Opinion of the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety

Adopted 2 May 2007

Risk assessment of health hazards from nickel, cobalt, zinc, iron, copper and manganese migrated from ceramic articles

SUMMARY

The Norwegian Food Safety Authority (Mattilsynet) has asked the Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) to assess potential health hazards linked to the intake of the metals nickel (Ni), cobalt (Co), zinc (Zn), iron Fe), copper (Cu) and manganese (Mn) from ceramic articles. The case has been assessed by the Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics.

Based on the conclusions in a risk assessment of possible health hazards related to the migration of lead, cadmium and barium from ceramic articles adopted by VKM in 2004, the Norwegian Food Safety Authority has recently established a national regulation with stricter migration limits for lead and cadmium than what is used in the European legislation. A national migration limit for the migration of barium from ceramic articles was also set. No harmonised international migration limits are established for other metals being used in the glazing of ceramic articles, such as nickel, cobalt, zinc, iron, copper and manganese.

In this opinion, the VKM Panel has assessed health risks associated with the migration of nickel, cobalt, zinc, iron, cobber and manganese from ceramic articles. The risk assessment is based on the results of a survey conducted by the Norwegian Food Control Authority in Oslo in 2003 in which the migration of different metals from ceramic articles was investigated. A total of 648 ceramic items had been tested for migration of the above-mentioned metals.

Based on the median and highest migration values, corresponding intakes of the metals from ceramic articles were estimated. The estimated median and high intakes were compared with tolerable intakes based on evaluations made by different international scientific bodies, such as the Scientific Committee for Food (SCF), the World Health Organisation (WHO) and expert groups organised under the Nordic Council of Ministers (NNR) and also the UK Food Standards Agency (FSA). The intake calculations carried out were based on the assumption that a person consumes one litre of liquid from the same article each day, and included other

dietary sources. The estimated high intakes therefore indicate a "worst case" scenario for the leakage of metals from ceramic articles.

This risk assessment based on a survey of 648 hand-crafted ceramic articles produced by individual potters sold on the Norwegian market in 2003, shows that most of these ceramic articles are safe with respect to leakage of the metals in question (median values of leakage). However, the median estimated intake of nickel from ceramic articles is in the same order as the tolerable daily intake, and nickel intake from ceramics could be of concern for a sensitised subpopulation.

Relatively few of the tested ceramic articles (0.5-15%) leached metals above the detection limits. However, for some articles, high leakage might cause substantial exceedance of tolerable intakes.

The highest estimated intakes of zinc and copper from ceramic articles may cause acute gastrointestinal effects.

For nickel, and to some extent cobalt and manganese, more sensitive analytical methods should be employed due to low margins between estimated high intakes and tolerable intakes.

Given the findings of neurotoxicity in growing rats, and therefore a potentially higher susceptibility of infants and children, oral exposure to manganese beyond the level normally present in food and beverages could represent a risk of adverse health effects without evidence of any health benefit.

BACKGROUND

Migration of high levels of heavy metals from ceramic articles is an issue that could be related to acute poisoning in humans. Several incidents of lead poisoning caused by lead migration from ceramic articles have recently been reported in Norway and Sweden (Amundsen *et al*., 2002; SNFA, 2004a; 2004b). The reported cases of lead poisoning were associated with high levels of lead migration found in imported Greek ceramic articles, and the problem of heavy metal migration from ceramic articles seems to be predominantly linked to hand-crafted articles made by potters, and not to industrially manufactured products.

To ensure that ceramic articles under normal or foreseeable conditions of use do not transfer their constituents to food in quantities which could endanger human health, migration limits have been established for migration levels of lead and cadmium used in glazing pigments in the legislation (EU Council Directive, 1984; SNT 1993). No harmonised international migration limits are established for other metals being used in the glazing of ceramic articles, such as barium (Ba), nickel (Ni), cobalt (Co), zinc (Zn), iron (Fe), copper (Cu) and manganese (Mn). In 2004, the Panel on Food Additives, Flavourings, Processing Aids, Materials in contact with Food and Cosmetics of the Norwegian Scientific Committee for Food Safety (Vitenskapskomiteen for mattrygghet, VKM) adopted a risk assessment of possible health hazards related to the migration of lead, cadmium and barium from ceramic articles (VKM, 2004). Based on the conclusions in this risk assessment, the Norwegian Food Safety Authority (Mattilsynet) has recently established a national regulation with stricter migration limits for lead (Pb) and cadmium (Cd) than what is used in the European legislation (SNT, 1993, last revised on 20 July 2005). A national migration limit for the migration of

barium from ceramic articles has also been established (SNT, 1993, last revised on 20 July 2005).

The metals Ni, Co, Zn, Fe, Cu and Mn are all used in pigments to colour the glaze used for ceramic articles in order to make the products more visually attractive. The metals can also have a functional role. For instance, green copper pigments used in combination with a glaze based on lead have been reported to result in a higher acidic solubility of the glaze. As mentioned above, no harmonised migration limits are established for these metals. However, in the Netherlands, migration limits have been set for nickel (1 mg/kg foodstuff), cobalt (0.1 mg/kg foodstuff) and manganese (3 mg/kg foodstuff) in glass and so-called glass ceramics. These kinds of products do not conform to the usual definition of ceramic articles and there is no European legislation for such products. The migration levels found and reported in a national survey conducted by the Norwegian Food Control Authority (Statens næringsmiddeltilsyn)[1] in 2003 (SNT, 2003) have in this opinion been used to assess if the detected levels of the migration of Ni, Co, Zn, Fe, Cu and Mn from ceramic articles could represent any health hazards for the consumer.

TERMS OF REFERENCE

The Norwegian Food Safety Authority has in a letter of 19 May 2005 asked the Norwegian Scientific Committee for Food Safety (VKM) to assess potential health hazards linked to the intake of nickel, cobalt, zinc, iron, copper and manganese from ceramic articles.

With reference to the VKM opinion on lead, cadmium and barium migrating from ceramic articles adopted on 19 October 2004, the Norwegian Food Safety Authority also wants an assessment of the tolerable daily intake levels for other metals that can migrate from ceramic articles. The risk assessment should be based on the results of a survey conducted by the Norwegian Food Control Authority (in Oslo) in 2003, which investigated the migration of different metals from ceramic articles.

The exposure levels from ceramic articles are requested to be examined in context with other known sources of intake of the above-mentioned metals. The risk assessment will be used as a basis for establishing migration limits for heavy metals from ceramic articles when the EU Commission considers amendments to the Council Directive relating to ceramic articles intended to come into contact with foodstuffs (EU Council Directive 84/500/EEC of 15 October 1984).

The Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics is requested to answer the following questions in this opinion:

- *What is the daily median and high intake of nickel, cobalt, iron, zinc, copper and manganese estimated from migration values reported in the surveillance survey conducted by the Norwegian Food Control Authority in Oslo in 2003*?
- *What are the health hazards associated with nickel, cobalt, iron, zinc, copper and manganese and the tolerable daily intakes for the respective metals?*

[1] The Norwegian Food Control Authority (Statens næringsmiddeltilsyn) became a part of and changed name to the Norwegian Food Safety Authority (Mattilsynet) on the 1st January 2004.

- *What are the chances, considering exposure from ceramic articles and other dietary sources, of exceeding the TDI or UL for nickel, cobalt, iron, zinc, copper and manganese, and what are the potential health risks if this occurs?*

OPINION

INTRODUCTION

Sampling

In 2003, the local Food Control Authority in Oslo conducted a survey on the migration of metals from ceramic articles commissioned by the Norwegian Food Control Authority (SNT, 2003). The survey consisted of 648 individual ceramic articles intended to come into direct contact with foodstuffs. Of these, 631 were hollow products, and 17 were flatware (less than 25 mm deep). Both the 631 hollow products and the 17 flatware products were tested for migration of Ni, Co, Zn, Fe, Cu and Mn. However, the migration levels from the 17 flatware products were negligible and are therefore not included in the exposure calculations in this opinion. The majority of the articles in the survey was hand-crafted by Norwegian potters and not manufactured industrially.

In 2005, the Norwegian Food Safety Authority carried out a new surveillance project to investigate if the recently introduced national regulations for the migration of lead, cadmium and barium from ceramic articles were respected (SNT, 1993, last revised on 20 July 2005). The survey was this time limited to industrially manufactured ceramic and porcelain articles imported and sold on the Norwegian market. A total of 106 products (98 hollow products and 8 flatware products) were analysed for the migration of the metals Pb, Cd, Ba, Ni, Co, Zn and Cu (Mattilsynet, 2005). The migration levels reported in this survey were lower than those reported in the survey from 2003 (SNT, 2003) and are therefore not included in the exposure calculations in this opinion.

Migration test

A standard method compliant with the EEC Council Directive of 15 October 1984 laying down basic rules for determining the migration of lead and cadmium (EU, 1984; SNT, 1993) was used for determining the levels of metal migration. In this migration test, the object is first washed, thereafter the surface is exposed to 4% acetic acid at room temperature for a period of 24 hours. Hollow objects are filled with acetic acid, the same are flatware, but the volume of liquid must be noted and the effective area exposed calculated. The amount of metal, which is leaked by hollow objects, is calculated per litre, whereas migration from flatware and rims are calculated in mg soluble metal per dm^2. The detection limits from hollow products were 0.3 mg/l for Ni, Co, Zn, Fe, Cu and Mn in the survey. For flatware, the detection limits vary somewhat according to the shape and size of the object (SNT, 2003).

The migration test's relevance to the exposure estimates

In the Norwegian Food Safety Authority's document "Migration of lead and cadmium from ceramics – note for discussion of safety and regulatory limits" (Brede and Fjeldal, 2004), the relevance of the migration test used in the survey for determining migration of metals to foodstuffs and beverages is discussed. Migration is a function of time, since a short exposure period, e.g. one hour, gives significantly lower levels of migration than exposure for longer time periods, e.g. 24 hours. In many cases, beverages would not be in contact with ceramic articles for as long as 24 hours. On the other hand, the contact period could be significantly

longer, for example, for jars used for storage of jam and juice, which could entail significantly higher levels of migration. Liquids could in some cases have a significantly higher temperature, which could also increase migration (2-10 times). In so far as using 4% acetic acid as a test simulant, this confers comparable migration as when using citric acid and lactic acid, and ought therefore to be deemed realistic. Repeated exposures could well lead to lower levels of migration, although this needs not to be the case. The standard test is thus not representative of a "worst case" scenario. In some cases, migration will be overestimated and in others underestimated.

A collaboration project between the Norwegian Food Safety Authority and the Swedish National Food Administration (Livsmedelsverket) to further evaluate the relevance of the standard method for the determination of migration of heavy metals from ceramics is currently taking place. This project will investigate how time, temperature and repeated consumption will influence the migration of lead from ceramic articles under realistic circumstances of exposure. A report from the project will be published during the first part of 2007.

RISK ASSESSMENT

The risk assessment for the metals nickel, zinc, iron, copper and manganese in this evaluation are based on opinions from the Scientific Committee for Food (SCF) or the European Food Safety Authority (EFSA) related to the tolerable upper intake levels (UL), and on the World Health Organisation (WHO) Guidelines for Drinking-water Quality. The UL established in the Nordic Nutrition Recommendations (NNR, 2004) is used in the risk assessment of iron. As neither SCF, EFSA nor WHO have given an opinion on the metal cobalt, the VKM panel has based the risk assessment of this metal on the review by the Expert group on vitamins and minerals of the Food Standards Agency (FSA, 2003).

SCF has defined the tolerable upper intake level (UL) as the maximum level of total chronic daily intake of a nutrient (from all sources) judged to be unlikely to pose a risk of adverse health effects to humans. "Tolerable intake" in this context connotes what is physiologically tolerable and is a scientific judgement as determined by assessment of risk, i.e. the probability of an adverse effect occurring at some specified level of exposure. ULs may be derived for various life stage groups in the population.

It is further stated by SCF that the UL is not a recommended level of intake, but an estimate of the highest level of intake which carries no appreciable risk of adverse health effects. To establish whether an exposed population is at risk requires a risk assessment to determine what is the fraction (if any) of the population whose intake exceeds the UL, and the magnitude and duration of the excessive intake (SCF, 2000a).

The tolerable upper intake level for nutrients is comparable to the term tolerable daily intake (TDI), which is used in risk assessments of contaminants in the food chain.

UNCERTAINTIES IN THE EXPOSURE DATA

Sampling/analysis

The samples were selected randomly from more than 100 potters located in all parts of Norway. Therefore, the selection of samples is assumed to be representative of the potential levels of heavy metals present in ceramic articles made by Norwegian artists and potters, although only random samples were taken and only one analysis was performed of each object. Uncertainty always remains as to how representative an analysis of a selection of hand-crafted individual articles can actually be (for example, the quantity of heavy metals in an article is expected to vary between bakings). The articles included in this survey, however, have been analysed using a standard method compliant with the EEC Council Directive of 15 October 1984 laying down basic rules for determining the migration of lead and cadmium (EU, 1984; SNT, 1993), and the analyses were performed at a laboratory with experience within these kinds of analyses going back to the 1980s.

Exposure assessment

In the exposure calculations, the VKM panel has assumed that a person is drinking one litre of liquid from the same article each day. In making such an assumption, some uncertainty is attached to the exposure estimates in the risk assessment. For example, some individuals could drink quantities of liquid even much higher than 1 l/day from the same object. The estimated intakes in this opinion provide a certain level of insight as to what a "worst-case" scenario for metal migration from these kinds of products can entail in terms of exposure.

The exposure calculations are based on the median migration levels of all samples where the metal in question was detected. It should be noted that the "worst-case" scenarios in this risk assessment are based solely on the highest migration value from ceramic articles reported for each metal.

There are some differences between the analytical values given in the text of the survey report (SNT, 2003) and the values given in the annexes of the report, with some migration values in the annexes being even much higher than those reported in the main text. However, the Norwegian Food Safety Authority has informed the VKM Panel that many of the products mentioned in the annexes of the report should not have been included in the survey. These products were faulty items due to errors in the baking process and were clearly not intended for sale to consumers. Thus, some of the migration values reported in the annexes are not included in this risk assessment.

NICKEL (Ni)

HAZARD IDENTIFICATION AND CHARACTERISATION OF NICKEL

Nickel occurs naturally in soil, water, plants and animals, and usually exists in the oxidation state of Ni^{2+}. It has not been shown to be essential for humans. The rate of absorption of nickel salts can be quite high in the fasting state, but is reduced significantly in the presence of food, such as milk, coffee, tea and orange juice (Solomons *et al.*, 1982). Absorbed nickel is mainly excreted in the urine, but to a minor extent also in bile and sweat. It is secreted into human milk (Heseker, 2000).

The acute oral toxicity of nickel compounds depends on their solubility. LD_{50} values for soluble nickel in rats were 42-129 mg Ni/kg body weight (bw) (ECETOC, 1989). Studies on subchronic toxicity in experimental animals have shown that the main targets for the toxicity of orally ingested nickel salts are kidneys, spleen, lungs and the myeloid system (ABC, 1988, Dieter *et al.*, 1988). Severe lesions in germ cells, particularly in spermatogenesis, have been observed in rats administered by gavage 25 mg nickel sulphate/kg bw/day over 120 days (Waltschewa *et al.*, 1972). In addition, perinatal mortality has been reported to increase in rats, even at the lowest administered dose of 1.3 mg Ni/kg bw/day (Smith *et al.*, 1993).

Twenty of 32 industrial workers, who accidentally drank water contaminated with nickel sulphate and nickel chloride, developed symptoms such as nausea, vomiting, diarrhoea, giddiness, lassitude, headache, cough and shortness of breath. The nickel doses that caused these symptoms were estimated to be in the range of 7-35 mg/kg bw (Sunderman *et al.*, 1988).

Contact allergy to nickel in humans is very common and is frequently associated with recurrent or chronic hand eczema. Individuals sensitised to nickel through dermal contact and who have allergic contact dermatitis could develop hand eczema from oral, as well as dermal, exposure to nickel salts. Oral intakes as low as 8 and 12 µg/kg bw/day have been reported to aggravate hand eczema in nickel sensitised subjects (Nielsen *et al.*, 1999; EFSA, 2005).

Allergic contact dermatitis arises from direct contact between the skin and the sensitiser and also from exposure via the respiratory route and the gastrointestinal tract (Hindsén *et al.*, 2001). Hindsén *et al.* (2001) found that eczematous recall reaction after oral nickel challenge to persons allergic to nickel was closely related to the dose, but also to the time since previous dermatitis had occurred. A meta-analysis on former nickel exposure investigations identified 17 relevant studies which were analysed statistically (Jensen *et al.*, 2006). Of these studies, 9 were included in a final dose-response analysis. The results show that 1% and 50% of these individuals may react with dermatitis at a daily oral nickel exposure of 220-350 µg Ni (equivalent to 3-5 µg Ni/kg bw), and 1270-2000 µg Ni (equivalent to 8-30 µg Ni/kg bw), respectively (Jensen *et al.*, 2006). Results from these studies show that the response to oral exposure to nickel may be dose-dependent. Exposure to increasing levels of nickel in food and drink may therefore lead to an increasing number of nickel-sensitive subjects reacting with dermatitis.

There is clear evidence for *in vitro* genotoxicity of nickel salts generally seen in studies on chromosomal effects. *In vivo*, soluble nickel salts resulted in induction of chromosomal aberrations and gave positive results in the Comet assay. Both positive and negative results were observed in the micronucleus assay for nickel chloride and nickel sulphate after intraperitoneal and oral administration (EU, 2005a,b,c,d,e).

Nickel sulphate, nickel chloride, nickel carbonate and nickel nitrate are classified as Mut3 with the risk phrase: R68 “Possible risk of irreversible effect” (EC, 2007a; ENIA, 2007)

The genotoxicity of soluble nickel salts, observed at chromosome level at high toxic doses is likely due to indirect mechanisms (EFSA, 2005).

Inhalation is an important route of exposure to nickel and its salts in relation to health risks. IARC concluded that nickel compounds are carcinogenic to humans (Group 1), whereas metallic nickel is possibly carcinogenic to humans (Group 2B) (IARC, 1990). Several nickel salts including nickel sulphate, nickel chloride, nickel nitrate and nickel carbonate are

considered as human carcinogens by inhalation and are proposed to be included in the 31st Adaptations to Technical Progress (ATP) by the European Commission (Classification: Carc. Cat.1, with the risk phrase R49 "May cause cancer by inhalation"). There is a lack of evidence of a carcinogenic risk from oral exposure to nickel compounds (EC, 2007a).

European Food Safety Autority (2005)
The EFSA Scientific Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) adopted an opinion related to the tolerable upper intake level of nickel in 2005 (EFSA, 2005). The NDA Panel concluded that it was not possible to establish a no observed adverse effect level (NOAEL) from the available studies and in the absence of adequate dose-response data for the relevant effects, EFSA did not find it possible to establish an UL (EFSA, 2005).

WHO Guidelines for Drinking-water Quality (2005)
In a background document for development of WHO Guidelines for Drinking-water Quality, a guideline value for nickel in drinking-water was established based on a NOAEL of 2.2 mg Ni/kg bw/day from a well conducted two-generation study in rats (WHO, 2005, SLI, 2000). The application of an uncertainty factor of 100 then gave a TDI of 22 µg/kg bw (WHO, 2005). However, according to a detailed discussion of this two-generation study in rats (SLI, 2000) in the Draft Risk Assessment Report of nickel sulphate prepared by the Danish Environmental Protection Agency for the European Union, the dose level of 2.2 mg Ni/kg bw/day could not be regarded as a clear NOAEL (EU, 2005b) since an increased postimplantation/perinatal lethality in the F1 generation was observed at this dose. The NOAEL for developmental toxicity was therefore set to 1.1 mg/Ni/kg bw/day (EU, 2005b).

It should be noted that the WHO background document and summary statement at present are being revised until 30 May 2007 (WHO homepage: http://www.who.int/water_sanitation_health/dwq/chemicals/nickel/en/). In the draft document available for review, WHO has now changed the NOAEL from 2.2 mg Ni/kg bw/day to 1.1 mg Ni/kg bw/day and derived a TDI of 11 µg/kg bw by applying an uncertainty factor of 100 (WHO, 2007).This value is therefore taken forward to the risk characterisation.

It should also be noted that the study from Springborn Laboratories Inc. (SLI, 2000) probably was not available for the EFSA opinion on UL for nickel from 2005 as it was especially prepared for the Nickel Producers Environmental Research Association.

Nickel sensitised individuals, for which a sufficiently high oral challenge could elicit an eczematous reaction, have also been discussed in the background document from WHO (WHO, 2005; 2007). It is referred to a lowest observed adverse effect level (LOAEL) of 12 µg/kg bw after provocation of fasted patients with an empty stomach (Nielsen *et al*., 1999). Since this LOAEL was based on a highly sensitive human population, WHO considered it not necessary to include an uncertainty factor when deriving a guideline value for drinking-water (WHO, 2005; 2007).

EXPOSURE CHARACTERISATION OF NICKEL

Exposure from ceramic articles
In the survey from the Norwegian Food Control Authority in 2003, all the 631 hollow products were analysed for nickel content. Nickel was measured in concentrations above the detection limit (>0.3 mg/l) in 3 products (0.5%). The highest nickel migration value found

was 0.9 mg/l and the median quantity of nickel in all samples where it was detected was 0.8 mg/l.

It is assumed an intake from ceramic articles of 1 l/day. The estimated daily intake from ceramic articles releasing the highest level of nickel would amount to 0.9 mg or 13 µg/kg bw for a person weighing 70 kg. The reported median migration level of 0.8 mg/l would give an estimated daily intake of 0.8 mg or about 11 µg/kg bw.

Exposure from other sources

Food

Food is the dominant source of nickel exposure in the non-smoking, non-occupationally exposed population. Generally nickel is found in low concentrations in foods, however, leaching of nickel into food from kitchen utensils may contribute significantly to oral intake (Jorhem *et al.*, 1998). Daily intake of nickel from food varies widely, according to different dietary habits. It can range from 100-800 µg/day, but the mean dietary nickel intake in most countries is 100-300 µg/day (IPCS, 1991). A Swedish market basket survey from1987 showed a content of 80 µg Ni/person per day from food, with tea, coffee and alcoholic beverages providing an additional 10-20 µg/person per day (Becker and Kumpulainen, 1991). According to the UK Total Diet Study, the population dietary exposures to nickel have decreased from 330 µg/day in 1976 to 130 µg/day in 1997 (MAFF, 1997). In an Italian study on commercial beverages it was found that release of nickel from black tea was between 1500-3700 µg/l, from coffee 100-300 µg/l, and from red wine about 56-105 µg/l (Dugo *et al.*, 2004).

EFSA estimated the intake of nickel from the average diet to be about 150 µg/day (about 2.5 µg/kg bw/day for a person weighing 60 kg), but it may reach 900 µg/day (about 15 µg/kg bw/day) or more when large amounts of food items with high nickel contents are consumed. In addition, first-run drinking water, which may contain up to 1000 µg/l, and leaching from kitchen utensils into food, may also contribute to nickel intake (EFSA 2005).

Drinking water

Water generally contributes with an amount of 5–25 µg daily (i.e. 2–11% of the total daily oral intake of nickel) (MAFF, 1985). These figures are similar to those presented in the European risk assessment for nickel (EU, 2005b). However, no account is taken of exposure from nickel-plated heating elements and other similar sources; for some individuals, therefore, there may be higher intakes that will fluctuate significantly with time (WHO, 2005). Overall, drinking water appears to contribute only a minor proportion of the daily intake, although exposure of some communities may be significant in specific circumstances where nickel levels in groundwater are unusually high (WHO, 2005).

Other sources

Daily skin contact with nickel-plated objects or nickel-containing alloys (e.g. jewellery, coins, clips) is an important factor in the induction and maintenance of contact hypersensitivity.

RISK CHARACTERISATION OF NICKEL EXPOSURE FROM CERAMIC ARTICLES

The estimated daily intake from ceramic articles releasing the highest level of nickel was calculated to be 0.9 mg or 13 µg/kg bw for a person weighing 70 kg. Compared with a TDI of

11 µg/kg bw (WHO, 2007; EU, 2005b), both the highest (13 µg/kg bw) and the median (11 µg/kg bw) estimated intake of nickel from ceramic articles would be in the same region as the TDI. The estimated daily intakes were also in the same region as the LOAEL of 12 µg/kg bw for individuals sensitised to nickel (WHO, 2005; Nielsen *et al*., 1999). According to the meta-analysis by Jensen (2006) up to 50% of nickel sensitised individuals could react to this dose.

Table 1. *The estimated highest and median intake of nickel by an adult (bw = 70 kg) drinking one litre of liquid from a ceramic article every day. The ratio between high or median intakes and the reference value is specified.*

Metal Nickel (Ni)	Reference value	Highest estimated intake value	Ratio	Median estimated intake value	Ratio
General population	TDI[1] = 11 µg/kg bw	0.9 mg or 13 µg/kg bw	1.2	0.8 mg or 11 µg/kg bw	1.0

[1]From WHO (2007) and EU (2005b).

Nickel was only detected in 3 out of the 631 analysed ceramic articles in the survey. Therefore, it is highly likely that the migration of nickel from most ceramics articles is below the detection limit of 0.3 mg/l. However, the limit of quantification corresponds to an intake, which is 34% of TDI. Therefore, analytical values below the quantification limit would have been of interest. It should also be noted that the highest intake value and the median intake value is almost the same, as the median is calculated from only 3 samples.

Both the highest and the median estimated intakes of nickel from the 3 samples could result in intake levels in the same order of magnitude as the TDI. The daily estimated intakes were also in the same region as the lowest effect level for individuals sensitised to nickel, and could therefore cause a reaction in some individuals, as no uncertainty factor for eczematous effects is applied.

The population's dietary exposure levels to nickel are difficult to assess due to exposure from multiple sources. The intake of nickel from the average diet is according to EFSA between 150 and 900 µg/person/day (equivalent to 2.5-15 µg/kg bw/day for a person weighing 60 kg). In addition, first-run drinking water, which may contain up to 1000 µg/l, and leaching from kitchen utensils into food, may also contribute to nickel intake (EFSA 2005). Some sources, e.g. tea and herbs can contribute considerably to the TDI. A "worst case" intake from tea or herbs, assuming that a person drinks 2 cups (one standard American cup of coffee is 180 ml) of tea or herbs per day can contribute about 1300 µg (3700 µg Ni/l). Also other food sources, e.g. chocolate, wine, beer and coffee, will contribute to the intake. The total "worst case" intake from all sources is calculated to be about 2500 µg/person per day, i.e. about 35 µg/kg bw/day. The contribution from ceramic articles (13 µg/kg bw/day) could amount to approximately 36% of the total intake.

The response to oral exposure to nickel may be dose-dependent in nickel-sensitised subjects. Exposure to increasing levels of nickel in food and drink may therefore lead to increasing number of reacting nickel-sensitive subjects. Exposure to nickel levels, e.g. from drinks kept in ceramic releasing about 200-900 µg Ni/l, may thus cause a relapse of contact dermatitis and probably also widespread chronic allergic skin reactions.

Comment

The VKM Panel is of the opinion that for nickel a more sensitive analytical method should be employed. The migration of nickel from ceramic articles should be as low as possible. It is

advised that individuals sensitised to nickel should take care and try to avoid consumption of foods and drinks with high nickel content. For this part of the population an additional contribution of nickel migrating from ceramic articles is undesirable and should be avoided. However, it is noted that only a few items leached nickel in amounts above the detection limit.

COBALT (Co)

HAZARD IDENTIFICATION AND CHARACTERISATION OF COBALT

The metal cobalt has not been evaluated by SCF or EFSA in order to establish a tolerable upper intake level. Only the cobalt containing vitamin B_{12} (cobalamins) was evaluated by SCF. Neither has cobalt been assessed in relation to the WHO Guidelines for Drinking-water. The VKM panel has therefore based the hazard identification and characterisation of cobalt on a review by the Expert group on vitamins and minerals of the Food Standards Agency (FSA, 2003).

Cobalt is a transition metal that exists in oxidation states Co^{+2} and Co^{+3}. It is an essential trace element, being an integral part of vitamin B_{12}, which is essential for folate and fatty acid metabolism. The extent of gastrointestinal absorption of cobalt depends upon the dose, with very low doses being almost completely absorbed, whereas larger doses are less well absorbed. Nutritional factors could also influence the absorption. The liver, where vitamin B_{12} is stored, contains the highest concentration of cobalt in the human body. Cobalt is mainly excreted in urine, but also in faeces. Most cobalt is eliminated rapidly independent of the exposure route, with a small proportion being eliminated slowly and having a half-life in the order of years (FSA, 2003).

Cobalt is known to have adverse effects on the heart in both animals and man. Cardiomyopathy was reported in heavy beer drinkers in the 1960s as a result of the use of cobalt chloride as a foam stabiliser, providing a cobalt intake of 6.8 mg/day. Ethanol and cobalt have an additive effect, reducing blood flow to the heart and thus causing anoxia and damage to the heart muscle. The combined effect of alcohol and cobalt, and possibly protein deficiency, was probably necessary to cause this condition. Cobalt chloride is no longer used for this purpose. Few other data on human toxicity are available where exposure is by ingestion. Case reports have suggested that acute intakes following ingestion of > 30 mg Co/day may cause gastrointestinal upset, skin rashes and hot flushes in man. In patients receiving cobalt intakes of 0.17-0.39 mg/kg for 6 days to eight months, usually for the treatment of anemia, a 20-90% depression of iodine uptake has been shown, resulting in goitres and classic signs of hyperthyroidism (Carson *et al.*, 1986).

An evaluation of the recent scientific evidence on genotoxicity of cobalt compounds (reviewed by Lison *et al*., 2001) indicates that a clear distinction between different cobalt compounds and mechanism of action is required for evaluation of genotoxic activity. Different *in vitro* and *in vivo* studies indicate that cobalt compounds exert their genotoxic potential by two different mechanism of action: DNA breakage induced by cobalt metal and especially hard metal particles by a Fenton like reaction (generation of oxygen radicals), and inhibition of DNA repair by cobalt(II) ions.

- There is clear evidence that soluble cobalt(II) cations have genotoxic activity *in vitro* and *in vivo* in experimental systems. Human evidence is lacking.
- There is some evidence of a genotoxic potential of cobalt metal in human lymphocytes *in vitro*.
- There is evidence that hard metal particles exert a genotoxic (and carcinogenic) activity both *in vitro* and in humans (after exposure by inhalation).
- There is insufficient information on cobalt oxide and other compounds.

IARC concluded that there was inadequate evidence for the carcinogenicity of cobalt and cobalt compounds in humans. Overall, taking into account the available human and animal data, IARC classified cobalt and cobalt compounds as possibly carcinogenic to humans (Group 2B). However, it should be noted that none of the data considered would appear to be from exposure to cobalt by ingestion (IARC, 1991).

The European Chemicals Bureau (ECB) has classified cobalt sulphate and cobalt dichloride with the risk phrase R49 "May cause cancer by inhalation") (EC, 2007b).

Expert group on vitamins and minerals of the Food Standards Agency (2003)
Overall, the Expert Group on Vitamins and Minerals of the UK Food Standards Agency concluded that there are insufficient data to set a Safe Upper Level (equivalent to UL) for cobalt. However, a guidance level was established based on a study in laboratory animals where cobalt has been associated with adverse effects on spermatogenesis and, ultimately, fertility (Pedigo *et al.*, 1988). Doses of 23 mg Co/kg bw/day caused minor testicular effects, the severity of the effect then increased in a dose-related manner. This is the lowest dose at which toxic effects have been observed in animals (LOAEL). There are no data available to establish whether the effects on spermatogenesis and fertility also occur in humans exposed to cobalt, but the UK Expert Group on Vitamins and Minerals considers that it would be prudent to assume that they do. By applying the conventional uncertainty factors (10 for LOAEL to NOAEL extrapolation x 10 for inter-species variation x 10 for inter-individual variation = 1000) for guidance purposes only, the UK Expert Group on Vitamins and Minerals is of the opinion that an intake of 0.023 mg/kg bw/day total cobalt would not be expected to result in any adverse effects. This guidance value of 0.023 mg/kg bw/day is equivalent to 1.6 mg/day in a 70 kg adult (FSA, 2003).

EXPOSURE CHARACTERISATION OF COBALT

Exposure from ceramic articles
In the survey from the Norwegian Food Control Authority in 2003, all the 631 hollow products were analysed for cobalt content. Cobalt was measured in concentrations above the detection limit (>0.3 mg/l) in 36 of the products (6%). The highest concentration measured was 20 mg/l. The median quantity of cobalt in samples above the detection limit was 0.75 mg/l.

It is assumed an intake from ceramic articles of 1 l/day. The estimated daily intake from ceramic articles releasing the highest level of cobalt would amount to 20 mg or 0.29 mg/kg bw for a person weighing 70 kg. The reported median migration level of 0.75 mg/l would give an estimated daily intake of 0.011 mg/kg bw.

Exposure from other sources

Food

The main potential source of cobalt exposure for the general population is food. Most of the cobalt that is ingested is inorganic. Vitamin $B_{12,}$ an organic cobalt complex, occurs in foods of animal origin but represents only a small fraction of cobalt intake. High concentrations of cobalt are found in fish, nuts, green leafy vegetables and fresh cereals (WHO, 2006). According to The Total Diet Study (FSA, 2003/MAFF, 1997), the average intake of cobalt in the UK population in 1994 was 0.012 mg/day. The 97.5^{th} percentile cobalt intake was estimated to 0.019 mg/day. The dietary intake of cobalt in Norway and Sweden has been reported to be in the range of 0.006-0.007 mg/day (Bibow and Salbu, 1986; Jorhem *et al.*, 1998).

Drinking water

IARC has estimated the exposure of cobalt from drinking water. Based on a range in water from 0.001-0.01 mg/l and a consumption of 2 l/day, the exposure was estimated to be up to 0.02 mg/day (IARC, 1991).

RISK CHARACTERISATION OF COBALT EXPOSURE FROM CERAMIC ARTICLES

The estimated daily intake from ceramic articles releasing the highest quantity of cobalt was calculated to be 20 mg or 0.29 mg/kg bw, for a person weighing 70 kg. The estimated intake is approximately 13 times above the level of 0.023 mg/kg bw/day considered to be safe by the UK Expert Group on Vitamins and Minerals. The estimated daily intake from ceramic articles releasing a median migration level of cobalt was calculated to be 0.75 mg or 0.011 mg/kg bw. This is about 50% of the guidance level.

Table 2. *The estimated highest and median intake of cobalt by an adult (bw = 70 kg) drinking one litre of liquid from a ceramic article every day. The ratio between high or median intakes and the reference value is specified.*

Metal	Reference value	Highest estimated intake value	Ratio	Median estimated intake value	Ratio
Cobalt (Co)	Guidance value[1] = 1.6 mg/day or 0.023 mg/kg bw/day	20 mg or 0.29 mg/kg bw	12.6	0.75 mg or 0.011 mg/kg bw	0.5

[1]Based on 70 kg bw and not 60 kg as in FSA (2003).

Cobalt was detected in about 6% of the samples analysed in the survey. The estimated median intake of cobalt was well below the highest estimated intake. This indicates that consumption of liquid from the majority of ceramic articles leaching cobalt will result in intakes of cobalt well below the guidance value of 1.6 mg/day.

Consumption of liquid from ceramic items leaching as much as 20 mg/l could result in an intake of cobalt which is 13 times the guidance value. Such a high intake over a prolonged time period would represent an erosion of the safety margin for cobalt exposure, and adverse effects cannot be completely excluded.

The maximum intake of cobalt from other sources, such as food and drinking water, has been estimated to 0.039 mg/day (0.019 + 0.02) by the Expert Group on Vitamins and Minerals of the UK Food Standards Agency (FSA, 2003). No potential high intake groups were identified. The dietary intake of cobalt in Norway and Sweden has been reported to be somewhat lower than in the UK population and in the range of 0.006-0.007 mg/day (Bibow and Salbu, 1986; Jorhem *et al.*, 1998). The intake from other sources in addition to the intake coming from ceramic articles is thus negligible in comparison with the guidance level of 1.6 mg/day.

ZINC (Zn)

HAZARD IDENTIFICATION AND CHARACTERISATION OF ZINC

Zinc is an essential element in the nutrition of mammals. In biological systems, zinc exists in the oxidation state Zn^{2+} and is present in all tissues and fluids in the body. It has been identified as an integral part of numerous enzyme systems.

The absorption of ingested zinc is highly variable (10-90%), and a number of dietary factors have been found to interfere with the absorption of zinc both in experimental animals and humans. There exist homeostatic mechanisms for the gastrointestinal absorption and excretion of zinc. High zinc concentrations are found in prostate, bone, muscle and liver. The excretion takes place mainly via the gastrointestinal tract, and to a smaller extent via urine and sweat. The biological half-life of zinc in humans is in the order of 1 year (Elinder, 1986).

Studies in laboratory animals have demonstrated that elevated levels of dietary zinc can have a negative effect upon copper balance and, in part, could be related to the induction of microcytic, hypochromic anemia in rats after ingestion of large amounts of zinc (references cited in SCF, 2003a). Other studies in rats have shown that high levels of zinc supplementation (0.5-2 g/kg bw) can affect iron storage and homeostasis, which could cause anaemia as a result of higher iron turnover (Walsh *et al.*, 1994). The activities of several important enzymes in various tissues could also be reduced by exposure to high levels of dietary zinc. These effects may also occur at lower levels of zinc exposure when the diet is deficient in copper. Generally, zinc is not teratogenic or causes adverse effects on the reproductive performance in laboratory animals. However, very high concentrations of 1 g/kg bw given female rats during pregnancy caused a significant reduction in foetal growth, birth weight and still births (references cited in SCF, 2003a).

Zinc is not stored in the body, and excess intakes result in reduced absorption and increased excretion. Most reports on toxic effects of zinc in humans relate to acute effects such as nausea, vomiting, epigastric pain, abdominal cramps and diarrhoea, and are usually associated with the ingestion of acid drinks or food that have been stored in galvanized vessels. In humans, the most prominent effects of acute zinc toxicity are gastrointestinal disturbances. The emetic dose of zinc has been estimated to correspond to 225-450 mg (Fosmire, 1990). These effects are due to acute irritation in the gastrointestinal tract.

Chronic zinc toxicity is associated with symptoms of copper deficiency. Adverse effects, such as anaemia, neutropaenia and impaired immune response, are evident only after intake of zinc in the form of dietary supplements in excess of 150 mg/day for long periods (SCF, 2003a).

Studies on copper balance and status indicate that the NOAEL for zinc is around 50 mg/day (Davis *et al.*, 2000; Milne *et al.*, 2001; SCF, 2003a).

No adequate experimental studies are available to evaluate the carcinogenic potential of zinc (IPCS, 2001).

WHO Guidelines for Drinking-water Quality (2003)
No health-based guideline value has been proposed by WHO for zinc in drinking water (WHO, 2003a).

Scientific Committee on Food (2003)
SCF expressed an opinion on the UL of zinc in 2003. A NOAEL of 50 mg/day based on the absence of any adverse effects on a wide range of relevant indicators of copper status (as the critical point) was used in their derivation of an UL. They established an UL for adults, including pregnant and lactating women, of 25 mg Zn/day by applying an uncertainty factor of 2 to the NOAEL of 50 mg/day (SCF 2003a).

EXPOSURE CHARACTERISATION OF ZINC

Exposure from ceramic articles
In the survey from the Norwegian Food Control Authority in 2003, all the 631 hollow products were analysed for zinc content. Quantifiable amounts of zinc (> 0.3 mg/l) were found in 87 of the articles (14%). The highest quantity measured was 316 mg/l. The median concentration of zinc in samples above the detection limit was 1.9 mg/l.

It is assumed an intake from ceramic articles of 1 l/day. The estimated daily intake from ceramic articles releasing the highest level of zinc would amount to 316 mg or 4.51 mg/kg bw for a person weighing 70 kg. The reported median migration level of 1.9 mg/l would give an estimated daily intake of 1.9 mg or 0.027 mg/kg bw.

Exposure from other sources

Food
Good sources of zinc are meat, milk and milk products and wholegrain cereals. Foods with a high content of fat and sugar have a low content of zinc (NNR, 2004).

An overview over mean and 97.5th percentile zinc intake (mg/day) from food and supplements in different European countries is shown in the SCF opinion from 2003. The mean intakes ranged from 7.5 mg/day (Irish women) to 12.1 mg/day (German men). Among the high consumers, UK women had the lowest intake at 13.6 mg/day, with Irish men having the highest intake at 23.5 mg/day (SCF, 2003a).

Drinking water
Drinking water seldom contains zinc at concentrations above 0.1 mg/l. However, levels in tap water can be considerably higher because of corrosion of pipings and fittings, and also as a result of use of old galvanized plumbing materials. Under such circumstances, tap water can provide up to 10% of the daily intake. No health-based guideline value has been proposed by WHO for zinc in drinking water. However, drinking water containing zinc at levels above 3

mg/l tends to be opalescent, develops a greasy film when boiled, and has an undesirable astringent taste (WHO, 2003a).

RISK CHARACTERISATION OF ZINC EXPOSURE FROM CERAMIC ARTICLES

The estimated daily intake from ceramic articles releasing the highest level of zinc was calculated to be 316 mg or 4.51 mg/kg bw for a person weighing 70 kg. Based on the UL for adults of 25 mg/day recommended by SCF, the estimated intake of zinc from ceramic articles would be approximately 13 times above. The estimated daily intake from ceramic articles releasing a median migration level of zinc was calculated to be 1.9 mg or 0.027 mg/kg bw. This estimate is approximately 8% of the UL.

Table 3. *The estimated highest and median intake of zinc by an adult (bw = 70 kg) drinking one litre of liquid from a ceramic article every day. The ratio between high or median intakes and the reference value is specified.*

Metal	Reference value	Highest estimated intake value	Ratio	Median estimated intake value	Ratio
Zinc (Zn)	UL[1] = 25 mg/day	316 mg or 4.51 mg/kg bw	12.6	1.9 mg or 0.027 mg/kg bw	0.1

[1]From SCF (2003).

Migration of zinc was found in 14% of the samples analysed in the survey. The estimated median intake of zinc was considerably lower than the highest estimated intake. Thus, the highest reported migration value of 316 mg/l is probably not representative for zinc migration from ceramic articles. Consumption of liquid from a ceramic item with such a high migration level could result in acute zinc poisoning with possible gastrointestinal disturbances as the dose would be within the emetic dose range of 225-450 mg (Fosmire, 1990).

However, the estimated median intake of zinc from ceramic articles was found to be well below the UL. The contribution to the daily intake of zinc from ceramic articles is small compared to the intake from food, which is the main source for zinc exposure. A "worst case" estimate from food (23.5 mg/day) and drinking water (10% of daily intake from food) could result in intakes in the same region as or above the UL.

IRON (Fe)

HAZARD IDENTIFICATION AND CHARACTERISATION OF IRON

Iron is an essential trace element for virtually all living organisms. It has many important metabolic functions in the body, including oxygen transport and storage. Iron also plays a vital part in many redox reactions. An important biological characteristic of iron is its ability to alternate between two oxidation states Fe^{2+} (ferrous) and Fe^{3+} (ferric) and thereby accepting or donating one electron.

Most iron is absorbed in the duodenum and upper jejunum. The absorption is regulated, and tissue concentrations and body stores of iron are controlled at three different levels (luminal iron, mucosal iron and post-mucosal iron). Total body iron in humans is usually about 50 mg/kg bw (men) and 34-42 mg/kg bw (women), respectively. The largest fraction is present

as haemoglobin, myoglobin and haem-containing enzymes. The other major fractions are stored in the body as ferritin and haemosiderin, mainly in the spleen, liver, bone marrow and striate muscle. The daily losses of iron in adults are small (1 mg/day) and due mainly to cell exfoliation from the gastrointestinal tract and the skin. Iron excretion via the kidneys and sweat is very low, while menstrual losses alone are variable and on average about 0.5-1.4 mg/day (NNR, 2004; EFSA, 2004; WHO, 2003b).

The hazard characterisation of excess intake of iron based on animal data is complicated since there are large species and strain differences in response to dietary iron overload. The acute effects of toxic doses of iron include depression, rapid and shallow respiration, coma, convulsions, respiratory failure and cardiac arrest. No effects on reproductive toxicity, embryotoxicty and teratogenicity have been reported in laboratory animals (WHO, 2003b).

Insufficient intake of iron results in the deficiency condition anaemia, adverse outcomes of pregnancy, impaired psychomotoric development and cognitive performance, and reduced immune function. Numerous cases of accidental poisoning with medicinal iron, particularly in young children, have been reported (IOM, 2001). An acute oral dose of 60 mg Fe/kg bw can be lethal, whereas oral doses below about 10-20 mg Fe/kg bw in humans do not cause acute systemic toxicity. Characteristically, poisoned subjects initially show nausea, vomiting and lethargy or coma, then an asymptomatic period for up to 24 hours, which is followed by gastrointestinal perforation, coma, convulsions, cardiovascular collapse, and hepatic and renal failure. A short-term oral dosage at 50-60 mg daily of supplemental non-haeme iron preparations has been shown to cause adverse gastrointestinal effects, particularly if taken without food (EFSA, 2004).

WHO Guidelines for Drinking-water Quality (2003)

No health-based guideline value for iron was proposed in the background document for the WHO Guidelines for Drinking-water Quality in 2003 (WHO, 2003b).

European Food Safety Authority (2004)

The EFSA NDA Panel adopted an opinion related to the UL of iron in 2004 (EFSA, 2004). The NDA Panel stated that the risk of adverse effects from iron overload in the general population, including those heterozygous for hereditary haemochromatosis (a genetic disorder of iron storage), is considered to be low. Their overall considerations were that local adverse gastrointestinal effects after short-term oral dosage at 50-60 mg daily of supplemental non-haem iron preparations were not suitable as a basis to establish an UL for iron from all sources. The Panel further concluded that an UL could not be established based on iron overload due to a poor correlation between iron intake, actual body stores and biochemical indicators of iron status. Neither could an UL be established on the basis of possible increased risk of chronic diseases such as cardiovascular disease, diabetes and cancer (EFSA, 2004).

Nordic Nutrition Recommendations (2004)

Iron overload (haemochromatosis), either genetically or because of a high iron intake of usually >160 mg/day, may result in induced liver iron cirrhosis. Under physiological conditions iron status is almost exclusively regulated by adaptation of intestinal iron absorption to demand. There are indications from several studies that this homeostatic regulation of iron absorption seems able to prevent iron overload at a total iron intake of 17.5-25 mg Fe/day (10 mg/day habitual dietary intake + 7.5-15 mg/day of supplements). However, Fleming *et al.* have reported that an additional intake of > 30 mg Fe/day (a total iron intake of 40 mg Fe/day) was associated with an increased risk of high iron stores, defined as plasma-

ferritin > 300 and 200 µg/l in men and women, respectively (Fleming *et al.*, 2002). A serum ferritin level above 300 µg/l, which is often referred to as "biochemical iron overload", when caused by elevated iron stores, is associated with an increased risk of slight liver fibrosis.

In the Nordic Nutrition Recommendations from 2004, a quantitative UL for iron intake additional to habitual dietary iron was set to 10 mg (non-haeme) Fe/day (average of 7.5-15 mg supplemental iron) in order to protect against "biochemical iron overload" (NNR, 2004).

EXPOSURE CHARACTERISATION OF IRON

Exposure from ceramic articles

In the survey from the Norwegian Food Control Authority in 2003, all the 631 hollow products were analysed for iron content. Iron was measured in concentrations above the detection limit (>0.3 mg/l) in 64 of the products (10%). The highest concentration measured was 37 mg/l and the median quantity of iron in samples above the detection limit was 0.7 mg/l.

It is assumed an intake from ceramic articles of 1 l/day. The estimated daily intake from ceramic articles releasing the highest level of iron would amount to 37 mg or 0.53 mg/kg bw for a person weighing 70 kg. The reported median migration level of 0.7 mg/l would give an estimated daily intake of 0.7 mg/day or 0.01 mg/kg bw.

Exposure from other sources

Food

The iron content of food could vary greatly due to factors such as the soil, climate conditions and processing. Foods rich in iron include liver, offal, game and beef, cereals and cereal products. Poor sources of iron include milk and dairy products, whereas pork, poultry and green vegetables contain intermediate concentrations (EFSA, 2004).

Recent dietary surveys in the Nordic countries have shown that iron intake among adult men and women is 10-15 mg/day on average, based on information from Norway and Denmark, and with iron fortified products included in the calculations. The intake was considerably lower among women than men. The majority of iron in the Nordic diet comes from cereal products. Some of these products, such as breakfast cereals, could be iron-fortified (NNR, 2004). The daily intake, fortified products included, among high consumers (97.5^{th} percentile) in Norway has been reported to be 27 mg for both men and women (EFSA, 2004; Johansson and Solvoll, 1999).

Drinking water

Iron may be present in drinking water as a result of the use of iron coagulants or the corrosion of steel and cast iron pipes during water distribution. Drinking water containing 0.3 mg/litre would contribute about 0.6 mg to the daily intake (WHO 2003b).

RISK CHARACTERISATION OF IRON EXPOSURE FROM CERAMIC ARTICLES

The estimated daily intake from ceramic articles releasing the highest level of iron was calculated to be 37 mg or 0.53 mg/kg bw for a person weighing 70 kg. The quantitative UL of

10 mg (non-haeme) Fe/day recommended in the Nordic nutrition recommendations (NNR, 2004) has been used as reference value in this risk characterisation. The estimated intake of iron from ceramic articles would exceed this level 3.7-fold. The estimated daily intake from ceramic articles releasing a median migration level of iron was calculated to be 0.7 mg or 0.01 mg/kg bw. This estimate is only 7% of the Nordic recommended UL of 10 mg Fe/day.

Table 4. *The estimated highest and median intake of iron by an adult (bw = 70 kg) drinking one litre of liquid from a ceramic article every day. The ratio between high or median intakes and the reference value is specified.*

Metal	Reference value	Highest estimated intake value	Ratio	Median estimated intake value	Ratio
Iron (Fe)	UL[1] = 10 mg/day (non-haeme)	37 mg or 0.53 mg/kg bw	3.7	0.7 mg or 0.01 mg/kg bw	0.1

[1]From NNR (2004).

Migration of iron was found in 10% of the samples analysed in the survey. The estimated median intake of iron from ceramic articles was found to be relatively small and well below the UL.

The highest estimated intake of iron was considerably higher than the median estimated intake and is probably not representative for iron migration from ceramic articles. The highest estimated intake (37 mg) is above the UL, and such high intakes over a prolonged time period would represent an erosion of the safety margin between iron exposure and adverse effects, and at least local effects in the gastrointestinal tract cannot be excluded.

The contribution to the daily intake from the majority of ceramic articles leaching iron is small compared with the intake from food, which is the main source of iron exposure.

COPPER (Cu)

HAZARD IDENTIFICATION AND CHARACTERISATION OF COPPER

Copper is both an essential nutrient and a drinking water contaminant. Two oxidation states of copper exist; cuprous (Cu^{+}) and cupric (Cu^{2+}). In biological systems, copper primarily exists as Cu^{2+} with small quantities of Cu^{+} being found in solution. Copper in living organisms, including humans, forms an essential component of many enzymes (cuproenzymes) and proteins, and the biochemical role for copper is primarily catalytic. The primary sources of copper exposure in developed countries are via food and water.

After oral exposure in mammals, absorption of copper occurs primarily in the upper gastrointestinal tract and is controlled by a complex homeostatic process that apparently involves both active and passive transport. Uptake of copper from the intestines may be competitively inhibited by other transition metals (particularly zinc and iron). The relative amount of absorbed copper is decreased when the ingestion of copper is high. The majority of copper is transported to the liver where it is incorporated into newly synthesised caeruloplasmin, metallothionein or cuproproteins. Excretion in the bile is the main route of elimination in humans, with only minor amounts being excreted in the urine (SCF, 2003b; WHO, 2004a).

Tolerance to high intakes of copper varies greatly between species and copper compounds. Sheep are most sensitive to copper poisoning, while rats and pigs have a higher tolerance to copper excess. Manifestations of copper toxicity include weakness, tremors, anorexia and jaundice. As tissue copper levels increase, haemolytic crises may lead to liver, kidney and brain damage. There is some evidence to indicate an effect of exposure to copper compounds on animal reproduction. Chronic oral exposure to 27-120 mg Cu/kg bw/day in rats has been shown to result in altered weight and/or histology of the testes, seminal vesicles, uterus or ovaries, albeit the results were not consistent (SCF, 2003b; IPCS, 1998).

Available data clearly show that copper can cause adverse effects in humans. Liver damage is observed almost exclusively in patients with Wilson's disease and children with Indian Childhood Cirrhosis (ICC) and Childhood Idiopathic Copper Toxicosis (ICT). Acute copper toxicity (gastrointestinal irritation) from drinking water appears to have a threshold of approximately 6 mg/l (Araya *et al.*, 2001). The occurrence of either acute or chronic systemic copper toxicity in humans, however, is rare, and tends to be confined to certain subpopulations, such as populations with high copper concentrations in drinking water, populations that utilise copper vessels e.g. for boiling and storing milk, and those individuals who have a hereditary predisposition to copper toxicity (SCF, 2003b).

In 1998, the International Programme on Chemical Safety (IPCS) concluded that the upper limit of the acceptable range of oral intake of copper in adults was uncertain, but most likely in the range of several (more than 2 or 3 mg/day), and not many, mg/day (IPCS, 1998). Their evaluation was based solely on studies of gastrointestinal effects of copper-contaminated drinking water. The data on gastrointestinal effects of copper must be used with caution, since the effects observed are influenced by temporal aspects of exposure and the concentration of ingested copper to a greater extent than the total mass of dose ingested in a 24-hour period. This is explained by the fact that a single glass of tap water with a concentration greater than 3 mg Cu/l being more likely to elicit nausea than a litre of water containing the same amount (mass) of copper, but ingested episodically throughout a day (WHO, 2004a).

WHO Guidelines for Drinking-water Quality (2004)

A guideline value for copper in drinking water of 2 mg/l in order to protect against adverse effects of copper and to provide an adequate margin of safety in populations with normal copper homeostasis was established in the WHO background document for development of WHO Guidelines for Drinking-water quality from 2004 (WHO, 2004a). However, there is still some uncertainty regarding the long-term effects of copper on sensitive populations, such as those with defects in the gene for Wilson's disease and other metabolic disorders of copper homeostasis. Adverse effects for these individuals have been found with copper intakes in the range of 1-10 mg/day (US NRC, 2000).

Scientific Committee on Food (2003)

SCF expressed an opinion on the UL of copper in 2003 (SCF, 2003b). Liver damage in humans was selected as the critical endpoint because it perhaps is a more reliable indicator of long-term chronic ingestion of cobber than local gastrointestinal effects. Although gastrointestinal effects of copper toxicity are better documented in humans than effects on the liver, gastrointestinal effects are more representative of acute copper poisoning. According to Araya *et al*. (2001), the acute copper toxicity in drinking water appears to have a threshold of approximately 6 mg Cu/l (1.2 mg Cu). SCF emphasised that the aim of a tolerable upper intake level is to identify safety of maximal copper intakes over a longer period of time.

A NOAEL of 10 mg/day was based on the absence of any adverse effects on liver function as the critical endpoint in humans. SCF derived an UL for adults of 5 mg/day based on the NOAEL of 10 mg/day and an uncertainty factor of 2 to allow for potential variability within the normal population. The UL of 5 mg/day was not considered applicable during pregnancy or lactation due to inadequate data related to this critical life stage (SCF, 2003b).

EXPOSURE CHARACTERISATION OF COPPER

Exposure from ceramic articles

In the survey from the Norwegian Food Control Authority in 2003, all the 631 hollow products were analysed for copper content. Quantifiable amounts of copper (> 0.3 mg/l) were found in 92 of the articles (15%). The highest quantity measured was 150 mg/l. The median concentration of copper in all samples above the detection limit was 3.95 mg/l.

It is assumed an intake from ceramic articles of 1 l/day. The estimated daily intake from ceramic articles releasing the highest level of copper would amount to 150 mg or 2.14 mg/kg bw for a person weighing 70 kg. The reported median migration level of 3.95 mg Cu/l would give an estimated daily intake of 3.95 mg or 0.06 mg/kg bw.

Exposure from other sources

Food

Food is a principal source of copper exposure for humans. Liver and other organ meats, seafood, nuts and seeds (including whole grains) are sources of dietary copper (IOM, 2001). Based on the results of the US Department of Agriculture 1989–1991 survey of food consumption, about 40% of dietary copper comes from yeast breads, white potatoes, tomatoes, cereals, beef, and dried beans and lentils (Subar *et al.*, 1998). In Scandinavian countries, copper intakes are in the range of 1.0–2.0 mg/day for adults. Intakes up to 3.5 mg/day have been reported for vegans (Pettersson and Sandstrum, 1995; IPCS, 1998).

Drinking water

Copper concentrations in drinking water vary widely as a result of variations in water characteristics, such as pH, hardness and copper availability due to leaching from pipes in the distribution system. Results from a number of studies from Europe, Canada and USA indicate that copper levels in drinking water can range from ≤0.005 to >30 mg/l (references cited in WHO 2004a). Concentrations can vary significantly with the period of time the water has been in contact with the pipes, and first-draw water would be expected to have a higher copper concentration than a fully flushed sample. The current EU standard given in Directive 98/83 is 2 mg/l for the maximum concentration of copper in drinking water (EC, 1998).

RISK CHARACTERISATION OF COPPER EXPOSURE FROM CERAMIC ARTICLES

The estimated daily intake from ceramic articles releasing the highest level of copper was calculated to be 150 mg or 2.14 mg/kg bw for a person weighing 70 kg. Based on the UL for adults of 5 mg/day recommended by SCF (SCF, 2003b), the estimated intake of copper from ceramic articles would be 30 times above. The estimated daily intake from ceramic articles releasing a median migration level of copper was calculated to be 3.95 mg or 0.06 mg/kg bw. This estimate is slightly below the UL.

Table 5. *The estimated highest and median intake of copper by an adult (bw = 70 kg) drinking one litre of liquid from a ceramic article every day. The ratio between high or median intakes and the reference value is specified.*

Metal	Reference value	Highest estimated intake value	Ratio	Median estimated intake value	Ratio
Copper (Cu)	UL[1] = 5 mg/day	150 mg or 2.14 mg/kg bw	30.0	3.95 mg or 0.06 mg/kg bw	0.8

[1]From SCF (2003b).

Copper was detected in about 15% of the samples analysed in the survey. The highest estimated intake of copper was considerably higher than the median estimated intake and is probably not representative for copper migration from ceramic articles.

The UL for copper is based on the absence of any adverse effects on liver function (NOAEL = 10 mg/day applying an uncertainty factor of 2). The dose for acute gastrointestinal effects of copper would be lower and a threshold of approximately 6 mg Cu/l has been reported by Araya *et al.* (2001). Consumption of liquid from the ceramic item with the highest reported migration level (150 mg/l) could therefore result in acute gastrointestinal effects.

The estimated median intake of copper from ceramic articles was found to be close to the UL. This median intake from ceramic articles is also relatively high compared to the intake from other sources. In the Scandinavian countries, copper intakes from food are in the range of 1.0–2.0 mg/day for adults (Pettersson & Sandstrum, 1995; IPCS, 1998). Assuming an intake of 2 litres of water per day, the contribution from drinking water could be up to 4 mg/day based on the current EU standard for the maximum concentration of copper in drinking water (EC, 1998). An additional contribution from ceramic articles based on the median intake value could therefore result in an exceedance of the UL.

MANGANESE (Mn)

HAZARD IDENTIFICATION AND CHARACTERISATION OF MANGANESE

Manganese is an abundant metallic element that can exist in a variety of oxidation states, of which Mn^{2+} and Mn^{3+} are most important in biological systems. It has been shown to be an essential element for some mammalian species. However, evidence of manganese deficiencies in man is poor. Manganese is present both naturally and as a result of contamination in soils, sediments and water.

About 3-8% of orally ingested manganese is absorbed in the gastrointestinal tract, but absorption appears to be higher in infants and young animals. The absorption of manganese is inversely related to the level of iron and calcium in the diet, and the highest tissue concentrations are found in the liver, kidney, pancreas, and adrenals. Preferentially, manganese is retained in certain regions of the brain in young animals and infants. Manganese is almost entirely excreted in the faeces, only a small proportion being eliminated in the urine. In humans, the elimination is biphasic, with half-lives of 13 and 34 days (WHO, 2004b).

The acute oral toxicity of manganese is relatively low, and appears to vary depending on the chemical species and whether exposure is via gavage or in diet. The central nervous system is the main target for manganese toxicity, with oral doses ranging from 1 to 150 mg/kg bw/day producing a number of neurological effects such as alterations in neurotransmitter and enzyme levels in the brain in rats and mice. In animal studies, haematological effects have also been reported. They indicate that the ingestion of manganese can delay reproductive maturation in male animals. Reduced testosterone levels and delayed growth of the testes have been observed, but these effects do not appear to be severe enough to affect male reproductive function (WHO, 2004b).

Positive results reported in several short-term genotoxicity tests are probably not due to intrinsic, direct genotoxicity of manganese, but to indirect mechanisms, as it occurs for other elements. The genotoxicity of manganese compounds seems to be mediated by the bivalent ion Mn^{2+} at relatively high and cytotoxic concentrations. Based on the presently available data, no overall conclusion can be made on the possible genotoxic hazard to humans (SCF, 2000b).

No studies are available on the potential carcinogenicity of manganese following inhalation or dermal exposure in humans or other animals (ATSDR, 2000). A 2-year oral study of manganese sulphate in rats and mice produced equivocal evidence of carcinogenicity (NTP, 1993). The significance of these results and their relevance to normal human exposure to manganese are questionable (WHO, 2004b).

The neurological effects of inhaled manganese dust and fumes have been well documented in humans chronically exposed to relatively high concentrations at the work place. The syndrome known as “manganism” is characterised by weakness, anorexia, muscle pain, apathy, slow speech without inflection, emotionless “mask-like” facial expression and slow, clumsy movement of the limbs. These effects are in general irreversible. There are also human studies reporting neurotoxic effects of manganese contained in drinking water. However, the limitations of these studies, including the uncertainty about the contribution of manganese from food, make firm conclusions difficult (SCF, 2000b).

Scientific Committee on Food (2000)

The Scientific Committee on Food expressed an opinion on the UL for manganese on 19 October 2000 (SCF, 2000b). It was stated that the dose-response relationship of adverse effects in experimental animals had not been clarified sufficiently, and therefore SCF could not derive NOAELs for the critical effects. The LOAELs following oral administration are 0.28 mg/kg bw/day in growing male rats, producing biochemical and neurological changes in the brain, and 0.36 mg/kg bw/day in adult female rats, decreasing their learning ability.

SCF concluded that exposure to manganese by inhalation is neurotoxic, and that oral intake of manganese, despite its poor absorption in the gastrointestinal tract, has also been shown to cause neurotoxic effects. Since the human data have certain limitations and there are no NOAELs for critical endpoints from animal studies the degree of uncertainty is considerable, and an UL for manganese could not be set. They further concluded that the margin between oral effect levels in humans as well as experimental animals, and the estimated intake from food, was very low. Given the findings on neurotoxicity and the potential higher susceptibility of some subgroups in the general population, oral exposure to manganese beyond the level

normally present in food and beverages could represent a risk of adverse health effects without evidence of any health benefit (SCF, 2000b).

WHO Guidelines for Drinking-water Quality (2004)

Manganese has also been evaluated in a background document for the development of WHO Guidelines for Drinking-water Quality in 2004 (WHO, 2004b). In the WHO background document it is referred to the fact that the US Food and Nutrition Board of the Institute of Medicine (IOM) has set a tolerable intake level at 11 mg/day for adults, based on a recent review (Greger, 1999; IOM, 2002) that stated that the average manganese intake for adults eating typical Western and vegetarian diets in various surveys ranged from 0.7-10.9 mg Mn/day. This upper range manganese intake value of 11 mg/day was considered a NOAEL by WHO (WHO, 2004b). A TDI of 0.06 mg/kg bw was calculated by dividing the NOAEL by an uncertainty factor of 3 (to allow for the possible increased bioavailability of manganese from water) and an adult body weight of 60 kg (WHO, 2004b). This is equivalent to a TDI of 0.05 mg/kg bw for a person weighing 70 kg.

EXPOSURE CHARACTERISATION OF MANGANESE

Exposure from ceramic articles

In the survey from the Norwegian Food Control Authority in 2003, all the 631 hollow products were analysed for manganese content. Manganese was measured in concentrations above the detection limit (>0.3 mg/l) in 15 of the products (2%). The highest concentration measured was 10 mg /l and the median quantity of manganese in all samples above the detection limit was 0.7 mg/l.

It is assumed an intake from ceramic articles of 1 l/day. The estimated daily intake from ceramic articles releasing the highest level of manganese would amount to 10 mg or 0.14 mg/kg bw for a person weighing 70 kg. The reported median migration level of 0.7 mg/l would give an estimated daily intake of 0.7 mg or 0.01 mg/kg bw.

Exposure from other sources

Food

Food is the most important source of manganese exposure for the general population. The concentrations in foodstuffs vary considerably, but are mostly below 5 mg/kg. Grain, rice and nuts, however, may have manganese levels exceeding 10 mg/kg or even 30 mg/kg in some cases. High concentrations have been found in tea; a cup of tea can contain 0.4-1.3 mg manganese. The dietary intake of adults has in different studies been estimated to range from 0.9-9.4 mg Mn/day. Results from the UK Total Diet Study show that the estimated average intake of manganese in the UK population in 1994 was 4.9 mg/day, including 2.3 mg/day from beverages. The consumption of tea may contribute substantially. The intake can be higher for vegetarians because higher levels of manganese occur in food of plant origin (SCF, 2000b). A recent review has stated that the average manganese intake for adults eating typical Western and vegetarian diets could be up to 10.9 mg Mn/day (Greger, 1999; IOM, 2002).

Drinking water

Manganese intake from drinking water is normally substantially lower than intake from food. Assuming a daily water intake of 2 litres, the median intake of manganese from drinking

water would be 0.02 mg/day for an adult. At levels exceeding 0.1 mg/l, manganese in water supplies causes an undesirable taste in beverages and stains sanitary ware and laundry. The presence of manganese in drinking water may lead to the accumulation of deposits in the distribution system, and even at a concentration as low as 0.02 mg/l, manganese can form a coating on pipes. Concentrations below 0.05 mg/l are usually acceptable to consumers, although this may vary with local circumstances (WHO, 2004b).

RISK CHARACTERISATION OF MANGANESE EXPOSURE FROM CERAMIC ARTICLES

The estimated daily intake from ceramic articles releasing the highest level of manganese was calculated to be 10 mg or 0.14 mg/kg bw for a person weighing 70 kg. Based on the TDI of 0.05 mg/kg bw (bw = 70 kg) derived by WHO (WHO, 2004b), the estimated intake of manganese from ceramic articles would exceed the TDI by a factor of 2.8. The estimated daily intake from ceramic articles releasing a median migration level of manganese was calculated to be 0.7 mg or 0.01 mg/kg bw. This estimate is about 20% of the TDI.

Table 6. *The estimated highest and median intake of manganese by an adult (bw = 70 kg) drinking one litre of liquid from a ceramic article every day. The ratio between high or median intakes and the reference value is specified.*

Metal	Reference value	Highest estimated intake value	Ratio	Median estimated intake value	Ratio
Manganese (Mn)	TDI[1] = 0.05 mg/kg bw	10 mg or 0.14 mg/kg bw	2.8	0.7 mg or 0.01 mg/kgbw	0.2

[1]Based on 70 kg bodyweight and not 60 as in WHO (2004b).

Manganese was found in 2% of the samples analysed in the survey. The estimated median intake of manganese was considerably lower than the highest estimated intake. This indicates that consumption of liquid from the majority of ceramic articles leaching manganese will not result in intakes of manganese close to the TDI of 0.05 mg/kg bw.

The daily intake from food and drinking water among adults could be up to approximately 11 mg/day, with food being the main source for manganese exposure. The median estimated intake of manganese from ceramic articles is small compared to exposure from other sources.

The highest reported migration value of 10 mg/l is probably not very representative for manganese migration from ceramic articles, but consumption of liquid from a ceramic item with such a high migration would result in an intake of manganese above the TDI. A high intake over a prolonged time period would represent an erosion of the safety margin for manganese exposure, and adverse effects can probably not be excluded.

Comment

The VKM Panel noted that growing rats were susceptible to oral manganese exposure producing neurotoxicity, and that the margin of safety therefore may be lower for infants and children.

CONCLUSIONS

This risk assessment based on a survey of 648 hand-crafted ceramic articles produced by individual potters sold on the Norwegian market in 2003, shows that most of these ceramic articles are safe with respect to leakage of the metals in question (median values of leakage) (Tables 1-7). However, the median estimated intake of nickel from ceramic articles is in the same order as the TDI, and nickel intake from ceramics could be of concern for a sensitised subpopulation.

Relatively few of the tested ceramic articles (0.5-15%) leached metals above the detection limits. However, for some articles, high leakage might cause substantial exceedance of tolerable intakes (Tables 1-7).

Table 7. *The estimated highest and median intakes of nickel, cobalt, zinc, iron, copper and manganese by an adult (bw = 70 kg) drinking one litre of liquid from a ceramic article every day. The ratios between high or median intakes and the reference values are specified. Ratios above 1 are shaded in grey.*

Metal (No. of samples detected)	Reference value	Highest estimated intake value	Ratio	Median estimated intake value	Ratio
Nickel **(3/631 = 0.5%)**	TDI[1] = 11 µg/kg bw	0.9 mg or 13 µg/kg bw	1.2	0.8 mg or 11 µg/kg bw	1.0
Cobalt **(36/631 = 6%)**	Guidance value[2]= 1.6 mg/day or 0.023 mg/kg bw/day	20 mg or 0.29 mg/kg bw	12.6	0.75 mg or 0.011 mg/kg bw	0.5
Zinc **(87/631 = 14%)**	UL[3] = 25 mg/day	316 mg or 4.51 mg/kg bw	12.6	1.9 mg or 0.027 mg/kg bw	0.1
Iron **(64/631 = 10%)**	UL[4] = 10 mg/day (non-haeme)	37 mg or 0.53 mg/kg bw	3.7	0.7 mg or 0.01 mg/kg bw	0.1
Copper **(92/631 = 15%)**	UL[5] = 5 mg/day	150 mg or 2.14 mg/kg bw	30.0	3.95 mg or 0.06 mg/kg bw	0.8
Manganese **(15/631 = 2%)**	TDI[6] = 0.05 mg/kg bw	10 mg or 0.14 mg/kg bw	2.8	0.7 mg or 0.01 mg/kgbw	0.2

[1]TDI from WHO (2005) and EU (2005b), [2]From FSA (2003), [3]From SCF (2003), [4]From NNR (2004), [5]From SCF (2003b), [6]From WHO (2004b).

The highest estimated intakes of zinc and copper from ceramic articles may cause acute gastrointestinal effects.

For nickel, and to some extent cobalt and manganese, more sensitive analytical methods should be employed due to low margins between estimated high intakes and tolerable intakes.

Given the findings of neurotoxicity in growing rats, and therefore a potentially higher susceptibility of infants and children, oral exposure to manganese beyond the level normally present in food and beverages could represent a risk of adverse health effects without evidence of any health benefit.

ASSESSED BY

Panel on Food Additives, Flavourings, Processing Aids, Materials in Contact with Food and Cosmetics:

Jan Alexander (chair), Mona-Lise Binderup, Knut Helkås Dahl, Trine Husøy, Kristine Naterstad, Jan Erik Paulsen, Tore Sanner and Inger-Lise Steffensen

Scientific coordinators from the secretariat: Tor Øystein Fotland and Arne Mikalsen

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