Nickel in drinking-water

Background document for development of WHO *Guidelines for drinking-water quality*

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Preface

To be completed by WHO Secretariat

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Acronyms and abbreviations

BMD	benchmark dose
$BMDL_{10}$	95% lower confidence limit on the benchmark dose for a 10% response
bw	body weight
CI	confidence interval
CONTAM	Panel on Contaminants in the Food Chain (European Food Safety Authority)
DNA	deoxyribonucleic acid
EFSA	European Food Safety Authority
FAO	Food and Agriculture Organization of the United Nations
GDWQ	*Guidelines for drinking-water quality*
GV	guideline value
$H_{12}NiO_{10}S$	nickel sulfate hexahydrate
L	litre
LOAEL	lowest-observed-adverse-effect level
NiO	nickel oxide
NiS	nickel sulfide
Ni_3S_2	nickel subsulfide
NOAEL	no-observed-adverse-effect level
OR	odds ratio
SCD	systemic contact dermatitis
TDI	tolerable daily intake
WHO	World Health Organization

Contents

Executive summary

To be completed by WHO Secretariat

1 General description

1.1 Identity

Nickel is a naturally occurring lustrous white, hard, ferromagnetic metal that is ubiquitous in the environment. It occurs naturally in five isotopic forms: 58 (67.8%), 60 (26.2%), 61 (1.2%), 62 (3.7%) and 64 (1.2%).

1.2 Physicochemical properties

Some physicochemical properties of nickel are shown in Table 1.

Table 1. Physicochemical properties of nickel

Property	Value
Boiling point	2837 °C
Melting point	1555 °C
Density	8.90 g/cm^3 at 25 °C

Nickel usually has two valence electrons, but oxidation states of +1, +3 or +4 may also exist. Metallic nickel is not affected by water, but is slowly attacked by dilute hydrochloric or sulfuric acid and is readily attacked by nitric acid. Fused alkali hydroxides do not attack nickel. Several nickel salts, including the acetate, chloride, nitrate and sulfate salts, are soluble in water. Carbonates and hydroxides of nickel are far less soluble, and sulfides, disulfides, subsulfides and oxides are practically insoluble in water. Alloys of nickel containing more than 13% chromium are largely protected from corrosion in many media by the presence of a surface film consisting mainly of chromium oxide (Morgan & Flint, 1989; Haudrechy et al., 1994).

Nickel oxide (NiO) has two forms: a black crystalline form (Antonsen, 1981) with a nickel content of 76–77%, and a more stable, green form with a nickel content of 78.5%. Nickel ammonium sulfate($Ni(NH_4)_2(SO_4)_2$), nickel chloride ($NiCl_2$) and nickel nitrate ($Ni(NO_3)_2$) usually exist as hexahydrates, whereas nickel acetate, nickel cyanide and nickel sulfamate are in the form of tetrahydrates (ATSDR, 2005).

1.3 Organoleptic properties

Nickel and its compounds have no characteristic odour or taste. Taste or odour thresholds for nickel compounds in water were not identified (ATSDR, 2005).

1.4 Major uses and sources

Nickel is used mainly in the production of stainless steels, non-ferrous alloys and super alloys. Other uses of nickel and nickel salts are in electroplating, as catalysts, in nickel–cadmium

batteries, in coins, in welding products, and in certain pigments and electronic products (IARC, 1990). It is estimated that 8% of nickel is used for household appliances (IPCS, 1991). Nickel is also incorporated in some food supplements, which can contain several micrograms of nickel per tablet (EU, 2008).

Nickel enters ambient waters primarily as nickel-containing particulate matter carried by rainwater and through the degradation/dissolution of nickel-containing rocks and soils (IPCS, 1991). The main anthropogenic sources of nickel in water are primarily nickel production, metallurgical processes, combustion and incineration of fossil fuels, chemical and catalyst production, and discharges of industrial and municipal wastes (EFSA, 2015). The primary source of nickel in drinking-water is leaching from metals that are in contact with drinking-water, such as in pipes and fittings.

Nickel is used principally in its metallic form, combined with other metals and non-metals as alloys. Nickel alloys are characterized by their hardness, strength, and resistance to corrosion and heat.

2 Environmental levels and human exposure

Environmental exposure to nickel of anthropogenic origin occurs locally from, among others: emissions of metal mining, smelting, and refining operations; industrial activities (nickel plating, alloy manufacturing, etc.); land disposal of sludges, solids, and slags; and disposal of effluents (IPCS, 1991). In general, nickel is found in the environment in a wide variety of chemical forms and concentrations are highly variable, reflecting the influence of nickel emissions from different types of sources (EFSA, 2015).

2.1 Water

Nickel occurs predominantly as the ion nickel hexahydrate ($Ni(H_2O)_6^{2+}$) in natural waters at pH 5–9 (IPCS, 1991). Complexes with ligands, such as hydroxide (OH^-), sulfate ($SO4^{2-}$), bicarbonate (HCO_3^-), chloride (Cl^-) and ammonia (NH_3), are formed to a minor degree in this pH range. Nickel that has leached from nickel-or chromium plated fittings is expected to be in a similar form.

Nickel concentrations in groundwater depend on the soil use, pH and depth of sampling. The average concentration in groundwater in the Netherlands ranges from 7.9 µg/L (urban areas) to 16.6 µg/L (rural areas). Acid rain increases the mobility of nickel in the soil and thus might increase nickel concentrations in groundwater (IPCS, 1991). In groundwater with a pH below 6.2, nickel concentrations up to 980 µg/L have been measured (RIVM, 1994). Concentrations of nickel in pristine surface waters may be so low as to be near the limits of current analytical methods (ATSDR, 2005).

Nickel concentrations in tap water can be influenced by the origin of the water (surface water, groundwater, geological layer), its subsequent treatment process, piping and tap material, and stagnation time. Some evidence suggests that corrosion of stainless steel pipes in domestic water distribution systems contributes nickel to water drawn from taps, especially during the first draw (De Brouwere et al., 2012).

In Canada, surveys of drinking-water supplies conducted between 1985 and 1988 in northern Alberta and the Atlantic provinces found that mean nickel concentrations were 2.1–2.3 µg/L (Health Canada, 1994). Mean concentrations were 0.2–7.2 µg/L in a survey of 96 plants across Ontario, with the exception of those in Sudbury (Health Canada, 1994). In the Sudbury area, drinking-water sampled between 1972 and 1992 had markedly higher mean concentrations of 26–300 µg/L. The median nickel concentrations in both treated and distributed provincial drinking-water measured in an extensive national survey of many Canadian municipalities were ≤0.6–1.3 µg/L for treated water and 1.8 µg/L for distributed water; the maximum value was 72.4 µg/L (ATSDR, 2005). Nickel levels in tap water from British Columbia, Prince Edward Island, the Yukon and the Northwest Territories were below the detection limit.

Potable tap water in the USA generally contains nickel at concentrations of 0.55–25 µg/L (ATSDR, 2005; OEHHA, 2012). In a Seattle (Washington) study, mean and maximum nickel levels in standing water were 7.0 µg/L and 43 µg/L, respectively, compared with 2.0 µg/L and 28 µg/L in running water (ATSDR, 2005). Nickel concentrations in tap water measured in the United States Total Diet Study 1991–1999 ranged from 0 to 25 µg/L, with a mean value of 2 µg/L. Analysis of data obtained during 1995–1997 from the National Human Exposure Assessment Study yielded median concentrations of nickel in tap water (used as drinking-water) of 4.3 µg/L (90th percentile 10.6 µg/L) in the Arizona study, and 4.0 µg/L (90th percentile 11 µg/L) in the United States Environmental Protection Agency Region 5 (Illinois, Indiana, Michigan, Minnesota, Ohio and Wisconsin) study. According to monitoring data collected by the California Department of Health Services between 1984 and 1997, the highest, average and median concentrations of nickel in water were 540 µg/L, 26 µg/L and 17.9 µg/L, respectively.

In Australia, nickel concentrations in drinking-water are typically <10 µg/L. In Sampleton, Australia, the mean nickel concentration in drinking-water sampled between January 2002 and December 2005 was 30 µg/L (range <10–220 µg/L); the concentrations intermittently exceeded the *Australian drinking water guidelines* value for nickel of 20 µg/L (Alam, Corbett & Ptolemy, 2008).

In Europe, drinking-water generally contains nickel at concentrations <10 µg/L (IPCS, 1991; ANSES, 2005; Cempel & Nikel, 2006; WHO, 2007; Bertoldi et al., 2011; De Brouwere et al., 2012). Concentrations up to 13 µg/L have been reported (IARC, 1990; WHO, 2000). In 2020, EFSA evaluated the results of several European surveys of nickel in drinking-water, which collectively included 17,831 quantified samples that were analyzed between 2009 and 2018, with the majority of the samples collected between 2009 and 2011. Approximately 73% of the samples were collected in Germany and approximately 19% of the samples were collected from Cyprus and Slovakia, with the remaining samples being collected elsewhere in Europe. The results for each sample were reported as lower and upper bounds, with mean lower and upper bounds for all samples of 2 and 3 µg/L (respectively), and 95th percentile lower and upper bounds of 7 µg/L for both parameters. In the UK, median concentrations of nickel in drinking-water were reported for England/Wales, Northern Ireland, and Scotland at 1.36, 1.14, and 0.3 µg/L, respectively (COT, 2018). 97.5th percentile concentrations of nickel in drinking-water in these three regions were 4.63, 4.47, and 1.95 µg/L, respectively. Nickel levels <1 µg/L have been reported from Denmark and Finland (Punsar et al., 1975; Gammelgaard & Andersen, 1985). Average dissolved nickel concentrations in surface water in the rivers Rhine and Meuse were <7 µg/L (RIWA, 1994).

Increased nickel concentrations in groundwater and municipal tap water (100–2500 µg/L) were reported in polluted areas and areas where natural nickel was mobilized (McNeely, Nechay & Sunderman, 1972). After smelter emissions decreased in the early to mid-1970s, nickel concentrations in potable water of Sudbury substantially decreased by the early 1980s (Hopfer, Fay & Sunderman, 1989). Water left standing overnight in plumbing fittings plated with chromium on a base of nickel contained a nickel concentration up to 490 µg/L, but low values were obtained after flushing; there was considerable variation at different times and from tap to tap (Andersen et al., 1983).

Certain stainless steel well materials were identified as the source of increased nickel concentrations in groundwater wells in Arizona, USA. Mean nickel levels were 8–395 µg/L; in some cases, nickel levels were in the range 1–5 mg/L (Oakley & Korte, 1996).

Leaching of nickel from new stainless steel pipework into drinking-water diminished after a few weeks. Chromium was rarely found in the water, indicating that the leakage of nickel was attributable to passive leaching of nickel ions from the surface of the pipes, rather than a corrosive process (Schwenk, 1992). Concentrations of nickel leaching from new stainless steel pipes used for drinking-water were <6 µg/L (Nickel Development Institute, personal communication, 2004). Higher concentration can occur if pipes are assembled with tinned copper and gunmetal fittings. Fittings, such as taps, that are chromium plated release much higher concentrations, which decrease significantly with time (EU, 2008). First draw water from chromium plated taps can show elevated nickel concentrations due to the exposed nickel plated base inside the tap.

Nickel concentrations in bottled mineral water depend on the source of the water and any treatment applied. Levels of nickel in a selection of bottled mineral waters were below the detection limit of 25 µg/L (Allen, Halley-Henderson & Hass, 1989). In a survey of the chemical composition of 571 European bottled mineral waters marketed in 23 European countries, nickel was above the detection limit of 1.9 µg/L in less than 12% of samples (median <1.9 µg/L; 90th percentile 2.2 µg/L); only two samples exceeded the European Commission limit of 20 µg/L, reaching the maximum of 30.3 µg/L (Bertoldi et al., 2011).

2.2 Food

Since nickel is usually measured in food as total nickel, the chemical form is not specified. nickel in food is normally considered to be in the form of complex bound organic nickel (EU, 2008). Nickel levels in food have been reported to be generally in the range of 0.01–0.1 mg/kg, but there are large variations (Booth, 1990; Jorhem & Sundström, 1993; Dabeka & McKenzie, 1995; Fødevaredirektoratet, 2000). Foods with high nickel content are mostly of plant-based origin, compared with foods of animal origin such as meat, fish, and honey, which have lower nickel concentrations (Babaahmadifooladi et al. 2020). Higher median levels of nickel (0.1–0.4 mg/kg) were found in wholemeal products (Smart & Sherlock, 1987; Fødevaredirektoratet, 2000), and markedly higher levels (1–6 mg/kg) were found in beans, seeds, nuts and wheat bran (Smart & Sherlock, 1987; Jorhem & Sundström, 1993). Even higher nickel levels (8–12 mg/kg) were found in cacao (Smart & Sherlock, 1987). More recently, the EFSA CONTAM Panel reviewed literature and concluded that in general, foods contained less than 0.5 mg nickel/kg (EFSA, 2015). In this assessment the CONTAM Panel used a data set of 18,885 food samples (2003 – 2012, in 15 EU countries), and high mean levels of nickel were reported for ‘Legumes, nuts and oilseeds’ (~ 2 mg/kg), certain types of

cocoa products (3.8 mg/kg), and 'Cocoa beans and cocoa products' (9.5 mg/kg) (EFSA, 2015). In 2020, data from 43,915 food samples (2000 – 2019, in 26 EU counties) was obtained; overall, the results reported in the scientific literature are in line with the concentrations reported to EFSA (EFSA 2020).
Nickel may be released from food contact materials, including packaging material, cooking utensils and storage containers, which may result in additional exposure. Stainless steel cooking utensils (e.g. oven pans, roasting pans) contributed markedly to the levels of nickel in cooked food; nickel levels sometimes exceeded 1 mg/kg in meat (Dabeka & McKenzie, 1995), although there may be some questions regarding analytical contamination in this study. In contrast, Flint & Packirisamy (1995) found only minor increases in nickel concentrations in acid foodstuffs when new stainless steel pans were used. In general, concentrations of nickel following migration are in the same order of magnitude as concentrations reported to occur in food. Differences are observed between studies, which may reflect a difference in quality of food contact materials. The available database is too limited to draw up a scenario on dietary exposure to nickel resulting from food contact material (EFSA, 2020).

As part of the 2014 Total Dietary Survey (TDS) conducted by the UK Food Safety Authority (FSA), food and drink samples representing 28 food categories were collected from 24 locations throughout the UK and were analyzed for nickel content (COT, 2014). The results from these assays were combined with data from the UK National Diet and Nutrition Survey to identify mean and upper-bound estimates of exposure to inorganic elements in food for various age groups. According to the results of the analysis, the mean nickel intakes from food in the UK were 4.4 – 5.2 µg/kg bw per day for children aged 1.5 to 3 years, 2.1 to 2.2 µg/kg bw per day for individuals aged 11 to 18 years, and 1.7 to 1.9 µg/kg bw per day for ages of 19 years to adulthood (the total mean exposure estimate for children aged 4 to 10 years was not provided in the available data report). Additionally, the upper-bound (97.5^{th} percentile) exposure estimates for nickel in food were 7.1 to 8.1 µg/kg bw per day for children aged 1.5 to 3 years, 6.5 to 7.3 µg/kg bw per day for children aged 4 to 10 years, 4.0 to 4.2 µg/kg bw per day for individuals aged 11 to 18 years, and 3.2 to 3.4 µg/kg-day for ages of 19 years to adulthood. Previously other publications have reported daily dietary intakes of nickel were 0.14–0.15 mg in the United Kingdom in 1981–1984 (Smart & Sherlock, 1987), 0.082 mg in Sweden in 1987 (Becker & Kumpulainen, 1991), 0.16 mg (mean; 95th percentile 0.27 mg) in Denmark (Fødevaredirektoratet, 2000) and 0.16 mg in the USA (Myron et al., 1978). In the United Kingdom, population dietary intakes of nickel have decreased since 1976 when they were 0.33 mg/day (COT, 2008).

In a Canadian study, the mean dietary intakes of nickel for various age groups were reported as 0.038 mg/day in 0–12-month-old infants (on average, 0.005 mg/kg bw/day), 0.19 mg/day in 1–4-year-old children, 0.275 mg/day in 20–39-year-old women and 0.406 mg/day in 20–39-year-old men (Dabeka & McKenzie, 1995). Infants fed evaporated milk were exposed to 0.004 mg/kg bw/day, whereas infants fed soy-based formula were exposed to 0.010 mg/kg bw/day (Dabeka, 1989). The United States Food and Drug Administration estimated an intake of 0.134 mg/day based on data from the north-eastern part of the USA (US FDA, 2000).

Because nuts and beans are important sources of protein for vegetarians, this subpopulation can be expected to have a markedly higher intake of nickel than that reported in the studies cited above. The nickel intake of eight volunteers ingesting normal diets averaged 0.13 mg/day

(range 0.06–0.26 mg/day), compared with 0.07 mg/day (range 0.02–0.14 mg/day) when diets containing low nickel levels were consumed. When food rich in nickel was ingested, the daily intake was 0.25 mg/day (range 0.07–0.48 mg/day) (Veien & Andersen, 1986). A duplicate-diet study of vegetarians in the United Kingdom indicated an average dietary intake of nickel of 0.17 mg/day (FSA, 2000). This was confirmed by the United Kingdom 2006 duplicate-diet study, which showed a small decline in exposure (COT, 2008).

Chronic exposure estimates were calculated for 44 different dietary surveys carried out in 23 European countries. The mean and the high (95th percentile) chronic dietary exposures were calculated by combining nickel mean occurrence values for food and drinking-water samples collected in different countries (pooled European occurrence data) with the average daily consumption of each food at individual level in each dietary survey. The highest estimated chronic dietary exposure to nickel was in the young age groups. Concerning the mean dietary exposure in total population, the highest estimated lower bound and upper bound exposure levels were in toddlers with a maximum exposure of 12.5 and 14.6 µg/kg bw per day, respectively. The highest 95th percentile lower bound and upper bound exposure was observed for infants with estimates of 28.1 and 29.9 µg/kg bw per day, respectively (EFSA 2020).

Acute dietary exposure to nickel was estimated using a probabilistic approach based on the method of random sampling with replacement of occurrence data. The random sampling captures the variability in occurrence values. A total of the 48 most recent dietary surveys carried out in 25 different European countries were used. Acute exposure was assessed for each reporting day by multiplying the total consumption amount for each food category by one upper bound occurrence level randomly drawn among the individual results available for that food category. Mean upper bound acute dietary exposure to nickel across the different dietary surveys and age classes ranged from 1.89 µg/kg bw/day (in the "Elderly" in a survey conducted in Greece) to 14.6 µg/kg bw/day (in "Toddlers" in a survey conducted in Belgium). The corresponding 95th percentile upper bound for acute dietary exposure ranged from 5.35 µg/kg bw/day (in the "Elderly" in a survey conducted in Greece) to 40.8 µg/kg bw/day (in "Toddlers" in a survey in Belgium).

Therefore, the highest mean upper bound for both acute and chronic exposure to nickel were observed in "Toddlers". Average acute exposure estimations did not differ much from those calculated for chronic exposure. This can be explained by the fact that nickel is present in many different foods that are regularly consumed (EFSA, 2020).

Daily intakes of nickel in total diet (including drinking-water) were investigated in six cities in Japan (Ohno et. al., 2010). The average total daily intake was 156 ± 35 µg/day (0.7 ± 0.6 µg/day for drinking-water), which corresponds to about 3 µg/kg bw/day.

2.3 Air

Nickel concentrations in air in remote areas are in the range of 1–3 ng/m^3 (IPCS, 1991), whereas concentrations in urban and industrialized areas can be up to tens or hundreds of ng/m^3 (EFSA 2015). In nickel occurs mostly as fine respirable particles that are removed by wet and dry deposition. Anthropogenic sources of air-borne nickel account for more than 80 % of the atmospheric nickel burden; the remainder to 100 % is accounted for by natural sources. In rainwater, nickel concentrations are on average measured in the range < 1 µg/L, although greater levels have been detected depending on location (EFSA, 2015). It has been estimated

that non-occupational exposure via inhalation is 0.2–1.0 µg/day in urban areas and 0.1–0.4 µg/day in rural areas (Bennett, 1984). The mainstream smoke of one cigarette contains about 0.04–0.58 µg of nickel (IARC, 1990).

2.4 Bioaccumulation

Nickel is not accumulated in significant amounts by aquatic organisms (Birge & Black, 1980; Zaroogian & Johnson, 1984). The concentration of nickel in a major carnivorous fish, the lake trout, in New York State, USA, did not increase appreciably with the age of the fish (Birge & Black, 1980). McGeer et al. (2003) assessed bioconcentration factors for nickel in various aquatic organisms (e.g. algae, arthropods, molluscs, fish), based on whole-body metal concentrations and exposure concentrations from the literature. There was no evidence that nickel biomagnifies in aquatic food webs. Two studies in voles and rabbits living on sludge-amended land did not indicate any accumulation of nickel in these herbivores or in the plants they ate (Dressler et al., 1986; Alberici et al., 1989).

The lack of significant bioaccumulation of nickel in aquatic organisms, voles and rabbits indicates that nickel is not biomagnified in the food chain (ATSDR, 2005).

2.5 Biomonitoring studies

Serum nickel levels of 1.5–19 µg/L were found in patients undergoing regular haemodialysis (Hopfer, Fay & Sunderman, 1989; Nixon et al., 1989). Significantly higher serum nickel levels were observed in people exposed non-occupationally from a heavily nickel-polluted area compared with people living in a control area (nickel concentrations in tap water 109 ± 46 µg/L vs 0.6 ± 0.2 µg/L; serum nickel levels 0.6 ± 0.3 µg/L vs 0.2 ± 0.2 µg/L) (Hopfer, Fay & Sunderman, 1989).

Tentative reference values for nickel in serum and urine have been proposed: 0.2 µg/L or lower in serum, and 1–3 µg/L in urine of healthy adults (Templeton, Sunderman & Herber, 1994). After reviewing monitoring data in occupationally exposed workers, Ohashi et al. (2006) determined reference values for nickel in urine among women of the general population of 11 prefectures in Japan. The observed geometric mean for urinary nickel was 2.1 µg/L (range <0.2–57 µg/L), corresponding to 1.8 µg/L (maximum 144 µg/L) after normalization by creatinine excretion. According to representative data on the internal nickel exposure of children aged 3–14 years from the German Environmental Survey (2003–2006), the urinary nickel levels (n = 1576) ranged from <0.5 to 15 µg/L; the geometric mean was 1.26 µg /L (Wilhelm et al., 2013).

2.6 Estimated total exposure and relative contribution of drinking-water

Food is the main source of nickel exposure in the non-smoking, non-occupationally exposed population. According to the United Kingdom Total Diet Study, and assuming a typical adult body weight of 60 kg, the mean nickel exposure from food among individuals aged 19 to adulthood ranges from 0.102 to 0.114 mg/day (97.5th percentile ranging from 0.192 to 0.204 mg/day) (COT, 2014). Recent studies, including a United Kingdom study on vegetarians, indicate that the intake from food is probably less than 0.2 mg/day.

In England and Wales, median and 97.5th percentile concentrations for nickel in drinking-water were 1.36 and 4.63 µg/L respectively (COT, 2018), or only 0.003 and 0.009 mg/day assuming a drinking-water intake rate of 2 L per day. Based on earlier data, water generally contributes 0.005–0.025 mg 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 Union risk assessment for nickel (EU, 2008).

Overall, drinking-water appears to contribute only a minor proportion of daily intake of nickel; however, the proportion of ingested nickel absorbed is greater in drinking-water than in food.

Drinking-water will contribute a higher proportion of daily intake under some circumstances, such as when natural nickel concentrations in source water, particularly groundwater, are elevated or when there is significant input from stainless steel materials or devices, particularly nickel-or chromium-plated fittings such as taps. For nickel in source water, the exposure is potentially long term. In contrast, for nickel- or chromium-plated fittings, exposure is likely to be either shorter or more intermittent, reflecting the variation in the use of first-draw water, which would be likely to result in the highest concentrations.

3 Toxicokinetics and metabolism in animals and humans

3.1 Absorption

Nickel is poorly absorbed from diets. Absorbed nickel is rapidly cleared from serum (IPCS, 1991).

The mechanism for intestinal absorption of nickel is not clear. Iron deficiency increased intestinal nickel absorption in vitro and in vivo, indicating that nickel is partially absorbed by the active transfer system for iron absorption in intestinal mucosal cells (Tallkvist, Wing & Tjälve, 1994). In perfused rat jejunum, saturation of nickel uptake was observed at high concentrations of $NiCl_2$ (Foulkes & McMullen, 1986). Iron concentrations in rat tissues were increased by dietary nickel exposure (Whanger, 1973). Nickel is bound to a histidine complex, albumin and alpha-2-macroglobulin in serum (Sarkar, 1984).

Absorption of soluble nickel compounds from drinking-water is higher than absorption from food. After 24 hours, 10–34% of a single oral dose of water-soluble nickel compounds ($NiSO_4$, $NiCl_2$ or $Ni(NO_3)_2$) was absorbed, whereas less than 2% of a single oral dose of insoluble or scarcely soluble nickel compounds (NiO, Ni, Ni_3S_2 or NiS) was absorbed. It is not known if the animals in this study were fasted before treatment. The highest nickel concentrations were found in the kidneys and lungs; nickel concentrations in the liver were low (Ishimatsu et al., 1995).

Following a 12-hour fast, a volunteer ingested 20 µg/kg bw of ^{61}Ni-enriched nickel as $Ni(NO_3)_2$ in 1 L of water. The serum nickel concentration peaked at 2 hours at 34 µg/L. By 96 hours, 27% of the ingested dose was excreted in the urine (Templeton, Xu & Stuhne-Sekalec, 1994). These findings are consistent with observations of an absorption of 27% ± 17% of a nickel dose (as $NiSO_4$) added to drinking-water in 10 volunteers after a 12-hour fast, versus a mean absorption of 0.7 ± 0.4% when administered in food (Sunderman et al., 1989). Intestinal absorption was only 1% of the given dose when $NiSO_4$ was added to scrambled eggs. The half-time for absorbed nickel averaged 28 ± 9 hours (Sunderman et al., 1989).

Plasma levels of nickel in fasting human subjects did not increase above fasting levels when 5 mg of nickel was added to an American breakfast or a Guatemalan meal rich in phytic acids (Solomons et al., 1982). The same amount of nickel added to water elevated the plasma nickel levels 4- to 7-fold. The absorption of nickel added to milk, tea, coffee or orange juice was significantly less than the absorption of nickel from water.

Two studies carried out to examine the influence of fasting and food intake on the absorption of nickel from drinking-water showed that a dose of 12 µg/kg bw given to fasted males in drinking-water was more rapidly absorbed if the dose was given 30 minutes or 1 hour before a meal of scrambled eggs than if given at the same time. The peak concentration in blood was also 13-fold higher. In a similar experiment in which ^{61}Ni was given to 20 nickel-sensitized women and 20 age-matched controls, there was no difference in nickel absorption and excretion (Nielsen et al., 1999).

3.2 Distribution

Whole-body retention in mice after oral exposure to Ni^{2+} was less than 1% of the administered dose 5 days after exposure (Nielsen, Andersen & Jensen, 1993). Severa et al. (1995) observed an accumulation of nickel in organs of rats orally exposed to nickel in drinking-water at concentrations of 100 mg/L for 6 months. The nickel concentration in liver was 10 times higher in exposed rats than in unexposed rats; in the kidney, the nickel level was only twice as high in exposed rats as in unexposed rats. Nickel levels in the kidney and blood were similar. There was no increase in nickel levels in organs between 3 and 6 months of exposure.

Several reports indicate that transplacental transfer of nickel occurs in animals (IPCS, 1991). Elevated concentrations of nickel were detected in fetuses after intramuscular administration of $NiCl_2$ to pregnant rats. The fetal organ with the highest nickel concentration was the urinary bladder (Sunderman et al., 1978). In human studies, nickel has been detected in fetal tissues at levels similar to the levels found in adults (McNeely, Nechay & Sunderman, 1972; Casey & Robinson, 1978).

3.3 Metabolism

Once absorbed, elemental nickel is not anticipated to undergo any metabolism. The extracellular metabolism of nickel consists of ligand exchange reactions (Sarkar, 1984). In human serum, nickel binds to albumin, L-histidine and alpha-2-macroglobulin. Binding in animals is similar. In humans, rats and bovines, the principal binding locus of nickel to serum albumins is the histidine residue at the third position from the amino terminus (Hendel & Sunderman, 1972, as cited by ATSDR, 2005).

3.4 Elimination

Absorbed nickel is eliminated mainly in the faeces and to a lesser extent in urine (IPCS, 1991). Nielsen et al. (1999) reported that the cumulative median amount of nickel excreted in urine within three days after dosing was 2.26% (1.03–4.71%) when nickel was ingested together with food or mixed into food. Increasing amounts of nickel were excreted in the urine as the interval between intake of water and meal increased, with a cumulative median amount of 25.8% (25.00 ± 11.02) excreted in urine when food was served 4 h prior to ingestion of nickel-containing drinking water. Biliary excretion of nickel subcutaneously administered to rats as

$NiCl_2$ was less than 0.5% of the given dose (Marzouk & Sunderman, 1985). In studying a fatal case of human nickel intoxication, the authors concluded that biliary excretion of nickel was of minor importance in humans (Grandjean, Nielsen & Andersen, 1989). Nickel is also eliminated in the milk of lactating women. In studies reported in the USA, the nickel concentration in breast milk was around 15 µg/kg (EU, 2008).

4 Effects on humans

4.1 Acute effects

A 2½-year-old girl died after ingesting about 15 g of $NiSO_4$ crystals. Cardiac arrest occurred after 4 hours; the autopsy revealed acute haemorrhagic gastritis (Daldrup, Haarhoff & Szathmary, 1983).

Thirty-two industrial workers accidentally drank water contaminated with $NiSO_4$ and $NiCl_2$ (1.63 g of nickel per litre). Twenty workers developed symptoms, including nausea, vomiting, diarrhoea, giddiness, lassitude, headache and shortness of breath. The nickel doses in people who developed symptoms were estimated to range from 7 to 35 mg/kg bw. In most cases, the symptoms lasted for a few hours, but they persisted for 1–2 days in seven cases. Transiently elevated levels of urine albumin, suggesting mild transient nephrotoxicity, were found in two workers 2–5 days after exposure. Mild hyperbilirubinaemia developed 3 days after exposure in two subjects, and elevated levels of blood reticulocytes were observed in seven workers 8 days after exposure. It is known from animal studies that intrarenal injection of nickel increases the renal production of erythropoietin, which may explain the reticulocytosis, and that nickel induces microsomal haem oxygenase activity in liver and kidney, leading to a secondary hyperbilirubinaemia. Serum nickel concentrations ranged from 13 to 1340 µg/L in people with symptoms (Sunderman et al., 1988).

Seven hours after ingesting $NiSO_4$ in drinking-water (nickel level of 50 µg/kg bw), a 55-year-old man developed left homonymous haemianopsia, which lasted 2 hours (Sunderman et al., 1989).

Nickel intoxication in 23 patients receiving haemodialysis was reported (Webster et al., 1980). The dialysate was contaminated by leachate from a nickel-plated stainless steel water heater tank. Symptoms such as nausea, vomiting, headache and weakness occurred rapidly after exposure at plasma nickel concentrations of about 3 mg/L and persisted for 3–13 hours after dialysis.

4.2 Reproductive and developmental effects

An epidemiological study looked at reproductive and developmental effects after occupational exposure in women working in a nickel hydrometallurgy refining plant in Russia. The level of exposure to nickel was estimated to be 0.11–0.31 mg/m^3 in the air, for an employment period of 1–16 years. The study reported 15.6% spontaneous abortions among 290 women working in the plant, compared with an 8.5% incidence in 336 female control workers (Chashschin, Artunina & Norseth, 1994). In the same study, the authors noted a statistically significant increase in structural malformations among offspring born to 356 workers (16.9%) compared with 342 controls (5.8%), and increased relative risks of 6.1 for cardiovascular defects and 1.9 for musculoskeletal defects in the offspring. Heavy manual activity and heat stress of the

exposed women were noted as potential confounders (see also OEHHA, 2012). This study was considered inconclusive by the European Union as a result of flaws in the study design and limited reporting (EU, 2008).

A follow-up register-based cohort study investigated whether pregnant women employed in 1973–1997 at nickel-exposed work areas had an elevated risk of delivering a newborn with a genital malformation (Vaktskjold et al., 2006). The study cohort comprised 23 141 liveborn or stillborn infants from a total of 24 534 deliveries. Exposure was classified into the three categories of background exposure (<10 μg/L), low exposure (10 to <70 μg/L) and high exposure (≥70 μg/L). No adverse effects of maternal exposure to water-soluble nickel were found. (The higher-exposure groups had a smaller sample size.) In a second study, Vaktskjold et al. (2007) reviewed 22 836 births (>27 weeks of gestation) and concluded that occupational exposure to water-soluble nickel during early pregnancy was not associated with an elevated risk of delivering a small-for-gestational-age newborn (defined as a newborn below the 10th percentile birth weight for gestational age in the source population). The risk of spontaneous abortion was not increased after maternal nickel exposure in the same geographical area, based on an adjusted odds ratio (OR) of 1.14 (0.95–1.37) in a case–control study (Vaktskjold et al., 2008a). Another study analysed the incidence of musculoskeletal defects in the offspring in the cohort described above. Among 22 965 births, 304 infants were diagnosed with isolated musculoskeletal defects(s). The authors concluded that, despite the high incidence of defects, there was no apparent association (adjusted OR 0.96; 95% CI 0.76–1.21) with maternal nickel exposure (Vaktskjold et al., 2008b).

Danadevi et al. (2003) examined semen quality of 57 workers who had been exposed to nickel for 2–21 years from a welding plant in south India and 57 controls in relation to blood nickel and chromium concentrations. In 28 workers and 27 control men selected randomly from each study group, blood nickel levels were significantly higher in the workers (123.3 ± 35.2 μg/L) than in the controls (16.7 ± 5.8 μg/L). Sperm concentrations of the workers were 14.5 ± 24.0 million/mL compared with 62.8 ± 43.7 million/mL in the control group. Rapid linear sperm motility was lower in exposed workers than in the controls, and there was a significant positive correlation between the percentage of sperm tail defects and blood nickel concentration in exposed workers. However, the study was limited by the small sample size and possible selection bias. As well, nickel exposure was determined only for a subset of workers using a single measure of nickel blood concentration in the presence of other heavy metals.

Figá-Talamanca & Petrelli (2000) studied the gender ratio among children of male workers in an Italian mint with different levels of exposure to metal fumes of nickel and Cr, depending on their job function (48 in administration, 74 technicians, 31 stampers and 63 founders). They observed a statistically significantly lower proportion of male children in founders compared with workers in administrative roles and the general population. This finding contrasts with the results from a large Danish cohort of more than 10 000 metalworkers where no change in the gender ratio was found in offspring of welders exposed to high levels of chromium and nickel (Bonde, Olsen & Hansen, 1992).

A nested case–control study evaluated the relationship between prenatal nickel exposure and the risk of delivery of preterm low-birthweight (PLBW) infants among pregnant women in Hubei province, China. The study included 102 PLBW cases and 306 matched controls. Conditional logistic regression analysis was used to explore the association between nickel levels and PLBW, as well as the effect of selenium (Se) on this association. A significant

association was observed between higher maternal urinary nickel levels and risk of PLBW (adjusted OR 2.80; 95% CI 1.44–5.44 for the highest tertile), and this association was more apparent among female infants than among male infants. Further analyses indicated that mothers with high urinary nickel and low urinary Se levels had a greater risk for PLBW (adjusted OR 2.87; 95% CI 1.09–7.56). The study indicates that prenatal exposure to nickel is a risk factor for PLBW, and Se might have a modifying effect on this association (Sun et al., 2018).

A longitudinal study investigated prenatal exposure to nickel as a risk factor for pre-term delivery (gestational age < 37 weeks) (Chen et al., 2018). Pregnant women (n = 7,291) were recruited in the longitudinal Healthy Baby Cohort in Wuhan, China. Preterm delivery was associated with statistically significantly higher urinary nickel concentrations (median 7.12 µg/g creatinine; n = 293) compared to full-term delivery (gestational age >/= to 38 weeks) (median 4.98 µg/g creatinine; n = 6,998). The authors concluded that higher maternal urinary nickel concentrations are associated with an increased risk of pre-term delivery.

To explore the association of nickel exposure and occurrence of congenital heart defects (CHD), a case–control study with 490 controls and 399 cases was conducted in China (Zhang et al., 2019). The cases included septal defects, conotruncal defects, right and left ventricular outflow tract obstruction, anomalous pulmonary venous return and other heart defects. The concentrations of nickel in the hair of pregnant woman and foetal placental tissue were measured. Logistic regression analysis was used to explore the relationship between nickel exposure and risk of CHD in the offspring. In the CHD group, the median concentration of nickel in maternal hair was 0.629 ng/mg compared to 0.443 ng/mg in the control group, and the median concentration of nickel in fetal placental tissue was 0.178 ng/mg compared to 0.148 ng/mg in the control group. The increased concentrations of nickel in maternal hair and foetal tissue in the CHD group were both statistically significant when compared to controls. Additionally, when all cases and controls were stratified into three equal groups based on concentration of nickel in maternal hair, the overall risk of CHD was significantly increased among the group with the highest concentrations of nickel in hair (greater than 0.7216 ng/mg) when compared to the group with the lowest concentrations (< 0.4111 ng/mg) (adjusted odds ratio: 1.326; 95% CI: 1.003–1.757; $p < 0.001$).

A study investigated the association between concentrations of nickel in umbilical cord tissues and risk of orofacial clefts(Ni et al., 2018). The median level of nickel in cases of orofacial cleft (38.92 ng/g) was significantly higher than in controls (21.22 ng/g), and umbilical cord nickel concentrations above the median was associated with an elevated oral facial clefts risk of 6.79-fold. Additionally, umbilical cord nickel concentration for cases of orofacial cleft subtypes (cleft lip with cleft palate or cleft lip only) was significantly higher compared to controls ($p < 0.001$).

In the EFSA 2015 assessment, recognizing the uncertainty in the level of exposure to nickel by ingestion, the CONTAM Panel noted that the results of human studies do not support an association between oral exposure to nickel and effects on reproduction and development. However, studies published since the previous opinion (e.g. Chen et al., 2018, Zhang et al., 2019, Ni et al., 2018) suggest that there may be an association between nickel exposure and adverse reproductive and developmental outcomes (EFSA 2020).

4.3 Immunological effects

Allergic contact dermatitis (type IV hypersensitivity) is the most prevalent effect of nickel in the general population (Hostynek, 2006). In the USA, nickel allergic contact dermatitis had an incidence of 14.3% in the 1994–1996 study period, and was on the rise from 10 years before, when the incidence was 10% (Silverberg et al., 2002). Similar figures were reported for the European Union, Asia and the USA (Schnuch et al., 2002), and from a cohort study of 1501 8th grade school children that lasted 15 years, in which nickel sensitization (see below) was observed in 11.8% of the study group (Mortz, Bindslev-Jensen & Andersen, 2013).

Occupational exposure to nickel can cause allergic asthma via type I allergic reactions in which serum from affected individuals shows specific IgE antibodies against serum albumin conjugates (Kusaka, 1993). Very few cases of immediate-contact urticaria to nickel have been reported. Whereas type I immune responses may underlie such conditions, it has also been postulated that nickel may act as a mast cell discharger on a non-immunological basis (Walsh, Smith & King, 2010).

Exposure to nickel through skin or by inhalation may lead to nickel sensitization. A rise in nickel sensitization has been presumed to represent an increased exposure to nickel in the environment – especially from costume jewellery and belt buckles (Silverberg et al., 2002). Consumption of an nickel-rich diet may elicit eczematous flare-up reactions in the skin in sensitized individuals, a phenomenon called systemic contact dermatitis (SCD) or haematogenous contact eczema (Christensen & Möller, 1975; Kaaber, Veien & Tjell, 1978; Cronin, DiMichiel & Brown, 1980; Veien et al., 1983; Hindsén, Bruze & Christensen, 2001; Erdmann & Werfel, 2006; Jensen, Menné & Johansen, 2006; Gangemi et al., 2009). On the other hand, experimental studies have also shown that repeated oral exposure to nickel may diminish sensitization. Sjövall, Christensen & Möller (1987), Santucci et al. (1988) and Bonamonte et al. (2011) reported reduction of nickel contact dermatitis after oral exposure to soluble nickel over a prolonged period.

Systemically induced flares of dermatitis are reported after oral challenge of nickel-sensitive women with 0.5–5.6 mg of nickel as $NiSO_4$ administered in a lactose capsule (Veien, 1989). At the highest nickel dose (5.6 mg), there was a positive reaction in a majority of the subjects; at 0.5 mg, only a few people responded with flares. Responses to oral doses of 0.4 or 2.5 mg of nickel did not exceed responses in subjects given placebos in double-blind studies (Jordan & King, 1979; Gawkrodger et al., 1986).

There are several reports on the effects of diets low or high in nickel, but it is not known whether naturally occurring nickel in food may worsen or maintain the hand eczema of nickel-sensitive patients, mainly because results from dietary depletion studies have been inconclusive (Veien & Menné, 1990). In a single-blind study, 12 nickel-sensitive women were challenged with a supplementary high-nickel diet (Nielsen et al., 1990). The authors concluded that hand eczema was aggravated during days 0–11 after the challenge and that the symptoms were nickel induced. However, in some subjects, the severity of the eczema (i.e. the number of vesicles on the palm of the hand) varied markedly between days 14 or 21 before the challenge period and the start of the challenge period.

Some studies have looked at the effects of prolonged low doses of nickel in reducing sensitization. Oral hyposensitization to nickel was reported after six weekly doses of 5 mg of nickel in a capsule (Sjövall, Christensen & Möller, 1987) or 0.1 ng of $NiSO_4$ daily for 3 years

(Panzani et al., 1995). Cutaneous lesions were improved in eight patients with contact allergy to nickel after oral exposure to 5 mg of nickel weekly for 8 weeks (Bagot et al., 1995). Nickel in water (as $NiSO_4$) was given to 17 of 25 nickel-sensitive women in daily doses of 0.01–0.04 mg/kg bw/day for 3 months after they had been challenged once with 2.24 mg of nickel. Of these women, 14 ended the trial without flare-up, and only three had to stop because of intense worsening of cutaneous manifestations (Santucci et al., 1988). In another study, Santucci et al. (1994) gave increasing oral doses of nickel in water (0.01–0.03 mg/kg bw/day) to eight nickel-sensitive women for up to 178 days. A significant improvement in hand eczema was observed in all subjects after 1 month.

In a study by Nielsen et al. (1999), two groups of 20 fasted female volunteers ingested nickel (characterized as "a stable nickel isotope, ^{61}Ni"), dissolved in drinking-water, at a dose of 12 µg/kg bw. All subjects were diagnosed with hand eczema; the experimental group included nickel-sensitized individuals, whereas the control group included non-sensitized individuals. Nickel exposure did not affect eczema severity in the control group; however, a flare-up of eczema symptoms was reported in nine of the 20 nickel-sensitized individuals. The 12 µg/kg bw dose is similar to the dose tested in a study in which 1 mg nickel (17 µg/kg bw) resulted in a flare-up of dermatitis in an earlier patch test site in two of 10 nickel-sensitive patients (Hindsén, Bruze & Christensen, 2001). The dose of 12 µg/kg bw was considered the acute LOAEL in fasting people on a 48-hour diet with reduced nickel content. A cumulative LOAEL could be lower, but a LOAEL in non-fasting people is probably higher because of reduced absorption of nickel ions when mixed in food.

A meta-analysis of nickel exposure investigations was conducted to provide the best possible estimate of threshold doses of nickel that may cause systemic contact dermatitis in nickel-sensitive people (Jensen, Menné & Johansen, 2006). The authors identified 17 investigations to study the dose relationship of responses to oral exposure to nickel in nickel-sensitive individuals. The reaction rate increased with increasing nickel dose. The results from the two most sensitive groups showed that 1% of these individuals may react with systemic contact dermatitis at normal daily nickel exposure from drinking-water and diet (i.e. 0.22–0.35 mg of nickel). The EFSA CONTAM Panel (EFSA, 2015) noted difficulties with accepting this meta-analysis as a basis for deriving a health-based guidance value for acute exposure to nickel. The authors had excluded some studies that exhibited a clear internal dose–response relationship and had included studies for which no internal dose–response relationship could be assessed (e.g. when only one exposure level had been used in the challenge).

The EFSA CONTAM Panel (EFSA 2015) examined 17 studies reviewed by Jensen, Menné & Johansen (Jensen et al., 2006). Of these, the study by Jensen et al. (2003) showed effects at the lowest doses, with incidences of reactions in 1/10, 4/10, 4/10 and 7/10 people at doses of 0, 0.3, 1 or 4 µg nickel per person, respectively. This study involved 40 nickel-sensitive individuals (39 female, 1 male) who were positive in patch testing to nickel. The patients were exposed to nickel sulfate hexahydrate ($H_{12}NiO_{10}S$) in lactose capsules as a single bolus in the morning after a 12-hour fasting period. No other dietary intervention was conducted. Each individual was exposed to nickel in three dose groups or placebo (lactose) in the control group, in addition to nickel exposure from the normal diet in this study; exposure from diet was not estimated. One day after the oral exposure, the status of the skin area previously exposed to patch testing with nickel was scored for objective clinical responses. The EFSA CONTAM Panel identified a LOAEL of 0.3 mg/person, the lowest dose tested from this study. This LOAEL corresponds to 4.3 µg/kg bw, assuming a body weight of 70 kg (EFSA 2020).

4.4 Genotoxicity and carcinogenicity

Nickel species hazardous to humans were investigated by the International Committee on Nickel Carcinogenesis in Man, which analysed 10 previously studied cohorts of men occupationally exposed to nickel (ICNCM, 1990). The Committee concluded that occupational exposure to sulfidic and oxidic nickel at high concentrations causes lung and nasal cancers. There was no correlation between exposure to metallic nickel and cancer in the lung or nose. Soluble nickel exposure increased the cancer risk and may also increase the risk associated with exposure to less soluble nickel compounds. The Committee also concluded that there was no substantial evidence that nickel compounds produce cancers other than in the lung or nose in occupationally exposed people.

In relation to health risks, inhalation is an important route of exposure to nickel and its salts. Nickel and nickel compounds have been classified by the International Agency for Research on Cancer (IARC, 2012) as human carcinogens causing cancers of the lung, nasal cavity and paranasal sinuses after inhalation. There is currently no consistency in the epidemiological data to suggest that nickel compounds cause cancer at additional sites or by additional routes. Moreover, no tumours have been found in oral carcinogenicity studies in experimental animals. Therefore, the EFSA CONTAM Panel considered it unlikely that dietary exposure to nickel results in cancer in humans (EFSA 2020).

5 Effects on experimental animals and in vitro systems

5.1 Acute exposure

Effects of nickel on kidney function, including tubular and glomerular lesions, have been reported by several authors after parenteral administration to rabbits and rats of high nickel doses of 1–6 mg/kg bw (IPCS, 1991).

5.2 Short-term exposure

Body weight gain, and plasma haemoglobin and alkaline phosphatase were significantly reduced, compared with controls, in weanling rats exposed to nickel (as nickel acetate) at concentrations of 500 or 1000 mg/kg/day in the diet (equivalent to 25 or 50 mg/kg bw/day) for 6 weeks (Whanger, 1973). No effects were observed in rats exposed to 100 mg/kg in the diet (equivalent to 5 mg/kg bw/day).

In a 13-week study in which Sprague–Dawley rats were given nickel at doses of 0, 44.7, 111.75 or 223.5 mg/L in drinking-water as $NiSO_4$ (corresponding to nickel doses of 0, 4.5, 11.2 or 22.4 mg/kg bw/day), no clinical signs of toxicity were observed. Final mean body weights were unaffected, except for a decrease in the top dose group compared with controls. Lymphocyte subpopulations (T- and B-cells) were induced at the lower doses but suppressed at the highest dose. No gross or microscopic changes were seen in any of the tissues examined (Obone et al., 1999). According to the data presented in the previous EFSA assessment (EFSA, 2015), the major effects observed in the short-term repeated-dose toxicity studies following oral administration were decreased body weight, changes in organ weight (liver and kidneys), and histopathological changes in the liver and the kidney. The short-term toxicity studies published since the previous assessment have reported similar effects. The effects of nickel exposure on bone and on gut microbiota were also discussed in the more recent EFSA (2020) assessment.

5.3 Long-term exposure

5.3.1 Systemic effects

Rats (25 per sex per dose) were exposed to nickel (as $NiSO_4$) in the diet at doses of 0, 100, 1000 or 2500 mg/kg diet (equivalent to 0, 5, 50 or 125 mg/kg bw/day, estimated using the dose conversion factors [IPCS, 2009]) for 2 years (Ambrose et al., 1976). Body weight was significantly reduced at 1000 and 2500 mg/kg diet – by more than 30% at the highest dose. However, there were indications that decreased food consumption might explain the decreased body weight, particularly at 2500 mg/kg diet. Survival was overall very poor (survival rates were 62–72%), especially in the male control and 2500 mg/kg diet groups. In females at 1000 and 2500 mg/kg diet, mean relative liver weights were decreased by about 20% and mean relative heart weights were increased by about 30% compared with the control group, in the absence of associated gross or histological pathology. The highest nickel concentrations were found in the kidneys. Although the study authors did not report a NOAEL, it can be considered as 5 mg/kg bw/day. However, the study does not meet current guidelines for long-term studies, mainly because of the low survival rate.

In a 2-year study, dogs (three per sex per dose) were exposed to nickel at doses of 0, 100, 1000 or 2500 mg/kg diet (equivalent to 0, 2.5, 25 or 62.5 mg/kg bw/day, estimated using the dose conversion factors [IPCS, 2009]). In the 2500 mg/kg diet group, decreased weight gain and food consumption, higher kidney to body weight and liver to body weight ratios, and histological changes in the lung were observed. The NOAEL was 25 mg/kg bw/day (Ambrose et al., 1976). This study may have been confounded by reduced palatability, since all high-dose dogs vomited during the first 3 days.

Increased relative kidney weight was observed in rats exposed to nickel (as $NiSO_4$) in drinking-water at a daily dose of about 7 mg/kg bw for up to 6 months (Vyskocil, Viau & Cizková, 1994). Excretion of albumin in urine was increased in females, without changes in total protein, beta-2-microglobulin, *N*-acetyl-beta-D-glucosaminidase or lactate dehydrogenase in urine.

5.3.2 Neurological effects

No experimental animal studies designed specifically to assess functional neurological effects after nickel exposure were identified.

5.3.3 Reproductive and developmental effects

Reduced numbers of live pups and reduced fetal body weights were observed after rat dams received a single intramuscular dose of $NiCl_2$ (a nickel dose of 16 mg/kg bw) on gestation day 8 or Ni_3S_2 (a nickel dose of 80 mg/kg bw) on gestation day 6. No congenital anomalies were found in the fetuses (Sunderman et al., 1978).

Velazquez & Poirer (1994) and ATSDR (2005) described a two-generation study in rats. $NiCl_2$ was administered in drinking-water at concentrations of 0, 50, 250 or 500 mg/L (equal to doses of nickel of 0, 7, 31 or 52 mg/kg bw/day) from 90 days before breeding. Food and water intakes were lower in the exposed animals, suggesting palatability issues. Along with changes in maternal body weight and liver weight at the 500 mg/L dose level in the P_0 generation, there

was a dose-related decrease in live litter size and pup weight, and increased neonatal mortality. In the F_1 generation, there was dose-related mortality at 3–7 weeks of age at the 250 and 500 mg/L dose levels. For the F_1 matings, there were also dose-related decreases in live litter size, and increased mortality per litter in the 500 mg/L group. The NOAEL for nickel in this study was 7 mg/kg bw/day; however, problems related to palatability, and sporadically elevated room temperature (6 °C higher than normal during certain gestation and early postnatal days) and lower humidity confound the interpretation.

Female Long–Evans rats were exposed to nickel as $NiCl_2$ in drinking-water for 11 weeks before mating, and during two successive gestation periods (G1 and G2) and lactation periods (L1 and L2) at concentrations of 0, 10, 50 or 250 mg/L (equal to nickel at 0, 1.3, 6.8 or 31.6 mg/kg bw/day) (Smith et al., 1993). Dams drinking water containing nickel at 31.6 mg/kg bw/day consumed less liquid and more food per kg bw than did controls. Maternal weight gain was reduced during G1 in the mid- and high-dose groups. There were no effects on pup birth weight, and weight gain was reduced only in male pups from dams in the mid-dose group. The proportion of dead pups per litter was significantly elevated at the high dose in L1, and at the low and high doses in L2; an increase at the middle dose in L2 approached statistical significance. The response in both experimental segments was dose related. The number of dead pups per litter was significantly increased at each dose in L2. The number of litters with dead pups and the total number of dead pups per litter in the control group were less in L2 than in L1. Plasma prolactin levels were reduced in dams at the highest dose level 1 week after weaning of the second litter. The authors concluded that 1.3 mg/kg bw/day represented the LOAEL; this was conservative, given the variations in response between the successive litters.

A range-finding study was carried out for a two-generation study investigating the potential for reproductive toxicity of nickel (SLI, 2000; EU, 2008). The range-finding and definitive studies for the rat two-generation reproduction study of $H_{12}NiO_{10}S$ were conducted using gavage as the route of exposure, due to palatability problems with nickel in drinking-water and bioavailability problems with nickel in food. The range-finding study was designed in two parts. The first part was a dose–response probe using small numbers of animals and $H_{12}NiO_{10}S$ exposures of 0, 5, 15, 25, 50, 75 or 150 mg/kg bw/day. (Note that the lower 95% confidence limit for lethality from $H_{12}NiO_{10}S$ is 170 mg/kg bw/day.) Lethality was observed at the 150 mg/kg bw/day exposure level.

The second part of the range-finding study (i.e. a one-generation reproductive toxicity study) used $H_{12}NiO_{10}S$ exposures of 0, 10, 20, 30, 50 or 75 mg/kg bw/day. These doses had no effect on parental survival, growth, mating behaviour, copulation, fertility, implantation or gestation length. However, evaluation of post-implantation/perinatal lethality among the offspring of the treated parental rats (i.e. the number of pups conceived minus the number of live pups at birth) showed statistically significant increases at the 30–75 mg/kg bw/day exposures, and more questionable increases at the 10 and 20 mg/kg bw/day levels. The decrease in perinatal survival evident in the one-generation range-finding study was anticipated from previous literature reports. The goal of the range-finding studies was to refine the NOAEL for this end-point. The one-generation study also showed that the mean live litter size was significantly decreased at the 75 mg/kg bw/day level and was lower than historical controls at or above 30 mg/kg bw/day.

Based on the results of the one-generation study, $H_{12}NiO_{10}S$ exposure levels of 1, 2.5, 5.0 and 10 mg/kg bw/day were administered by gavage to five groups of male and female rats in the definitive two-generation study. These dose levels were chosen to ensure that the study would have a measurable NOAEL for the post-implantation/perinatal lethality variable. Males of the

parental (F_0) generation were dosed during growth and for at least one complete spermatogenic cycle, to elicit any possible adverse effects on spermatogenesis. Females of the F_0 generation were dosed during growth and for several complete estrous cycles, to elicit any possible adverse effects on estrus. The test substance was administered to F_0 animals during mating, during pregnancy and through the weaning of their first-generation (F_1) offspring. At weaning, exposure was continued to F_1 offspring during their growth into adulthood, mating and production of an F_2 generation, and until the F_2 generation was weaned. Clinical observation and pathological examination were performed for signs of toxicity, with special emphasis on effects on the integrity and performance of the male and female reproductive systems, and on the growth and development of the offspring. The results from the two-generation study indicated that the NOAEL was 5 mg/kg bw/day for $H_{12}NiO_{10}S$ or 1.1 mg/kg bw/day for nickel in adults and offspring. This was based on the effects observed at the highest $H_{12}NiO_{10}S$ dose of 10 mg/kg bw/day (a nickel dose of 2.2 mg/kg bw/day), including on post-implantation/perinatal lethality (SLI, 2000; EU, 2008).

In a three-generation study in rats in which animals were administered nickel as $NiSO_4$ in the diet at levels of nickel of 250, 500 or 1000 mg/kg diet (equivalent to 12.5, 25 or 50 mg/kg bw/day), a higher incidence of stillborns in the first generation was observed compared with the control group (Ambrose et al., 1976). Body weights were decreased in weanlings at 1000 mg/kg diet in all generations. The number of pups born alive per litter and the number of pups weaned per litter were progressively fewer with increasing nickel dose, but no statistical analysis of the results was presented. Decreased weanling body weight was a clear-cut effect in the 1000 mg/kg diet dose group. No teratogenic effects were observed in any generation at any dose level. No histological lesions were observed in the third generation at weaning.

Decreased litter sizes were observed in a three-generation study in rats administered nickel in drinking-water at 5 mg/L, corresponding to 0.2 mg/kg bw/day (Schroeder & Mitchener, 1971). This study predates current guidelines for multigeneration reproduction toxicity studies and has several limitations, including limited reproductive end-points assessed, only one exposure dose tested, and only one breeding pair used for the parent generation.

Alterations in milk composition were observed in lactating rats exposed to four daily subcutaneous injections of nickel at doses of 3–6 mg/kg bw (Dostal et al., 1989). Liver weights were decreased in pups whose dams received 6 mg/kg bw. These findings may explain the effects seen on litter size and body weights of the pups in the studies described above.

In a study in which $NiCl_2$ was administered to male mice in pellets incorporated in the feed to give a dose of 10 mg/kg bw/day for 3, 6, 9 or 12 weeks, significant morphometric changes in the histology of the testis were reported. However, the study had a number of uncertainties that require confirmation (Toman et al., 2012).

5.3.4 Genotoxicity and carcinogenicity

Nickel compounds are generally inactive in bacterial mutation assays but active in mammalian cell systems (IPCS, 1991). However, nickel-induced responses were concluded to be secondary to cell toxicity in all gene mutation studies in mammalian cells.

Chromosomal gaps, deletions and rearrangements, DNA–protein cross-links and sister chromatid exchanges in response to nickel are reported in mammalian systems, including

human cell systems. Chromosomal aberrations occur in all chromosomes, particularly in the heterochromatic centromeric regions (IPCS, 1991; Rossman, 1994).

In several experimental systems, nickel ions have been shown to potentiate the effects of other mutagenic agents. This may be explained by the capacity of nickel to inhibit DNA repair (Lynn et al., 1994; Rossman, 1994).

The genotoxicity of nickel compounds has been reviewed by Toxicology Excellence for Risk Assessment (TERA, 1999) and as part of the European Union risk assessment (EU, 2008). Most studies relate to water-soluble compounds. TERA (1999) concluded that "evidence for genotoxicity is mixed, although water soluble nickel compounds have been generally consistent in inducing effects in certain kinds of mammalian assays, particularly mutagenic responses and DNA damage in vitro, chromosomal effects including aberrations and sister-chromatid exchanges in vitro and in vivo, and carcinogenic transformation of mammalian cells in vitro. Responses in many of these assays were weak and occurred at toxic doses".

A number of studies have been conducted on the carcinogenicity of nickel compounds in experimental animals (IARC, 1990; Aitio, 1995). Generally, tumours are induced at the site of administration of the nickel compound. For instance, several nickel compounds induced injection-site sarcomas (Sunderman, 1984). A marked variation in the incidence of injection-site sarcomas between different strains of mice has been reported (Rodriguez et al., 1996).

Only a limited number of studies have looked at carcinogenic effects after oral exposure to nickel compounds. The incidence of tumours was no higher in rats exposed to drinking-water containing nickel at 5 mg/L throughout their lifetime than in control rats (Schroeder, Mitchener & Nason, 1974). As well, no difference in tumour incidence was observed in a lifetime study in rats exposed to nickel in the feed at 5, 50 or 125 mg/kg bw/day compared with controls (Ambrose et al., 1976). However, a high death rate and lack of information on cause of death mean that this study is of minor value in evaluating carcinogenicity after oral exposure to nickel. A similar 2-year study in dogs also revealed no increase in tumours (Ambrose et al., 1976).

A carcinogenicity study in which Fischer 344 rats were dosed daily with $NiSO_4$ ($6H_2O$) at 10, 30 or 50 mg/kg bw/day by oral gavage for 104 weeks did not produce an exposure-related increase in any common tumour type or any increase in rare tumours (Heim et al., 2007).

5.4 Mode of action

Nickel can cross-link amino acids to DNA, lead to formation of reactive oxygen species and mimic hypoxia. These changes may activate some signalling pathways and subsequent transcription factors, and eventually alter gene expression and cellular metabolism (Forgács et al., 2012).

The EFSA (2020) CONTAM Panel concluded that oxidative stress and an elevation of reactive oxygen species (ROS) are involved in the reproductive toxicity, genotoxicity, immunotoxicity and neurotoxicity of nickel. In addition to ROS-mediated toxicity, EFSA (2020) suggested that nickel might interfere with iron homeostasis via competitive inhibition of the transport of divalent iron into cells via DMT1, as well as competitive inhibition of iron binding sites on prolyl hydroxylases (enzymes that modify hypoxia inducible factor-1a (HIF-1a)) (EFSA 2020).

Interactions of metal ions with proteins and the role of immune responses have been reviewed (Martin, Merfort & Thierse, 2006). There is evidence that the combination of nickel with circulating or tissue protein gives rise to antigen-specific responses, and thus nickel can act as a contact allergen to cause sensitization. The antigens are taken up by antigen-presenting cells that migrate to draining lymph nodes, resulting in activation of nickel-specific T-lymphocytes. Contact sensitivity is expressed as either type I or type IV hypersensitivity, mediated by reagins and allergen-specific T-lymphocytes, leading to a wide range of cutaneous eruptions following dermal or systemic exposure. An alternative, but not mutually exclusive, hypothesis is that the metal interferes with the antigen recognition step of the immune response – that is, it binds to major histocompatibility complex (MHC) and/or MHC-bound peptides and T-cell receptors, leading to activation of nickel-specific T-cells (EFSA, 2015).

The EFSA (2020) assessment reviewed additional studies published more recently than the earlier EFSA (2015) assessment, which support the hypothesis that the binding of nickel to proteins is responsible for the induction of specific immune responses, leading to allergic reactions. Specifically, these studies suggest that nickel induces inflammatory reactions through toll-like receptors and NF-κB signalling pathways, which may contribute to allergic reactions and immunotoxicity (EFSA, 2020). The CONTAM panel also suggested these mechanisms may lead to apoptosis and reduced production of immunoglobulins which may have an adverse impact on host resistance. Although these effects are primarily associated with dermal exposure, oral exposure to nickel may cause flare-up reactions in already sensitised individuals (EFSA, 2020).

5.5 Other effects

With respect to the immune system, nickel salts affect the T-cell system and suppress the activity of natural killer cells in rats and mice (IPCS, 1991). Mitogen-dependent lymphocyte stimulation was inhibited in human lymphocytes (Sikora & Zeromski, 1995) and in spleens of mice exposed to nickel (IPCS, 1991). Dose-related decreased spleen proliferative response to lipopolysaccharide was observed in mice exposed to $NiSO_4$ in drinking-water for 180 days. At the lowest dose of nickel (44 mg/kg bw/day), decreased thymus weight was observed, but there was no nickel-induced immunosuppression of NK cell activity or response to T-cell mitogens.

Parenteral administration of nickel to rabbits, chickens and rats, and oral administration of nickel to rabbits induced hyperglycaemia. In rats, it reduced the levels of prolactin releasing factor (IPCS, 1991).

The myeloid system was affected – that is, there was a decrease in bone marrow cellularity and dose-related reductions in the bone marrow proliferative response – when mice were exposed to $NiSO_4$ in drinking-water at doses of nickel of 0, 44, 108 or 150 mg/kg bw/day for 180 days (Dieter et al., 1988). The LOAEL for nickel in this study was 44 mg/kg bw/day.

6 Overall database and quality of evidence

6.1 Summary of health effects

In assessing health hazards and potential risk from nickel exposure in drinking-water, it is appropriate to consider only data relating to water-soluble nickel salts, which will reflect the toxicity of the nickel ion.

In humans, oral exposure to nickel was associated with effects on the gastrointestinal, haematological, neurological and immune systems. Gastrointestinal and neurological symptoms were the most commonly reported following acute exposure.

In experimental animals, oral ingestion of soluble nickel salts resulted in a wide range of adverse effects, including nephrotoxicity, hepatotoxicity and metabolic effects. Nickel can cross the placental barrier and affect the developing embryo or fetus. Prenatal and perinatal mortality were increased in the offspring of pregnant rats ingesting nickel salts. These adverse effects occur at the lowest doses. The EFSA CONTAM Panel identified reproductive and developmental toxicity as the critical effect for the risk characterisation of chronic oral exposure to nickel (). Recent human studies suggest an association between nickel exposure and adverse reproductive and developmental outcomes (EFSA 2020). The most reliable dose–response information for reproductive and developmental effects was identified in a one-generation dose-range-finding study performed with nickel sulfate hexahydrate in rats (SLI, 2000a) and in the subsequent main two-generation study (SLI, 2000b). The incidence of litters with post implantation loss per treatment group was identified as the relevant and sensitive endpoint for the chronic dose–response assessment (EFSA, 2020).

Exposure to nickel through skin or by inhalation may lead to nickel sensitization. Whereas oral exposure to nickel is not known to lead to sensitization, oral absorption of nickel can elicit eczematous flare-up reactions in the skin (SCD) in nickel-sensitized individuals. These reactions may develop following a single oral exposure to nickel salts. Several studies analysing SCD elicited in nickel-sensitive humans after acute oral exposure to nickel were identified as suitable for an acute dose–response analysis.

6.2 Quality of evidence

Several kinetic studies in humans and experimental animals indicate that oral absorption of soluble nickel species is more efficient when administration is via drinking-water or other beverages under fasting conditions than via solid food (see section 3.1). There is uncertainty in the systemic absorption rate in the key studies identified to derive acute and chronic reference values. In these studies, nickel was administered via gavage using an aqueous solution as vehicle in the rat, or via drinking-water or lactose capsules under fasting conditions in human volunteers.

From the identified chronic exposure studies, it is appropriate to calculate $BMDL_{10}$ values for reproductive and developmental toxicity based on data from a well-conducted two-generation study in rats using post-implantation loss in the F_0/F_1 generation per litter as the most suitable end-point (SLI, 2000; EFSA, 2020). This end-point could be analysed using aggregate data such as the incidence of litters with post-implantation loss per treatment group, or using the raw individual data on the offspring (presence or absence of an effect occurring between implantation and birth).

Observations in humans showed toxicity of nickel at very high doses after accidental or intended oral, occupational or other intoxication. Epidemiological data from well-conducted studies on human dietary exposure to nickel are limited; however, several case-control and longitudinal studies suggest an association between nickel exposure and adverse reproductive and developmental outcomes. Additionally, although studies in humans who were primarily exposed to nickel via inhalation in occupational settings are suggestive of carcinogenic

potential in the lungs and nose, these effects are of limited relevance to drinking-water exposure.

7 Practical aspects

7.1 Analytical methods and achievability

The two most commonly used analytical methods for nickel in water are atomic absorption spectrometry and inductively coupled plasma atomic emission spectrometry. Flame atomic absorption spectrometry is suitable in the range of 0.1–10 mg/L (ISO, 1986, reaffirmed in 2017). Inductively coupled plasma atomic emission spectrometry can be used for the determination of nickel with a limit of detection of about 10 µg/L (ISO, 1996). Methods for the analysis of nickel approved by the United States Environmental Protection Agency include inductively coupled plasma atomic emission spectrometry, inductively coupled plasma mass spectrometry, atomic emission spectroscopy and graphite furnace atomic emission spectroscopy. These methods have limits of detection of 0.5–5 µg/L (US EPA, 1994a,b,c, 2003).

7.2 Source control

Nickel can be found in drinking-water as a result of its presence in alloys used in drinking-water contact applications such as stainless steel, or through nickel or chromium plating of taps. It is also present in water sources, usually as a consequence of dissolution from naturally occurring nickel-bearing strata in groundwater. In the first two cases, the most important means of control is by product specifications delivered through an appropriate certification scheme for materials in contact with drinking-water. Consumers should flush chromium- or nickel-plated taps before using the water, particularly after periods of stagnation.

7.3 Treatment methods and performance

Conventional surface water treatment, comprising chemical coagulation, sedimentation and filtration, can achieve 35–80% removal of nickel, depending on a number of factors including the coagulant dosage, the age of the activated carbon and pH (Zemansky, 1974; Hunter, Stephenson & Lester, 1987; Duguet & Rizet, 1996; Maleki, Roshani & Karakani, 2005). Better nickel removal may occur with waters containing high concentrations of humic substances (Doig & Liber, 2007); for waters low in solids, addition of powdered activated carbon can improve nickel removal (Welté, 2002). Increasing pH and the presence of high turbidity both favour nickel removal. The optimum pH for removal on activated carbon was reported to be pH 8 (Duguet & Rizet, 1996). However, other studies have reported that nickel is rather poorly adsorbed on activated carbon (Seco et al., 1997; Rosińska and Dąbrowska, 2016).

Effective removal of nickel from groundwater can be achieved using chelating ion-exchange resins (Stetter, Dördlemann & Overath, 2002). Specialized ion exchange resins can achieve 83.5–90% nickel removal (aarama & Lehto, 2003; Demirbas et al., 2005). Various adsorbents could potentially be used to remove nickel from groundwater (Duguet & Rizet, 1996; Welté, 2002).

8 Conclusion

8.1 Derivation of the guideline value

The reassessment of the risk posed by nickel in drinking-water supports maintaining the guideline value of 70 µg/L. The reassessment takes into account improved science and methods, including a meta-analysis of epidemiological data and an updated BMD approach that enabled an improved determination of a POD for chronic oral exposure. The reassessment also identified weaknesses in the original study used to derive a guideline value (Nielsen et al., 1999, WHO, 2005). Although this study no longer forms the basis for the guideline value, the guideline value remains the same.

The critical effect for the risk characterization of chronic oral exposure to nickel is reproductive and developmental toxicity. EFSA (2020) derived a $BMDL_{10}$ for nickel of 1.3 mg/kg bw, based on the incidence of litters with post-implantation loss in rat dams. The BMD modelling was performed on data from a dose range-finding one-generation study and on data from a subsequent two-generation study (SLI, 2000), and was conducted according to updated BMD guidance (EFSA, 2017). The EFSA CONTAM Panel noted that the use of individual animal data from both studies provided the most robust results. Applying a BMR of 10%, using model averaging and using the study as covariate, the resulting $BMDL_{10}$ for post-implantation loss of 1.3 mg /kg bw per day for the F0 and F1 data of the two-generation study was selected as a point of departure.

The well-conducted two-generation study in rats is a key study for derivation of a health-based value, because inadequate quantitative data are available from human studies of chronic reproductive or developmental effects. The application of an uncertainty factor of 100 (10 to account for interspecies differences and 10 to account for intraspecies variation) to the $BDML_{10}$ of 1.3 mg /kg bw per day gives a tolerable daily intake (TDI) of 13 µg/kg bw/day. Drinking-water intake contribution to the total daily intake appears to be minor. The contribution of drinking water to the mean dietary exposure in the total EU population was rather low (up to 3% in infants) (see Section 2.6). However, the nickel absorption from drinking-water is greater than in food; data indicate that a mean of 25-27% of the administered nickel dose is absorbed when exposure occurs via drinking-water versus a mean of 0.7-2.5% when exposure occurs via food (EFSA 2020 and see section 3.1). Therefore, the default allocation factor of 20% (the floor value) is appropriate for derivation of the health-based value for drinking-water. The health-based value of 80 µg/L (13 µg/kg bw/day × 60 kg bw, with water consumption of 2 L/day) is protective of chronic systemic toxicity.

For acute toxicity, the SCD elicited in nickel-sensitive humans after exposure to nickel through water is the most sensitive and critical effect. Most studies had small sample sizes and were case–control or volunteer studies, with nickel-sensitive patients orally exposed to 0.3–5 mg of nickel. These human studies support a dose-related response after low-dose exposures. EFSA CONTAM Panel used both Gawkrodger et al. (1986) and Jensen et al. (2003) reported the incidence of flare-up reactions together with the development of new physical signs for benchmark dose modelling. Because the populations studied by both research groups are comparable (based on comparison of age, sex, type of exposure and region where the study was conducted). Using model averaging, the resulting $BMDL_{10}$ - $BMDU_{10}$ interval for the incidence of clinically cutaneous reactions was 0.0124–2.43 mg nickel/person. However, the large BMDL–BMDU interval and that $BMDL_{10}$ of 0.0124 mg nickel/person is outside the dose

range. The large uncertainty in the BMD can be related to the small group size even though several dose groups were used in this case (EFSA 2020). Therefore, a GV for acute effects could not be derived, and the LOAEL of 4.3 µg nickel/kg bw was selected as a reference point for MOE evaluation. Comparison of the mean UB acute dietary exposure to the LOAEL results in MOE values that range from 0.3 to 2.3 across dietary surveys. EFSA CONTAM Panel concluded that the calculated MOEs raise a health concern for young age groups and also for nickel-sensitised individuals. For example, if nickel-sensitised individual intakes a specific food containing high nickel content, the SCD may be elicited. Bioavailability of nickel under fasted conditions is higher compared to the ingestion with food. Therefore, a scenario was elaborated to estimate the dietary exposure when drinking water containing the chronic health-based concentration (80 µg/L) of nickel under fasted conditions. The acute exposure from a glass of tap water (c.a. 200 ml) was 0.26 µg/kg bw and the MOE is about 16. Considering that the SCD elicited in the Jensen et al. (2003) study was associated with a bolus exposure with higher concentration of nickel under fasted conditions, in contrast to the intermittent nature of a normal drinking-water exposure scenario, the MOE value for the acute scenario will be low health concern. Daily drinking of the water at the chronic health-based value concentration (80 µg/L) of nickel therefore does not raise a significant acute nor long term health concern.

This updated risk assessment supports the GV of 70 µg/L as protective of health. Its achievability is further supported by available source control measures, current treatment technologies, and measurability by analytical methods. Considering these factors and that the revised HBV (80 ug/L) is only slightly higher than the previous GV (70 ug/L), and when factoring in the imprecision inherent in risk assessment procedures, this difference is not judged significant enough to warrant a minimal relaxing of the GV and the GV is therefore retained at 70 ug/L. This also would avoid triggering unnecessary revision of national drinking-water regulations and standards.

8.2 Considerations in applying the guideline value

The GV is based on the most sensitive effects of reproductive and developmental toxicity in rats. Some related toxicological effects were suggested in human studies. From the point of view of protection of chronic health effects, the GV of 80 µg/L would be prophylactic. However, little information is available about daily nickel consumption in humans, especially in nickel-sensitive patients. Furthermore, the study used for the acute GV derivation did not consider the contribution of dietary exposure in the estimation of the nickel doses tested in human volunteers. Because the major source of nickel in drinking-water results from leaching from stainless steel devices or nickel or chromium plated taps used in plumbing, flushing the tap before drinking is recommended for nickel-sensitive patients. As nickel is usually found in drinking-water at concentrations below the GV, monitoring and inclusion in drinking-water regulations and standards would usually only be necessary if there were indications that a specific pollution or problem might exist. The most important means of control is by product specifications delivered through an appropriate certification scheme for materials in contact with drinking-water.

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