Meeting

Discussion paper on the EFSA Draft Opinion for Public Consultation on “Re-evaluation of the existing health-based guidance values for copper and exposure assessment from all sources”

This is a draft statement for discussion.

It does not reflect the final views of the Committee and should not be cited**.**

Introduction

1. The European Food Safety Authority (EFSA) Scientific Committee (SC) were asked to review the existing scientific evidence and all new relevant studies with the aims:

- to provide a scientific opinion on an Acceptable Daily Intake (ADI) for copper which can be used as a reference value for copper containing regulated products
- to take into account all sources of exposure and integrate different approaches and scenarios, to perform a new estimation of the overall copper intake which includes contributions from all major sources of exposure.

2. This paper provides a summary of the approach used by the EFSA Scientific Committee to establish the ADI for copper and a brief summary of the approaches and studies used to reach the conclusions in order for the Members to discuss and submit their comments. The EFSA Opinion is attached in Annex A of this paper.

Background

Previous evaluations

3. Copper has been the subject of a number of evaluations. The World Health Organisation (WHO) addressed the upper limit to the safe range of intake of copper in 1996, setting the Health Based Guidance Value (HBGV) of 0.18 mg/kg bw day for male (65 kg = 12 mg/day) and females (55 kg = 10 mg/day) based on human studies. No critical endpoint was stated and a no observed adverse effect level (NOAEL) of 10 mg/day was given using an uncertainty factor (UF) of 1 (WHO, 1996).

4. The US Institute of Medicine (IOM) reached a similar conclusion when looking at the tolerable upper level in 2001 with a HBGV of 10 mg/day which included pregnant and lactating women. This was based on human data with a critical endpoint of liver damage and a NOAEL of 10 mg/day (UF = 1). The rationale for this decision was based on no adverse effects in humans being observed following daily consumption of 10 to 12 mg/day of copper in foods and the rarity of liver damage observed in the population with normal copper homeostasis from copper exposure.

5. In 2003, the EU Scientific Committee on Food (SCF) established a HBGV of 5 mg/day (excluding pregnant and lactating due to lack of data) based on human clinical studies using liver damage as the critical endpoint. An UF of 2 was used to allow for potential variability within the normal population. The findings of the Turnland et al. studies (1990; 1991) supported this HBGV as the findings showed that as copper intake increased there was a decrease in copper absorption. Measurements of copper in plasma, erythrocyte SOD, caeruloplasmin and in urinary excretion were resistant to change except where the dietary conditions were extreme. The Nordic Council of Ministers in 2012 and the Norweigian Scientific Committee for Food Safety (VKM) in 2017 both based their recommendations on the SCF HBGV of 5 mg/day.

6. The Expert Group on Vitamins and Mineral (EVM) when reviewing copper (also in 2003) established a safe upper level of of 10 mg/day (or 0.16 mg/kg bw day). This was based on a 90 day rat study (Hebert, 1993) with supporting evidence from human studies (Pratt et al., 1985; Turnland, 1989; Olivares et al., 1998; Pizarro et al. 1999). An UF of 100 was applied to the rat study to incorporate interspecies and intraspecies difference, whereas the UF for the human supporting studies was 1.

7. The Committee on Toxicity (COT) used the HBGV for the safe upper level of copper set by the EVM in its 2018 statement on the potential risks of

copper in the diet of infants and children (up to the age of 5 years) which concluded that there was no toxicological concern for the health of infants and young children with normal copper homeostasis (COT, 2018).

8. France, in their framework report in 2007, when looking at the ADI established a HBGV of 0.15 mg/kg bw day. The decision was based on a 1 year dog study with a critical endpoint of elevated serum glutamic pyruvic transaminase (SGPT) = alanine aminotransferase (ALT),which was supported by a 90 day study in rats observing liver and kidney damage and human clinical studies observing liver damage (Shanaman et al. 1972; Harrisson et al. 1954; Hebert 1993; Mylchreest 2005; Pratt et al. 1985). The NOAEL for rats, dogs and humans were 16, 15 and 10 mg/day respectively. The UFs used for both rat and dogs studies were 100, however for humans the UF was 1 as the vast majority of the population were considered to be similar and using a safety factor of 10 for individual variation would be considered too high (France, 2007). The HBGV was reassessed by France in 2017 when it looked at the ADI of copper. It confirmed the HBGV of 0.15 mg/kg bw per day based on the WHO findings in 1996 and liver damage with NOAEL of 0.2 and 0.15 mg/kg per day for adults and children respectively.

9. In 2008, EFSA considered the upper limit for copper, basing their decision on the human data (and dog study as supporting evidence from Shanaman et al. 1972) used by the WHO in 1996 (EFSA, 2008). EFSA determined the same HBGV as France the previous year of 0.15 mg/kg bw per day with NOAEL of 0.2 mg/kg per day for adults and 0.15 mg/kg per day for children. In 2018, EFSA reconsidered copper and the ADI. It held the previous HBGV value of 0.15 mg/kg bw per day using liver damage as the critical endpoint (EFSA, 2018).

10. The Agency for Toxic Substances and Disease Registry (ATSDR) are currently seeking public comment on a toxicological profile with a deadline of 26 July 2022. They previously looked at the chronic oral minimal risk level, but there was inadequate data (ATSDR, 2004).

Summary of 2022 EFSA evaluation

Copper physiology, homeostasis and toxicology

Copper chemistry

11. Ionic copper is the biologically active form of copper and cycles between the reduced cuprous (Cu^{+}) and oxidise cupric (Cu^{2+}) ionic states due to its redox reacitivty. The major intracellular form of copper is the cuprous ion and extracellularly is usually the oxidised cupric state.

12. An essential element for the function and structure of several cuproproteins, copper is ubiquitous in humans and highly conserved in mammalian species. It is estimated that the average adult human body contains 1.4-2.1 mg/kg bw or 50-150 mg of copper with roughly 40% found in the muscles. Copper is found in red blood cells with ≈60% of the copper in the form of superoxide dismutase (SOD). Copper is also found in other organs such as the liver, brain, heart, kidney and the skeleton with concentrations ranging from 4.8 to 12 µg/g and 1 to 2 µg/g in the lung, spleen and intestine.

13. Copper is transported during lactation and passes to the nursing infant via milk; this process is regulated by prolactin.

14. Once absorbed, the systemic fate of copper involves protein binding and cellular transport via copper transporting ATPases including ATP7A and ATP7B. ATP7A assists in the release of copper from enterocytes into the blood stream, binding to albumin and possibly transcuprein. ATP7B assists the exretion of copper bound to metallothioneins by the liver into the bile as part of homeostatic regulation.

15. Some individuals have a genetic mutation of ATP7A which can lead to insufficient absorption of copper and copper deficiency, whereas an ATP7B genetic mutation can result in reduced biliary excretion and copper retention.

16. To understand copper physiology, it is necessary to have an understanding of how copper and zinc homeostasis interact and this is dependent on their interactions with metallothioneins (MTs). Intracellularly, MTs bind copper in its cuprous ionic state (Cu^{+}). MT4 is classified as the copper MT while MT1 and 2 carry more zinc than copper, although due to its higher binding affinity for MT, copper may bind to MTs by either displacing zinc or in addition to zinc that is already bound to the MT.

Toxicokinetics

17. In 2015, copper physiology and metabolism was addressed in the Panel on Nutrition, Novel Foods and Food Allergens (NDA) Opinion on Dietary Reference Values (DRVs) for copper (EFSA NDA Panel, 2015).

Copper homeostasis in adults

18. To assess the absorption, excretion and estimated balance of copper the first conducted studies used copper isotope 65Cu (Turnlund et al., 1982; Turnlund, 1983; Turnlund et al., 1985; Jacob et al., 1987; Turnlund, 1988; Turnlund et al., 1988).

19. In 1989, Turnlund used a ^{65}Cu isotope to characterise copper homeostasis using three dose levels (one high intake level and two to represent the recommended intake levels derived from earlier balance studies). The study had 11 male participants aged 22-35 years old who each received three levels (1.7 mg/day over an equilibration period, 0.8 mg/day as a low dose period and 7.5 mg/day as a high dose period) of copper in the diet for a total period of 90 days. The background level of copper was estimated as 1-1.5 mg/day. Copper absorption was measured as 0.61, 0.44 and 0.93 mg/day during equilibrium, low and high copper exposure respectively. Copper excretion in the faecal matter increased during the high copper exposure from 4 mg/dy to 9 mg/day. During the low and high copper exposure periods, the average copper balance was 0.002 ± 0.034 and 0.941 ± 0.16 mg/day respectively. It was suggested that there was adaption to the copper levels during the high copper period due to a linear decline in the copper balance, although this was not sufficient to equilibrate to the high copper diet, leading to retention of copper on average of 0.94 mg/day (Turnlund, 1989). It was also suggested that there was substantial individual variability in the ability to adapt to the high levels of copper intakeas half of the participants still had a positive copper balance 24 days after the high copper intake.

20. Comparisons were made of plasma copper, caeruloplasmin concentrations, erythrocyte SOD and salivary and urinary copper during the three testing level periods with no differences observed (Turnlund et al. 1990).

21. The data from 11 participants were analysed in a subsequent study for true and mean copper absorption and excretion for the three levels. Oral copper intakes of 0.66 mg/day for 24 days, 0.38 mg/day for 42 days and 2.49 mg/day for 24 days were assessed in half the participants. True copper absorption was 73%, 77% and 66% and mean copper absorption was found to be 54%, 67% and 44% respectively for the three time periods (Turnlund et al., 1998). Excretion was assessed using intravenous infusions of ^{65}Cu in the other half of the participants. In the first 12 days after infusion, copper excretion increased as the intake increased and was 26%, 12% and 34% of the dose over the three time periods. The total amount of copper excreted included recently (last 12 days) excreted

dietary copper and endogenous copper but did not account for recently absorbed dietary copper. The excretion rate was faster in the first 18 days after oral exposure increased. At the higher doses the difference of absorption was due to an increase in biliary excretion. However, there were also indications that there was an adaption in the changes in copper intakes during the low and high intakes.

22. A study using 12 men as participants to investigate copper absorption and retention was conducted by Harvey et al. (2003). Participants received daily copper of 0.7, 1.6 or 6 mg during 8 week periods with intervening washout periods of 4 weeks. The apparent and true absorption during the low copper period showed no significant difference with the high copper period, while endogenous copper losses were higher during the high copper exposure in comparison to the low and medium copper diet. However, as these endogenous copper losses were calculated based on the orally administrated copper instead of infused copper, the SC noted that they can not be compared directly. There were no observable differences of erythrocyte SOD, serum copper concentration and plasma caeruloplasmin concentration and activity.during the three time periods (Harvey et al., 2003).

23. Turnlund et al, (2004; 2005) considered longer term adaption to high copper intake in a study group of 9 men. Each participant consumed 1.6 mg/day copper for the first 18 days under controlled conditions. Their usual diets were then supplemented for 129 days with 7 mg/day of copper under free living conditions and then the final 18 days were under controlled conditions, again with an intake of 7.8 mg/day copper. It was estimated that the copper content in the free living conditions was on average 1.6 mg/day based on the 5 day diaries and nutrition database (Nutrition Coordinating Center, University of Minnesota, 1998) and therefore the total copper intake during this time period was on average 8.6 mg/day. Excretion of copper was significantly higher in the higher intake level periods. However, the total balance of copper was positive at the end of the final 18 days which was associated with a higher urinary excretion and hair copper concentrations (0.0256 mg/day and 0.0211 mg/day respectively) (Turnlund et al., 2004; Turnlund et al., 2005). These studies also indicated that when the oral intake is high the endogenous copper is processed faster which was shown from significantly higher caeruloplasmin activity, erythrocyte SOD and benzylamine oxidase at the end of the final intakes, whereas plasma concentrations were unaffected. The study predicted that the body burden would double within 100-150 days of continuously consuming on average 8 mg/day of copper but the SC identified there was uncertainty in these projections. The absorption and excretion measurements was of the period immediately before the copper intake

and therefore the subjects were still retaining copper at the end of the periods.

24. Biliary excretion of copper appears to be the main excretion mechanism.

25. There was limited data that compared homeostasis in men and women as there were differences in the diets and, copper absorption in women was not assessed in the above studies, however absorption appears to be similar for comparable intakes of copper.

26. There are similarities in copper absorption between pregnant and non-pregnant women.

27. Minor routes of copper excretion include through urine, sweat, skin and hair. Copper can also be excreted into the GI tract from saliva, gastric, pancreatic and duodenal juices (Linder, 2020).

Copper homeostasis in infants and children

28. The available information was limited for infants and there was no relevant information for children older than 16 weeks of age.

29. Data on copper homeostasis in infants 16 weeks old cannot be extrapolated to older infants or adults because the homeostatic mechanisms develop in the first four months after birth and therefore the copper physiological requirements would not be similar. Children are also expected to have higher requirements of nutrients (including copper) for growth and the retained copper is likely to be dispersed throughout the body.

Copper homeostasis in animals

30. Two 90 day rat studies were used as supporting evidence (Hebert, 1993; Kumar et al., 2015). Both studies showed that with increasing intake of copper (cupric/copper sulphate pentahydrate), hepatic copper increased, although there were significant quantitative species differences between the hepatic copper concentration and the intake dose. Doses were administered in rats which ranged from 18 to 300 fold higher than the human doses, which resulted in a single case reported of liver failure. At dose levels ~100 fold higher than intake levels used in human experiments (0.07-0.09 mg/kg per day) there was observed increased tissue copper concentrations in rats.

Toxicity

31. Previous assessments on copper toxicity have concluded that there is no concern for genotoxicity or carcinogenicity from copper intake in humans (Scientific Committee on Health and Environmental Risks, 2008; France, 2017). This EFSA Opinion concentrated on human data of copper toxicity from observational studies, from those with diseases affected by copper overload and experimental animal studies were used as supportive evidence. Summaries of these can be found in Appendices B.2, B.3, B.4 and B.5 of the Opinion.

32. Copper toxicity has not been reported under usual dietary exposure conditions or in humans with Wilson's disease.

33. There was limited toxicity data on long term exposure to copper. However, one case of severe toxicity has been described in a young man who had ingested 30 mg Cu/day for 30 months and then 60 mg Cu/day for 12 months resulting in abdominal swelling, jaundice, malaise, acute renal failure, and liver cirrhosis requiring a liver transplant. It was determined that the concentration of copper in the liver was 3.23 mg/g dry weight which equates to 100 times that of the standard copper liver content (O'Donohue et al., 1999; Bush et al., 1995; Nuttall et al., 2003).

Observational studies

34. Two cross sectional studies have looked at the effects of copper levels in drinking water ranging from 0.5 mg/L (87.4% of households) to 2.6 mg/L in Dassel de Vergara et al. (1999) and >0.8 mg/L to 4.2 mg/L in Zietz et al. (2003). In both studies, no changes in liver function were reported and only one infant showed elevated serum copper and C-reactive protein in the 1999 study.

35. Two retrospective cohort studies also investigated childhood liver cirrhosis, although the SC concluded that there was insufficient information to be able to conclude an association between adverse effects in children from high copper intake. Scheinberg and Sternlieb 1994 investigated children between 0 and 5 years old in Massachusetts between 1969 and 1991 with copper water levels of 8.5-8.8 mg/L with no reported cirrhosis-related deaths. Dieter et al., 1999 identified 5 cases from 103 of childhood cirrhosis as being due to excessive copper exposure of 9-26.4 mg Cu/L in drinking water.

Controlled intervention studies

36. There is limited data due to a lack of sensitive and reliable specific biomarkers of the early adverse effects of copper toxicity (Danzeisen et al., 2007;

Bost et al., 2016).

37. In the Turnlund et al., 2004 study (para.23 above), urinary markers for lipid peroxidation were used (thiobarbituric acid reactive substances (TBARS)) which the SC concluded were neither sensitive or robust as a biomarker. Plasma maondialdehyde concentration (MDA) was considered a more reliable marker, but this was unaffected by the copper intake (Section 3.3.2 and Appendix B.2 of the Opinion). Other endpoints used in the study were not markers for toxicity, while liver function was not examined. Other studies used ex vivo assays which have limited value when examining oxidative damage in vivo.

Individuals with Wilson's disease and related genetic disorders

38. The toxicological effects seen in conditions such as copper retention seen in Wilson's disease can be informative as to the effects that could be seen in the general population. The high levels of copper accumulating in the liver can lead to a release of copper which then accumulates in other organs such as the brain and kidneys leading to further damage.

Supporting evidence from animals and mechanistic studies

39. The SC considered animal studies as supporting evidence. These included rodent and dog studies. These studies reported consistent findings with high oral dose levels showing increased hepatic copper levels and renal and hepatic toxicity.

40. Although the animal studies are informative, especially for the adverse effects from oxidative stress, the SC highlighted that it was difficult to attribute the results to human exposure due to the multiple aetiologies and that these are not sensitive or specific to signify copper toxicity in humans.

Relationship between copper intake, hepatic copper retention and toxicity

41. The SC recognised that there is uncertainty in modelling hepatic copper levels due to the complexity of the interactions between copper homeostasis and other nutritional factors.

Alzheimer's disease

42. The SC considered that the scientific evidence is not sufficient to conclude that increased copper intake can contribute or exacerbate Alzheimers disease. An overview of the data is available in Appendix B.4 of the Opinion.

Weight of evidence assessment for copper kinetics and dynamics and reference point for establishing HBGVs

43. In Tables 2 and 3 of the Opinion, an assessment of weight of evidence approach is shown for copper kinetics and dynamics respectively. Using this weight of evidence approach, the SC were able to identify a reference point of 5 mg/Cu/day which replaced the previous reference point of 10 mg/day based on the NOAEL. An uncertainty factor was not necessary as the SC considered it was sufficiently conservative to account for identified uncertainties (see Section 4.1 of the Opinion).

Total copper exposure

44. The estimates for total copper exposure from the diet collated from European dietary surveys are shown in Tables 4 and 5 of the Opinion and gave a mean dietary exposure range of 0.014 mg/kg bw per day in the elderly to 0.084 mg/kg bw per day in infants.

45. The 95^{th} percentile of dietary exposure ranged from 0.024 to 0.155 mg/kg bw per day in adults/elderly and infants respectively.

46. It was reported in the Opinion that copper utilisation is higher in children than adults which is expected during physical growth and thus higher nutrient demand is required. Although there is uncertainty in the level of copper intake that would exceed these higher requirements, it is not expected to be maintained at excessive levels throughout childhood. The SC concluded that an exceedance of the HBGV would not pose a lifetime risk for those in the younger age categories and are not a cause for concern.

47. The food categories of “grains and grain based products” (2-44%), “fruit and fruit based products” (2-24%), “meat and meat products” (1-21%), “vegetables and vegetable products” (2-24%), “coffee, cocoa, teas and infusions”(1-21%), “food products for young population” (1-57%) and “milk and dairy products” (2-33%) were the main contributing categories (Table 8 of the Annex in the Opinion).

48. Food and feed additives, nutrient use and fertiliser and plant protection products (PPP) contributed to 10% to the dietary exposure to total copper. The specific assessment for these can be found in section 3.4.2 of the Opinion. The SC noted that long term increases of copper in the soil could occur from PPP use and therefore monitoring was recommended. It was also highlighted that the copper concentration in mammal liver could substantially exceed the current MRLs and that this has previously been noted by the FEEDAP Panel Scientific Opinion in 2016 and the EFSA Opinion on MRL review of copper as a PPP (2018).

49. The amount of copper available from non-oral routes was considered negligible in comparison to dietary exposure in the general population.

Hazard assessment and establishing a HBGV

50. This EFSA Opinion implements the principles for establishing HBGVs outlined in a previous SC statement by the SC in 2021 for substances that were added to food as regulated products and also nutrients (EFSA Scientific Committee et al., 2021). It was noted that an overall risk must be assessed using the total and added risk concepts. To use a harmonised approach to establish a HBGV of essential elements, the concept of an acceptable oral intake range should be used (WHO/IPCS, 2002). However, these would not apply to infants under 16 weeks old or to a susceptible population.

51. The SC noted that previous decisions that identified the NOAEL of 10 mg/day of copper was based on the study by Pratt et al., 1985. However, there were significant limitations to this study as there were only 7 participants, one dose level and inappropriate endpoints. No effects were noted on the liver enzymes in the Pratt et al. 1985 study nor in the Kessler et al., 2008 study after 1 year of dosing of 8 mg Cu/day. Another study that showed no hepatic injury was, Olivares et al., 1998, which tested copper intake in drinking water in children aged 4 to 12 months.

52. Although no hepatic injury was detected in the above three studies, the SC highlighted that the effects may not have occurred in the timeframe of the studies and therefore the endpoints were not sensitive enough to predict copper toxicity.

53. The SC regarded copper balance as an early marker of potential adverse effects and could be used to identify a reference point for copper toxicity. The Turnlund et al., (2005) study was seen as the pivitol study by the SC as the balance could not be restored after 5 months of daily exposure to 8 mg copper.

Another study examining copper retention was by Harvey et al., (2003) although this was 6 mg Cu/day for only 8 weeks, the SC recognised that the homeostatic capacity may be exceeded. Due to the findings in the Turnlund et al., (2005) study of 8 mg/day the SC concluded the previous NOAEL of 10 mg/day was no longer appropriate.

54. The SC concluded that the copper homeostasis studies provided evidence that could be accepted as predictive adverse effects that could occur if there was no reduction in intake following the SC HBGV Statement (2021). The SC recognised that the studies examining copper homeostasis have limitations, However, despite these limitations, the SC recognised the strengths of the studies as they assessed early biological changes in copper toxicity pathways and included controlled diets and dose administration as well as faecal and urinary sample collections.

55. The SC recognised that the HBGV was conservative and therefore protective for most consumers with an intake over a long term period and therefore no uncertainty factor was required.

56. No uncertainties were assigned as high priority with most being classed as low priorities and therefore would not have a substantial impact on the exposure assessment.

57. Based on the weight of evidence approach, the SC concluded that the retention of copper was not expected to occur with an intake of 5 mg Cu/day. This is equivalent to an ADI of 0.07 mg/kg bw for adults. This replaces the previous ADI of 0.15 mg/kg bw (EFSA, 2008; EFSA et al., 2018b).

58. The Members are invited to read the Opinion and Annexes attached as Annex A on this paper and comment on the approach used by EFSA.

Questions to the Committee

i. Does the Committee agree with the selection of the Turnlund et al., (2005) and Harvey, 2003 studies for the derivation of an HBGV?
ii. Do Members agree on the harmonised approach used by EFSA for the derivation of an HBGV?
iii. Do Members agree on the HBGV and ADI established?
iv. Do Members have any further comments?

Secretariat

July 2022

List of Abbreviations

ADI	Acceptable Daily Intake
ALT	Alanine Aminotransferase
ATP	Adenosine Tri-phosphate
ATSDR	Agency for Toxic Substances and Disease Registry
COT	Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment
Cu	Copper
Cu^{+}	Cuprous
Cu^{2+}	Cupric
DRV	Dietary Reference Values
EFSA	European Food Safety Authority
EVM	Expert Group on Vitamins and Minerals
FEEDAP	Scientifc Panel on Feed Additives and Products or Substances Used in Animal Feed
FSA	Food Standards Agency

GI	Gastrointestinal
HBGV	Health Based Guidance Value
IOM	Institute of Medicine
IPCS	International Programme on Chemical Safety
MDA	Maondialdehyde
MRL	Maximum Residue Level
MT	Metallothionein
NDA	Panel on Nutrition, Novel Foods and Food Allergens
NOAEL	No Observed Adverse Effect Level
PPP	Plant Protection Product
SC	Scientific Committee
SCF	Scientific Committee on Food
SGPT	Serum Glutamic-Pyruvic Transaminase
SOD	Superoxide Dismutase
TBARS	Tiobarbituric Acid Reactive Substances
UF	Uncertainty Factor

VKM	Norweign Scientific Committee on Food Safety
WHO	World Health Organisation

References

ATSDR (Atlanta GA: U.S. Department of Health and Human Services, Public Health Service.), 2004. Toxicological profile for Copper. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

Agency for Toxic Substances and Disease Registry (ATSDR). 2022. Toxicological Profile for Copper (Draft for Public Comment). Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. Available at: Copper | Toxicological Profile | ATSDR (cdc.gov)

COT, 2018. Statement on the potential risks from copper in the diet of infants aged 0 to 12 months and children aged 1 to 5 years. Available at: [ARCHIVED CONTENT] COT Statement on Copper | Food Standards Agency (nationalarchives.gov.uk)

EFSA (European Food Safety Authority), 2008. Conclusion regarding the peer review of the pesticide risk assessment of the active substance copper compounds. EFSA Journal 2008;6:187, pp.1-101. Available at: Conclusion regarding the peer review of the pesticide risk assessment of the active substance copper compounds - - 2008 - EFSA Journal - Wiley Online Library

EFSA (European Food Safety Authority), 2018. Review of the existing maximum residue levels for copper compounds according to Article 12 of Regulation (EC) No 396/2005. EFSA Journal 2018; 16:e05212, 135 pp. Available at: Review of the existing maximum residue levels for copper compounds according to Article 12 of Regulation (EC) No 396/2005 (wiley.com)

EFSA (European Food Safety Authority), Arena M, Auteri D, Barmaz S, Bellisai G, Brancato A, Brocca D, Bura L, Byers H, Chiusolo A, Court Marques D, Crivellente F, De Lentdecker C, Egsmose M, Erdos Z, Fait G, Ferreira L, Goumenou M, Greco L, Ippolito A, Istace F, Jarrah S, Kardassi D, Leuschner R, Lythgo C, Magrans JO, Medina P, Miron I, Molnar T, Nougadere A, Padovani L, Parra Morte JM, Pedersen R, Reich H, Sacchi A, Santos M, Serafimova R, Sharp R, Stanek A, Streissl F, Sturma J, Szentes C, Tarazona J, Terron A, Theobald A, Vagenende B, Verani A and Villamar-

Bouza L, 2018b. Peer review of the pesticide risk assessment of the active substance copper compounds copper(I), copper(II) variants namely copper hydroxide, copper oxychloride, tribasic copper sulfate, copper(I) oxide, Bordeaux mixture. EFSA Journal 2018;16:e05152. Available at: Peer review of the pesticide risk assessment of the active substance copper compounds copper(I), copper(II) variants namely copper hydroxide, copper oxychloride, tribasic copper sulfate, copper(I) oxide, Bordeaux mixture (wiley.com)

EFSA FEEDAP Panel (EFSA Panel on Additives and Products or Substances used in Animal Feed), 2016. Revision of the currently authorised maximum copper content in complete feed. EFSA Journal 2016;14:e04563, 100 pp. Available at: Revision of the currently authorised maximum copper content in complete feed (wiley.com)

EVM, 2003. Safe upper levels for vitamins and minerals. Minerals EgoVa. 360 pp. Available at: vitmin2003.pdf (food.gov.uk)

France, 2007. Assessment Report (DAR) on the active substance copper compounds prepared by the rapporteurMember State France, in the framework of Commission Implementing Regulation (EU) No 844/2012.

France, 2017. Draft Renewal Assessment Report prepared according to the Commission Regulation 2980 (EU) N° 1107/2009. Copper Compounds, 1. 203 pp.

Harvey LJ, Majsak-Newman G, Dainty JR, Lewis DJ, Langford NJ, Crews HM and Fairweather-Tait SJ, 2003. Adaptive responses in men fed low- and high-copper diets. British Journal of Nutrition, 90, 161–168. Available at: Adaptive responses in men fed low- and high-copper diets (cambridge.org)

Hebert C, 1993. NTP technical report on the toxicity studies of cupric sulfate (CAS No. 7758-99-8) 3045 Administered in Drinking Water and Feed to F344/N Rats and B6C3F1 Mice. Toxicity Report Series, 3046 29, 1–D3. Available at: TOX-29: Cupric Sulfate (CASRN 7758-99-8) (nih.gov)

IOM (Institute of Medicine), 2001. Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. 797 pp. Available at: Free Executive Summary (nih.gov)

Jacob RA, Skala JH, Omaye ST and Turnlund JR, 1987. Effect of varying ascorbic acid intakes on copper absorption and ceruloplasmin levels of young men. Journal of Nutrition, 117, 2109–2115. Available at: Effect of Varying Ascorbic Acid Intakes

on Copper Absorption and Ceruloplasmin Levels of Young Men | The Journal of Nutrition | Oxford Academic (oup.com)

Kumar V, Kalita J, Misra UK and Bora HK, 2015. A study of dose response and organ susceptibility of copper toxicity in a rat model. Journal of Trace Elements in Medicine and Biology: Organ of the Society for Minerals and Trace Elements, 29, 269–274. Available at: A_study_of_dose_response_and_organ_susce20160422-29333-1rhf473-with-cover-page-v2.pdf (d1wqtxts1xzle7.cloudfront.net)

Linder MC, 2020. Copper homeostasis in mammals, with emphasis on secretion and excretion. A review. 3179 International Journal of Molecular Sciences, 21. Available at: IJMS | Free Full-Text | Copper Homeostasis in Mammals, with Emphasis on Secretion and Excretion. A Review (mdpi.com)

Nordic Council of Ministers N, 2012. Nordic nutrition recommendations 2012. Integrating nutrition and physical activity. Copenhagen, Nordic Council of Ministers, 2014. Available at: Nordic Nutrition Recommendations 2012 (norden.org)

Olivares M, Pizarro F, Speisky H, Lönnerdal B and Uauy R, 1998. Copper in infant nutrition: safety of World Health Organization provisional guideline value for copper content of drinking water. Journal of Pediatric Gastroenterology and Nutrition, 26, 251–257. Available at: item_0031910923.pdf (uchile.cl)

Pizarro F, Olivares M, Uauy R, Contreras P, Rebelo A and Gidi V, 1999. Acute gastrointestinal effects of graded levels of copper in drinking water. Environmental Health Perspectives, 107, 117–121. 3311 Available at: Acute gastrointestinal effects of graded levels of copper in drinking water. (nih.gov)

Pratt WB, Omdahl JL and Sorenson JR, 1985. Lack of effects of copper gluconate supplementation. American Journal of Clinical Nutrition, 42, 681–682. Available at: Lack of effects of copper gluconate supplementation | The American Journal of Clinical Nutrition | Oxford Academic (oup.com)

Scientific Committee on Food (SCF), 2003. Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of copper. 10 pp. Available at: Opinion of the Scientific Committee on Food on the Tolerable Upper Intake Level of Copper (ernaehrungsdenkwerkstatt.de)

Turnlund JR, 1988. Copper nutriture, bioavailability, and the influence of dietary factors. Journal of the American Dietetic Association, 88, 303–308. Available at: Copper nutriture, bioavailability, and the influence of dietary factors | Elsevier

Enhanced Reader

Turnlund JR, 1989. Stable isotope studies of the effect of dietary copper on copper absorption and excretion. Advances in Experimental Medicine and Biology, 258, 21–28.

Turnlund JR, Michel MC, Keyes WR, Schutz Y and Margen S, 1982. Copper absorption in elderly men determined by using stable 65Cu. American Journal of Clinical Nutrition, 36, 587–591. Gf9254 (silverchair.com)

Turnlund JR, King JC, Gong B, Keyes WR and Michel MC, 1985. A stable isotope study of copper absorption in young men: effect of phytate and alpha-cellulose. American Journal of Clinical Nutrition, 42, 18–23. Available at: 18-with-cover-page-v2.pdf (d1wqtxts1xzle7.cloudfront.net)

Turnlund JR, Wada L, King JC, Keyes WR and Acord LL, 1988. Copper absorption in young men fed adequate and low zinc diets. Biological Trace Element Research, 17, 31–41. Available at: Copper absorption in young men fed adequate and low zinc diets - PubMed (nih.gov)

Turnlund JR, Keen CL and Smith RG, 1990. Copper status and urinary and salivary copper in young men at three levels of dietary copper. American Journal of Clinical Nutrition, 51, 658–664.

Turnlund JR, Keyes WR, Hudson CA, Betschart AA, Kretsch MJ and Sauberlich HE, 1991. A stable isotope study of zinc, copper, and iron absorption and retention by young women fed vitamin B-6 deficient diets. American Journal of Clinical Nutrition, 54, 1059–1064. Available at: A-stable-isotope-study-of-zinc-copper-and-iron-absorption-and-retention-by-young-women-fed-vitamin-B-6-deficient-diets.pdf (researchgate.net)

Turnlund JR, Keyes WR, Peiffer GL and Scott KC, 1998. Copper absorption, excretion, and retention by young men consuming low dietary copper determined by using the stable isotope 65Cu. American Journal of Clinical Nutrition, 67, 1219–1225. Available at: Gf9254 (silverchair.com)

Turnlund JR, Jacob RA, Keen CL, Strain JJ, Kelley DS, Domek JM, Keyes WR, Ensunsa JL, Lykkesfeldt J and Coulter J, 2004. Long-term high copper intake: effects on indexes of copper status, antioxidant status, and immune function in young men. American Journal of Clinical Nutrition, 79, 1037–1044. Available at: znu00604001037.pdf (silverchair.com)

Turnlund JR, Keyes WR, Kim SK and Domek JM, 2005. Long-term high copper intake: effects on copper absorption, retention, and homeostasis in men. American Journal of Clinical Nutrition, 81, 822–828. 822.pdf (silverchair.com)

VKM, 2017. Assessment of copper intake in relation to tolerable upper intake levels. Opinion of the Panel on Nutrition, Dietetic Products, Novel Food and Allergy of the Norwegian Scientific Committee for Food Safety. Available at: Assessment of copper intake in relation to tolerable upper intake levels (vkm.no)

WHO (World Health Organization), 1996. Trace elements in human nutrition and health. 360 pp. Available at: Trace elements in human nutrition and health (who.int)

Annex A

This Annex contains the EFSA Opinion on “Re-evaluation of the existing health-based guidance values for copper and exposure assessment from all sources”

This opinion can also be accessed at:

Public Consultation: (europa.eu)

Secretariat

July 2022