit of 0.16 mg Cu/kg body weight/day is derived from a wide weight of evidence, including animal studies as well as human studies.

The UL of 0.16 mg Cu/kg body weight/day is protective to adults and children.

An adult UL of 10 mg/day/60 kg person is derived

3. Rationale for a copper SRL protecting adults (60kg)

The UL of 0.16 mg/kg/day or 10 mg/day (60 kg) is used in combination with an evaluation of copper intake levels from various sources

An extensive literature research was done in the copper Risk Assessment (2008), to assess copper exposure levels to the general population from:

a. Copper exposures from food and beverages, estimated from a wide range of duplicate diet studies and market basket analysis consistently show copper intakes ≤2 mg/day (Table 1). An overall median copper intake of **1.25 mg Cu/day** was derived.

b. The use of dietary copper supplements may add **2 mg Cu/day**.

c. Dermal exposure (e.g. handling of coins) is negligible due to very low dermal adsorption of copper.

d. Inhalation exposures are generally very small and hardly contribute to the overall copper intake of the European citizens.

The typical and reasonable worst case exposure of adults to copper therefore range between 1 and 4 mg/day.

These estimations are based on duplicate diet and market basket studies and therefore include general uses of copper in contact with food and drinking water. Detailed investigations on the use of copper in contact with drinking water is outside the scope of this paper

The use of copper materials in contact with food was further investigated and revealed the following uses:

- Traditional materials (cheese, chocolate, and distillery) are the main uses of copper in contact with food.
- A few additional marginal uses of copper in contact with food were identified:
    - Lead free copper alloy is used for connecting pieces which are applied to connect plastic water pipes in coffee machines.
    - Copper tubes used as heating coils which are applied in coffee machines and water boilers. Heating coils are coated with tin or other materials and therefore the release of copper is not expected.
    - Uses of silver coated Cu-Zn-Ni alloys as cutlery and table hollowware was identified from EN ISO 8442-2:1997 British Standard Materials and articles in contact with foodstuffs. The standard specifies the thickness of the silver coating and therefore, release of copper is not expected.

To conclude: With exceptions of the "traditional materials", the releases of copper from "materials in contact with food" are negligible.

Consequently, combining the UL of 10 mg/day (60 kg) and the reasonable worst case copper intake for the general population (4 mg/day) allows to confirm the safety of the food contact SRL of 5 mg Cu/kg food as derived for plastic materials. Assuming the consumption of 1 kg food in contact with copper, would still lead to a total copper intake below the acceptable daily copper intake (10

mg/day) and the value would be consistent with the guideline set for plastic materials.

To conclude, a SRL for adults of 5 mg/kg food is deducted. The value is consistent with the limit value derived for plastic materials.

4. Rationale for a copper SRL protecting children

The 2-generation study (Mylchreest, 2005) demonstrated the absence of age-related effects. The UL of 0.16 mg/kg/day is therefore applicable to adults and children with normal copper homeostasis. A body-weight translation from adults to children is justified.

The application of such additional body-weight translation is however not consistently used for all the food contact materials and therefore its application for copper is questioned.

If the body weight translation from adults to children is carried out, a body weight translation and food consumption translation is needed.

- A body weight translation of the adult upper limit (10 mg/day 60 kg) results in an upper limit of 2.2 mg/day for a 1-3 years old child (13 kg).
- Children of 1-4 years old consume on average 91.2 g food /kg bw/day, corresponding to 63.8 g packaged food/kg bw/day (Foster and Adamson, 2006) or 0.83 kg packaged food intake/day for a 1-3 yr (13 kg). This is a very conservative value because the contribution of metal packaged food in such small children is only 3.5 to 4.5 g metal packaged food/kg body weight day (Foster and Adamson, 2006) or <0.06 kg metal packaged food/day for a 1-3 yr old (13 kg).
- The contribution of food that has been in contact with copper materials is actually negligible (plastic water pipes for coffee machines have no relevance to children – see section 3).

The UK Total Diet Study (FSIS 2004) estimated total consumer dietary exposure to copper in different age groups. Toddlers (1.5 -4.5 years) have a mean daily intake of 46 µg Cu/kg body weight, or 0.6 mg/day for a 13 kg child. This copper intake value corresponds to the result from a duplicate diet studies reported in the copper risk assessment (Table 2)[1].

Considering that the actual copper intake from copper releases following contact of copper or copper alloys with children food is not expected, the need for a SRL for children (1-3 years) is again questioned.

If a limit for children still needs to be set, the assumption of 0.83 kg copper-contacted food intake /day for small children can be used as extremely conservative value. Such intake would result in a conservative SRL for children (13 kg) of 2.6 mg/kg. Considering that the releases from food contact materials are part of the dietary intakes, and no "food –contact uses for copper" were identified, no additional allocation factor is needed.

Following a body weight translation, a SRL of 2.6 mg/kg food to protect young children can be considered. This is a very conservative SRL because the contribution of children food in contact with copper is actually negligible.

[1] releases from food contact materials are included in these estimates.

5. Copper concentrations in fresh food items

The table 3 (developed by the CoE in the framework of previous discussions) summarizes the copper levels of fresh food. The table shows typical mean copper concentrations in food ranging between 0.1 and 36 mg/kg.

Several cheeses (e.g. Comté, Appenzel, Tilsit, Beaufort and Parmiggiano) are produced with "traditional copper materials" and have copper levels exceeding 5 mg/kg. Similarly, some spirits and home-produced beverages also have copper levels more than 5 mg/L. An exemption for traditional materials is therefore needed (more information from Van Lysbetten et al, 2010).

6. Summary and conclusions for the copper SRL

The copper Voluntary Risk Assessment (VRA, 2008) is based on reports from international experts (e.g. IPCS (1098), IOM (2001), SCF (2003), WHO (2004)), broad literature searches and the development of new data. The copper RA report was peer reviewed by TCNES and SCHER. The report and the reviews are available from the European Chemicals Agency website: http://echa.europa.eu/chem_data/transit_measures/vrar en.asp.

This most recent peer reviewed assessment, leads to the derivation of a safe UL of 0.16 mg/kg body weight/day or adult UL of 10 mg/day (60 kg) and is consistent with the IOM (2001), the WHO water quality guidance (2004 and 2008) and the UK Expert Group on Vitamins and Minerals.

The new information allows the derivation of Specific Release Limits (SRL) for respectively adults and children:

- **The Specific Release Limit (SRL) value of 5 mg Cu/kg food, proposed for plastics, is adequate to protect the general adult population (60 kg).**
- **A SRL of 2.6 mg Cu/kg food is derived for children (1-3 yr). This very conservative SRL value is acceptable if translation of an upper limit from adults to children is consistently used for all food contact materials.**

The exemption for "*traditional materials*" is still needed (see "Release due to traditional use, as referred to in Regulation (EC) No 1935/2004, falls outside the scope of this SRL.")

In line with the comment made for iron, the following amendment is proposed: "*The EVM noted that the guidance value is not meant to protect "a small portion of the population who has increased susceptibility to copper overload, via a mechanism of unregulated absorption from the diet, associated with Wilson disease and other metabolic disorders of copper homeostasis*".

Table 1: Summary of dietary exposure to copper for adults (mg/day) – from the Copper Risk assessment 2008 (Human Health exposure).

Reference	Year	Country	Study Type	All beverages Included	n	Sex	Age	Mean (10-90th percentiles) M	F
Abdullah et al.	1989	Sweden	Dup diet (24hrs)	Yes	~300	m+f	20-55	1.33 (0.8-1.9)	
							>65	1.27 (0.7-1.8)	
Anke et al.	1990	Germany	Dup diet (1wk)	Yes	56	m+f	20-60	0.83 (0.4-1.3) (note 1)	0.66 (0.3-1.0)
Bro et al.	1990	Denmark	Dup diet (48hrs)	Yes	100	m	30-34	1.2 (0.4-2.0)	
Ellen et al	1990	Netherlands	Dup diet (24hrs)	yes	110	m+f	18-74	1.2	
Becker and Kumpulainen	1991	Sweden	Mkt bskt + anal	No	Adult population			1.2	
Pennington and Young	1991	USA	Mkt bskt +anal	No	Pop	m+f	25-30	1.22	0.94
							60-65	1.18	0.86
Buss and Rose	1992	UK	Food weighed+database	Yes	2200	m+f	16-64	1.49	1.13
Swerts et al.	1993	Belgium	Dup diet	No	Note 2	m+f	Elderly	1.1 (0.8-1.4)	
Lamand et al.	1994	France	Mkt bskt + anal	No	Pop	m+f	25-60	1.3	1.1
							>60	1.2	1.0
Pelus et al.	1994	France	Dup diet (5 days)	Yes	14	m	25-35	1.23 (1.0-1.5)	
Van Cauwenbergh et al.	1995	Belgium	Dup diet (7 days)	Yes	n/a	m+f	<60	1.73-1.83	
Jorhem et al.	1998	Sweden	Dup diet (1 wk)	yes	15	f	27-46		1.0 (0.6-1.4)
Pokorn et al.	1998	Slovenia	Dup diet (24hrs)	?	51	m+f	>65	0.9 (0.3-1.5) (note 3)	
Rodriguez-Palmero et al.	1998	Spain	Dup diet (21 days)	No	n/a	m+f	>60	1.0	
Ysart et al.	1999	UK	Mkt bskt + anal	No	Adult population			1.2-1.4	
Bates et al.	1999	UK	Diet rec + d'base (4 days)	No	~600	m+f	65-79	1.13(0.3-2.0)	0.90 (0.1-1.7)

Table 2: Summary of dietary exposure to copper for children (mg/day) – from the Copper Risk assessment 2008 (Human Health Exposure).

	Reference or number of studies	Typical	10P-RWC	90P-RWC
Children and adolescents				
<15 months	Richmond et al, 1993	0.6		
2 yrs	Smart et al., 1987	0.45	0.4	0.5
2-3 yrs	Boscher et al., 2002	0.7	0.45	0.95

Table 3: Copper levels in food items

	Mg de cuivre/ kg de matière fraîche	
	Moyennes	**Fourchette**
Céréales	**1,5**	
Farine	1,5	0,95 – 2,9
Pain blanc	1,5	0,89 – 2,2
Sucre blanc	2	–
Miel	0,5	–
Poudre de cacao	36,4	33- 410
Lait chocolaté	3	–
Fruits	**0,65**	
Pommes	0,25	0,21 - 0,31
Poires	0,81	0,48 – 2,7
Bananes	0,91	0,7 – 1,2
Légumes	**0,59**	
Pommes de terre	0,72 et 0,96 (0,84)	0,26 - 2,2
Carottes	0,4 et 0,61 (0,50)	0,26 – 0,95
Laitue	0,47 et 0,72 (0,54)	0,20 – 1,4
Tomates	0,36 et 0,55 (0,45)	0,29 – 1,1
Poissons	**0,42**	
Morue	0,19	0,12 – 0,28
Thon	0,64	0,48 – 0,80
Viandes	**1,2**	
Bœuf	0,8 et 1,1 (0,95)	0,74 – 1,6
Porc	0,9 et 1,4 (1,15)	0,44 – 7,22
Agneau	1,6	1,10 – 1,90
Lait	0,06	Traces – 0,14

7. Proposed changes to the "Safety aspects" section (page 21) of chapter #3.5. Copper: Cu

- Recently (2008), a comprehensive copper ESR RA Report, endorsed by the EC Technical Committee on New and Existing Substances (TC NES) and the EC Scientific Committee for Health and Environmental Risk (SCHER), concluded on a NOAEL of 10 mg Cu/day (60 kg). The value is based on high-quality animal dietary studies (90 days study and 2-generation study) with dietary copper sulphate and ministrations and the application of an overall assessment factor of 100. The human NOAEL derived from animal data is confirmed by human data (Pratt et al, 1985).
- Kessler et al., 2008a and Kessler et al., 2008b evaluated oral copper supplementation (dietary supplementation of 8 mg Cu/day; corresponding to a total dietary intake of 9 to 10 mg Cu/day) for 12 months for the treatment of mild Alzheimer Disease (AD) in a prospective, randomized, double blind, placebo-controlled phase 2 clinical trial. Sixty-eight subjects were randomized. The copper treatment demonstrated a positive effect on an AD biomarker (CSF Aß42 level). Copper was well tolerated and no significant adverse effects were detected at any time as an effect of Cu treatment.
- WHO (2004) concluded: "Based on the studies by Araya et al. (2001, 2003), Olivares et al. (1998,2001), Pizarro et al. (1999, 2001) and Zeitz et al. (2003), the guideline value of 2 mg/liter is no longer provisional. It should permit consumption of 2 or 3 liters of water per day, use of a nutritional supplement and copper from foods without exceeding the tolerable upper intake level of 10 mg/day (IOM, 2001) or eliciting an adverse gastrointestinal response."
- WHO (2008) confirmed the drinking water standard of 2 mg/L and upper intake level of 10 mg/day.
- IOM (2001) proposed a safe limit value of 10 mg Cu/day.

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