Nickel in Drinking-water

Draft Background document for development of WHO Guidelines for Drinking-water Quality

26 September 2019
Preface

To be updated by WHO Secretariat
Acknowledgements

The first draft of the background document on nickel in drinking-water for the development of the WHO Guidelines for Drinking-water Quality was prepared by Dr Akihiko Hirose of the National Institute of Health Sciences of Japan.

To be updated by WHO Secretariat
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1.0 EXECUTIVE SUMMARY

Nickel (Ni) is a naturally-occurring element. Food is the dominant source of Ni exposure in the non-smoking, non-occupationally exposed population. The primary source of Ni in drinking-water is leaching from metal alloys in contact with drinking-water. Toxicity data for water-soluble Ni salts are the most relevant to assessing potential health risks from Ni exposure in drinking-water. Human oral exposure to Ni is primarily associated with gastrointestinal and neurological symptoms after acute exposure and exposure through skin or by inhalation may lead to Ni sensitization. Whereas oral exposure to Ni is not known to lead to sensitization, oral absorption of Ni is able to elicit eczematous flare-up reactions in the skin in Ni-sensitized individuals. The GV of 40 µg/L for Ni is the same whether based on the most sensitive adverse effect from experimental animal studies or based on SCD in Ni-sensitive patients. The most sensitive effects in experimental animal studies were reproductive and developmental toxicity in rats, recognizing that no related toxicological effects were demonstrated in human studies. Individuals sensitised to Ni through dermal contact and who have allergic contact dermatitis may develop eczematous flare-up reactions in the skin (SCD) from single oral exposure to Ni salts. Since systemic Ni absorption via drinking-water may be at least 10 times more than that via food, very low levels of Ni in drinking-water may cause SCD in Ni-sensitive patients, such as those with systemic contact dermatitis via Ni exposure from daily food intake. As the major source of Ni in drinking-water results from leaching from stainless steel devices or materials used in water supply systems, flushing the tap before drinking is recommended for Ni-sensitive patients.

2.0 GENERAL DESCRIPTION

2.1 Identity

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

2.2 Physicochemical properties

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<tr>
<td>Specific density</td>
<td>8.90 g/cm³</td>
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<tr>
<td>Melting point</td>
<td>1555 °C</td>
</tr>
<tr>
<td>Boiling point</td>
<td>2837 °C</td>
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Ni usually has two valence electrons, but oxidation states of +1, +3, or +4 may also exist. Metallic Ni 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 Ni. Several Ni salts, such as the acetate, chloride, nitrate, and sulfate, are soluble in water, whereas carbonates and hydroxides are far less soluble and sulfides, disulfides, subsulfides, and oxides are practically insoluble in water. Alloys of Ni containing more than 13% chromium are to a high degree 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).

Ni oxide (NiO) has a black crystalline form (Antonsen, 1981) with a Ni content of 76–77% compared with 78.5% for the more stable, green NiO. Ni ammonium sulfate, NiSO₄, NiCl₂, and Ni(NO₃)₂ usually exist as hexahydrates, while Ni acetate, Ni cyanide, and Ni sulfamate are in the form of a tetrahydrate (ATSDR, 2005).
2.3 Organoleptic properties
Ni and its compounds have no characteristic odor or taste. Taste or odor thresholds for Ni compounds in water were not identified (ATSDR, 2005).

2.4 Major uses and sources
Ni may be present in groundwater as a consequence of dissolution from Ni ore-bearing rocks. The primary source of Ni in drinking-water is leaching from metals in contact with drinking-water, such as from pipes and fittings.

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

Ni is used mainly in the production of stainless steels, non-ferrous alloys, and super alloys. Other uses of Ni and Ni salts are in electroplating, as catalysts, in Ni–cadmium batteries, in coins, in welding products, and in certain pigments and electronic products (IARC, 1990). It is estimated that 8% of Ni is used for household appliances (IPCS, 1991). Ni is also incorporated in some food supplements, which can contain several micrograms of Ni per tablet (EU, 2008).

3.0 ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

3.1 Water
Ni occurs predominantly as the ion Ni(H2O)6²⁺ in natural waters at pH 5–9 (IPCS, 1991). Complexes with ligands, such as hydroxide (OH⁻), sulfate (SO₄²⁻), bicarbonate (HCO₃⁻), chloride (Cl⁻), and ammonia (NH₃) are formed to a minor degree in this pH range. Ni present as a consequence of leaching from Ni-plated fittings is expected to be in a similar form.

Ni 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 Ni in the soil and thus might increase Ni concentrations in groundwater (IPCS, 1991). In groundwater with a pH below 6.2, Ni concentrations up to 980 µg/L have been measured (RIVM, 1994).

In Canada, in surveys of drinking-water supplies conducted between 1985 and 1988 in Northern Alberta and the Atlantic Provinces, the mean concentrations ranged from 2.1 to 2.3 µg/L and from 0.2 to 7.2 µg/L in a survey of 96 plants across Ontario, with the exception of those for Sudbury (Health Canada, 1994). Levels in drinking-water in the Sudbury area sampled between 1972 and 1992 were markedly higher, with mean concentrations ranging from 26 to 300 µg/L. The median Ni 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 reaching 72.4 µg/L (ATSDR, 2005). Ni levels in tap waters from British Columbia, Prince Edward Island, the Yukon, and Northwest Territories were below detection limit.

Potable tap water generally contains Ni at concentrations ranging from 0.55 to 25 µg Ni/L in the United States (ATSDR, 2005; OEHHA, 2011). In a Seattle (Washington) study, mean and maximum Ni levels in standing water were 7.0 and 43 µg/L, respectively, compared with 2.0 and 28 µg/L in running water (ATSDR, 2005). Ni concentrations in tap water measured in the US Total Diet Study 1991–1999 ranged from 0 to 25 µg/L with a mean value of 2 µg Ni/L. Analysis of data obtained during 1995–1997 from the National Human Exposure Assessment
Study (NHEXAS) yielded median concentrations of Ni in tap water (used as drinking-water) of 4.3 μg Ni/L (10.6 μg Ni/L, 90th percentile) in the Arizona study and 4.0 μg Ni/L (11 μg Ni/L, 90th percentile) in the US Environmental Protection Agency Region 5 (Illinois, Indiana, Michigan, Minnesota, Ohio, and Wisconsin) study. According to the monitoring data collected by the California Department of Health Services between 1984 and 1997, the highest, average and median concentrations of Ni in water were 540 μg/L, 26 μg/L, and 17.9 μg/L, respectively.

In Australia, Ni concentrations in drinking-water are typically < 10 μg/L. In Sampleton, Australia, the mean Ni concentration in drinking-water sampled between January 2002 and December 2005 was 30 μg/L (range < 10–220 μg/L) and intermittently exceeded the Australian Drinking Water Guidelines value for Ni of 20 μg/L (Alam et al., 2008).

In Europe, reported Ni concentrations in drinking-water were generally < 10 μg/L (IPCS, 1991). Ni levels < 1 μg/L have been reported from Denmark and Finland (Punsar et al., 1975; Gammelgaard & Andersen, 1985). Average dissolved Ni concentrations in surface water in the rivers Rhine and Meuse were < 7 μg/L (RIWA, 1994). Ni concentrations in drinking-water in European countries of 2-13 μg/L have been reported (IARC, 1990; WHO, 2000). Drinking-water generally contains Ni at concentrations < 10 μg/L (ANSES, 2005; Cempel & Nikel, 2006; WHO, 2007; Bertoldi et al., 2011; De Brouwere et al., 2012).

Increased Ni concentrations in groundwater and municipal tap water (100–2500 μg/L) in polluted areas and areas in which natural Ni was mobilized have been reported in 1972. After diminished smelter emissions, Ni concentrations in potable water of Sudbury were substantially reduced by the early 1980s (McNeely et al., 1972; Hopfer et al., 1989). Water left standing overnight in plumbing fittings plated with chromium on a base of Ni contained a Ni concentration up to 490 μg/L, but low values were obtained after flushing, and there was considerable variation from time to time and from tap to tap (Andersen et al., 1983).

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

Leaching of Ni from chromium–Ni stainless steel pipework into drinking-water diminished after a few weeks; as chromium was rarely found at any time in the water, this indicates that the leakage of Ni is not of corrosive origin, but rather attributable to passive leaching of Ni ions from the surface of the pipes (Schwenk, 1992). Concentrations of Ni 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, which are chromium-plated, release much higher concentrations that decrease significantly with time (EU, 2008).

Concentrations of Ni in water boiled in electric kettles may, depending on the material of the heating element, be markedly increased, especially in the case of new or newly decalcified kettles. The greatest concentrations are associated with Ni-plated elements; however, leaching decreases over time. Ni concentrations in the range 100–400 μg/L, with extreme values over 1000 μg/L, have been reported (Rasmussén, 1983; Pedersén & Petersén, 1995; Berg et al., 2000; United Kingdom Drinking Water Inspectorate, 2002; EU, 2008).

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

3.2 Food

Since Ni is usually measured in food as total Ni, there is uncertainty as to the chemical form, although it is normally considered to be in the form of complex bound organic Ni, which may be less bioavailable than other forms (EU, 2008). Ni levels in food are generally in the range 0.01–0.1 mg/kg, but there are large variations (Booth, 1990; Jorhem & Sundström, 1993; Dabeka & McKenzie, 1995; Fødevaredirektoratet, 2000). Higher median levels of Ni (0.1–0.4 mg/kg) were found in wholemeal products (Smart & Sherlock, 1987; Fødevaredirektoratet, 2000), whereas markedly higher levels (1–6 mg/kg) were found in beans, seeds, nuts, and wheat bran (Smart & Sherlock, 1987; Jorhem & Sundström, 1993). Even higher Ni levels (8–12 mg/kg) were found in cacao (Smart & Sherlock, 1987).

Stainless steel cooking utensils (e.g., oven pans, roasting pans) contributed markedly to the levels of Ni in cooked food, sometimes exceeding 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 Ni concentrations in acid foodstuffs when new stainless-steel pans were used.

Daily dietary intakes of Ni 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; 95% fractile, 0.27 mg) in Denmark (Fødevaredirektoratet, 2000), and 0.16 mg in the USA (Myron et al., 1978). Population dietary intakes of Ni at the level (0.127-0.129 mg/day) in the 2006 total diet study and comparable to results from the 2000 study (0.13 mg/day) have decreased since 1976 (0.33 mg/day) in the UK (COT 2008).

The estimates of dietary exposures to nickel for mean- and high-level intake by pre-school children and high-level intake by young people exceeded (by up to about 2-fold) the total nickel intake level of 4.3 μg/kg body weight/day (COT 2008). The dietary intake of Ni in a Canadian study ranged from 0.19 mg/day for 1- to 4-yearold children to 0.406 mg/day for 20- to 39-year-old males. The Ni intake for 20- to 39-year-old women was on average 0.275 mg/day (Dabeka & McKenzie, 1995). Dietary Ni intake by 0- to 12-month-old infants was on average 0.005 mg/kg bw per day (equal to 0.038 mg/day). Infants fed evaporated milk were exposed to 0.004 mg/kg bw per day, whereas infants fed soy-based formula were exposed to 0.010 mg/kg bw per day (Dabeka, 1989). Ni is found in both human and cow’s milk at concentrations reported to range from 0.001 to over 0.1 mg/L, although concentrations in studies in the USA indicate levels in the region of 0.015 mg/kg (EU, 2008). USFDA (2000) estimated an intake of 0.134 mg/day based on data from the northeastern part of the USA.

As nuts and beans are important sources of protein for vegetarians, this subpopulation can be expected to have a markedly higher intake of Ni than that reported in the studies cited above. The Ni 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 Ni levels were consumed. When food rich in Ni 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 Ni of 0.17 mg/day (FSA, 2000). This was confirmed by the UK 2006 duplicate-diet study, which showed a small decline in exposure (COT, 2008).
Chronic exposure estimates were calculated for 26 different dietary surveys carried out in 17 different European countries. The mean and the high (95th percentile) chronic dietary exposures were calculated by combining Ni mean occurrence values for food and drinking-water samples collected in 15 countries (pooled European occurrence data) with the average daily consumption for each food at individual level in each dietary survey. Mean chronic dietary exposure to Ni across the different dietary surveys and age classes ranged from 2.0 μg/kg bw per day (minimum LB, ‘Elderly’) to 13.1 μg/kg bw per day (maximum UB, ‘Toddlers’). The 95th percentile dietary exposure ranged from 3.6 μg/kg bw per day (minimum LB, ‘Elderly’) to 20.1 μg/kg bw per day (maximum UB, ‘Toddlers’). As observed for chronic exposure to Ni, the highest levels for acute exposure were observed in ‘Toddlers’ and ‘Other children’. Average acute exposure estimations did not differ much from those calculated for the chronic exposure. This can be explained by the fact that Ni is present in many different foods which are regularly consumed. (EFSA, 2015).

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

### 3.3 Air

Ni concentrations in remote areas are in the range of 1–3 ng/m³, whereas concentrations in rural and urban air range from 5 to 35 ng/m³. 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 Ni (IARC, 1990).

### 3.4 Bioaccumulation

Ni is not accumulated in significant amounts by aquatic organisms (Birge & Black 1980; Zaroogian & Johnson 1984). The concentration of Ni in a major carnivorous fish in New York State, the lake trout, was the lowest, and the concentration did not increase appreciably with the age of the fish (Birge & Black, 1980). In the work of McGeer et al. (2003), bioconcentration factors (BCFs) for Ni in various aquatic organisms (e.g., algae, arthropods, mollusks, and fish) was assessed based on whole-body metal concentrations and exposure concentrations that were obtained from the literature. There was no evidence that Ni biomagnifies in aquatic food webs. Two studies concerning levels in voles and rabbits living on sludge-amended land did not indicate any accumulation of Ni in these herbivores or in the plants they fed upon (Alberici et al., 1989; Dressler et al., 1986). Thus, the lack of significant bioaccumulation of Ni in aquatic organisms, voles, and rabbits indicates that Ni is not biomagnified in the food chain (ATSDR, 2005).

### 3.5 Biomonitoring studies

Serum Ni levels in the range 1.5–19 μg/L were found in patients undergoing regular haemodialysis (Hopfer et al., 1989; Nixon et al., 1989). Significantly higher serum Ni levels were observed in non-occupationally exposed subjects from a heavily Ni-polluted area compared with levels in subjects living in a control area (Ni concentrations in tap water 109 ± 46 vs 0.6 ± 0.2 μg/L; serum Ni levels 0.6 ± 0.3 vs 0.2 ± 0.2 μg/L) (Hopfer et al., 1989). Tentative reference values for Ni 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 et al., 1994b). After reviewing monitoring data in occupationally exposed workers, Ohashi et al. (2006) determined reference values for Ni in urine among women of the general population of 11 prefectures in Japan. The observed geometric mean for urinary Ni 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 the representative data to describe the internal Ni exposure of children aged 3–14 years from the German Environmental Survey (2003-2006), the urinary Ni levels (n = 1 576) ranged from < 0.5 to 15 µg /L, the geometric mean being 1.26 µg /L (Wilhelm et al., 2013).

3.6 Estimated total exposure and relative contribution of drinking-water

Food is the dominant source of Ni exposure in the non-smoking, non-occupationally exposed population. According to the United Kingdom Total Diet Study, the contribution from food is 0.127–0.129 mg/day per person (COT, 2008). Recent studies, including a United Kingdom study on vegetarians, indicate that the intake from food is probably less than 0.2 mg/day. Water generally contributes 0.005–0.025 mg daily (i.e., 2–11% of the total daily oral intake of Ni) (MAFF, 1985). These figures are similar to those presented in the European Union risk assessment for Ni (EU, 2008). However, no account is taken of exposure from Ni-plated elements and other similar sources; for some individuals, therefore, there may be higher intakes that will fluctuate significantly with time. Overall, drinking-water appears to contribute only a minor proportion of daily intake. However, there are some circumstances, such as when natural Ni concentrations in source water, particularly groundwater, are elevated or where there is significant input from Ni-plated fittings, when drinking-water will contribute a higher proportion of daily intake. In the case of the former, the exposure is potentially long term, whereas in the case of the latter, 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.

4.0 TOXICOKINETICS AND METABOLISM IN ANIMALS AND HUMANS

4.1 Absorption

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

The mechanism for intestinal absorption of Ni is not clear. Iron deficiency increased intestinal Ni absorption in vitro and in vivo, indicating that Ni is partially absorbed by the active transfer system for iron absorption in the intestinal mucosal cells (Tallkvist et al., 1994). In perfused rat jejunum, saturation of Ni uptake was observed at high concentrations of NiCl₂ (Foulkes & McMullen, 1986). Iron concentrations in rat tissues were increased by dietary Ni exposure (Whanger, 1973). Ni is bound to a histidine complex, albumin, and alpha-2-macroglobulin in serum (Sarkar, 1984).

Absorption of soluble Ni compounds from drinking-water is higher than that from food. After 24 h, 10–34% of a single oral dose of water-soluble Ni compounds (i.e., NiSO₄, NiCl₂, Ni(NO₃)₂) was absorbed, whereas less than 2% of a single oral dose of insoluble or scarcely soluble Ni compounds (i.e., NiO, Ni, Ni₃S₂, NiS) was absorbed. It is not known if the animals were fasted before treatment. The highest Ni concentrations were found in the kidneys and lungs, whereas Ni concentrations in the liver were low (Ishimatsu et al., 1995).

Following a 12-h fast, a volunteer ingested 20 µg of ⁶¹Ni-enriched Ni per kg bw as Ni(NO₃)₂ in 1 L of water. The serum Ni concentration peaked at 2 h at 34 µg/L. By 96 h, 27% of the ingested dose was excreted in the urine (Templeton et al., 1994a). These findings are consistent with the observations made by Sunderman and co-workers, who reported an absorption of 27 ± 17% of the given Ni dose (as NiSO₄) added to drinking-water in 10 volunteers after a 12-h fast. Intestinal absorption was only 1% of the given dose when NiSO₄ was added to scrambled eggs. The half-time for absorbed Ni averaged 28 ± 9 h (Sunderman et al., 1989). Plasma levels in fasting human subjects did not increase above fasting levels when 5 mg of Ni were added to an American breakfast or a Guatemalan meal rich in phytic
acids (Solomons et al., 1982). The same amount of Ni added to water elevated the plasma Ni levels 4- to 7-fold. The absorption of Ni added to milk, tea, coffee, or orange juice was significantly less than the absorption of Ni from water. Two studies carried out to examine the influence of fasting and food intake on the absorption of Ni 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 min or 1 h 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 64Ni was given to 20 Ni-sensitized women and 20 age-matched controls, there was no difference in Ni absorption and excretion (Nielsen et al., 1999).

4.2 Distribution

Whole-body retention in mice after oral exposure to Ni2+ was less than 1% of the administered dose 5 days after exposure (Nielsen et al., 1993). Severa et al. (1995) observed an accumulation of Ni in organs of rats orally exposed to Ni in drinking-water at concentrations of 100 mg/L for 6 months. The Ni concentration in liver was 10 times higher in exposed rats than in unexposed rats; in the kidney, the Ni level was only twice as high in exposed rats as in unexposed rats. Ni levels in the kidney and blood were similar. There was no increase in Ni levels in organs between 3 and 6 months of exposure.

Several reports indicate that transplacental transfer of Ni occurs in animals (IPCS, 1991). Elevated concentrations of Ni were detected in fetuses after intramuscular administration of NiCl2 to rats. The fetal organ with the highest Ni concentration was the urinary bladder (Sunderman et al., 1978). In human studies, Ni has been detected in fetal tissues at levels similar to the levels found in adults (McNeely et al., 1972; Casey & Robinson, 1978).

4.3 Metabolism

Once absorbed, elemental Ni is not anticipated to undergo any metabolism. The extracellular metabolism of Ni consists of ligand exchange reactions (Sarkar, 1984). In human serum, Ni binds to albumin, L-histidine, and α2-macroglobulin. Binding in animals is similar. The principal binding locus of Ni to serum albumins is the histidine residue at the third position from the amino terminus in humans, rats, and bovines (Hendel & Sunderman, 1972- as cited by ATSDR, 2005).

4.4 Elimination

Absorbed Ni is eliminated mainly in the faeces and to a lesser extent in urine (IPCS, 1991). Biliary excretion of Ni subcutaneously administered to rats as NiCl2 was less than 0.5% of the given dose (Marzouk & Sunderman, 1985). In studying a fatal case of human Ni intoxication, the authors concluded that biliary excretion of Ni was of minor importance in humans (Grandjean et al., 1989). Ni is also eliminated in the milk of lactating women. In studies reported in the USA, the Ni concentration in milk was in the region of 15 µg/kg (EU, 2008).

5.0 EFFECTS ON HUMANS

5.1 Acute effects

A 2½-year-old girl died after ingesting about 15 g of NiSO4 crystals. Cardiac arrest occurred after 4 h; the autopsy revealed acute haemorrhagic gastritis (Daldrup et al., 1983).

Thirty-two industrial workers accidentally drank water contaminated with NiSO4 and NiCl2 (1.63 g of Ni per L). The Ni doses in persons who developed symptoms were estimated to
range from 7 to 35 mg/kg bw. Twenty workers developed symptoms, including nausea, vomiting, diarrhoea, giddiness, lassitude, headache, and shortness of breath. In most cases, these 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 hyperbiliruinaemia developed on day 3 after exposure in two subjects, and elevated levels of blood reticulocytes were observed in seven workers on day 8 post-exposure. It is known from animal studies that Ni after intrarenal injection enhances the renal production of erythropoietin, which may explain the reticulocytosis, and that Ni induces microsomal haem oxygenase activity in liver and kidney, leading to a secondary hyperbiliruinaemia. Serum Ni concentrations ranged between 13 and 1340 µg/L in persons with symptoms (Sunderman et al., 1988).

Seven hours after ingesting NiSO₄ in drinking-water (50 µg of Ni per kg bw), a 55-year-old man developed left homonymous haemianopsia, which lasted 2 h (Sunderman et al., 1989).

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

5.2 Reproductive and developmental effects

A first epidemiological study on reproductive and developmental effects after occupational exposure (estimated to be 0.11 to 0.31 mg Ni/m³ in the air, employment period for 1-16 years) is that of Chashschin et al. (1994) who reported 15.6% spontaneous abortions among 290 women working in a Ni hydrometallurgy refining plant in Russia, compared to 8.5% incidence in 336 female control workers. In the same study, the authors also noted a statistically significant increase in structural malformations among offspring born to 356 workers (16.9%) compared to 342 controls (5.8%) and increased relative risks of 6.1 for cardiovascular defects and 1.9 for musculoskeletal defects. Heavy manual activity and heat stress of the exposed women was noted as potential confounders (see also OEHHA, 2011). This study was considered inconclusive by the European Union due to flaws in the study design and limited reporting (EU RAR, 2008).

In a follow-up register-based cohort study, Vaktskjold et al. (2006) investigated whether pregnant women employed in the period 1973–1997 at Ni-exposed work areas had an elevated risk of delivering a newborn with a genital malformation. The study cohort comprised 23,141 live- or stillborn infants from a total of 24,534 deliveries. Exposure was classified into the three categories of background, low and high exposure (< 10, 10 to < 70, and ≥ 70 µg/L). The authors concluded that no adverse effects of maternal exposure to water-soluble Ni was found, recognizing the smaller sample size in the higher exposure groups. In a second study, Vaktskjold et al. (2007) reviewed 22,836 births (> 27 weeks of gestation) and concluded that occupational exposure to water-soluble Ni during early pregnancy was not associated with an elevated risk of delivering a newborn small-for-gestational-age (SGA defined as below the 10th percentile birth weight for gestational age in the source population). Vaktskjold et al. (2008a) found that the risk of spontaneous abortion was not increased after maternal Ni exposure in the same geographical area based on an adjusted odds ratio of 1.14 (0.95–1.37) in a case-control study. Another study by Vaktskjold et al. (2008b) analysed the incidence of musculoskeletal defects in the offspring in the cohort described above and observed among 22,965 births, 304 infants (13.3/1 000 births; 95% C.I. 11.9–14.7) diagnosed with isolated musculoskeletal defects(s) concluding that despite the high incidence of defects there was no apparent association (adjusted OR 0.96, 95% C.I: 0.76–1.21) with maternal Ni exposure.
Danadevi et al. (2003) examined semen quality of 57 workers who had been exposed for 2–21 years from a welding plant in South India and 57 controls in relation to blood Ni and chromium concentrations. In twenty-eight workers and 27 control men selected randomly from each study group, blood Ni level was significantly higher in the workers (123.3 ± 35.2 μg/L) compared to the controls (16.7 ± 5.8 μg/L). Sperm concentrations of the workers were 14.5 ± 24.0 millions/mL compared to 62.8 ± 43.7 millions/mL in the control group. Rapid linear sperm motility was decreased in exposed workers compared to controls and there was a significant positive correlation between the percentage of sperm tail defects and blood Ni concentration in exposed workers. However, the study was limited by the small sample size and possible selection bias and the fact that Ni exposure was determined only for a subset of workers using a single measure of Ni blood concentration in the presence of other heavy metals.

Figá-Talamanca and Petrelli (2000) studied the gender ratio among children of male workers differently exposed to metal fumes of Ni and Cr, depending on their job function (n = 48 in administration, n = 74 technicians, n = 31 stampers and n = 63 founders) in an Italian mint and observed a statistically significantly reduced portion of male children in founders compare to workers with administrative roles and the general population. This finding is in contrast to 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 Ni (Bonde et al., 1992).

Allowing for the uncertainty on the level of exposure to Ni by ingestion, the CONTAM Panel of the European Food Safety Authority (EFSA) noted that the results of these reported human studies do not support the association of effects on reproduction and developmental with oral exposure to Ni (EFSA, 2015).

A nested case-control study was conducted to evaluate the relationship between prenatal Ni exposure and the risk of delivery of preterm low birth weight (PLBW) infants among pregnant women (including 102 PLBW cases and 306 matched controls) in Hubei province, China. Conditional logistic regression analysis was conducted for exploring the association between Ni levels and PLBW, as well as the effect modification by Se on this association. A significant association was observed between higher maternal urinary Ni levels and risk of PLBW [adjusted odds ratio (OR) = 2.80 (95% confidence interval (CI): 1.44, 5.44) for the highest tertile], and this association was more apparent among female infants than that among male infants. Further analyses indicated that mothers with high urinary Ni and low urinary Se levels had a more increased risk for PLBW [adjusted OR = 2.87 (95% CI: 1.09, 7.56)]. The study indicates that prenatal exposure to Ni was a risk factor for PLBW, and Se might have the potential modifying effect on this association (Sun et al., 2018).

5.3 Immunological effects

Allergic contact dermatitis, i.e. type IV hypersensitivity, is the most prevalent effect of Ni in the general population (Hostynek, 2006). In the USA, Ni allergic contact dermatitis has an incidence of 14.3%, and is on the rise from 10 years ago, when the incidence was 10%. Similar figures were reported by Schnuch et al. (2002), who reviewed information from EU, Asia and USA, and by Mortz et al. (2013), reporting on a cohort study of 1,501 8th grade school children, that lasted 15 years, and in which Ni sensitization was observed in 11.8% of the study group.

A rise in Ni sensitization has been presumed to represent an increased exposure to Ni in the environment-especially in costume jewelry and belt buckles (Silverberg et al., 2002).
Occupational exposure to Ni 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 Ni have been reported. Whereas Type I immune responses may be underlying such conditions, it has also been postulated that Ni may act as a mast cell discharger on a non-immunological basis (Walsh et al., 2010).

Consumption of Ni-rich diet may elicit eczematous flare-up reaction in the skin in sensitized individuals, a phenomenon called systemic Ni contact dermatitis (SCD) or haematogenous contact eczema (Erdmann & Werfel, 2006; Jensen et al., 2006). Indeed, ingested Ni may have consequences for the expression of skin conditions in sensitized individuals, such as flare-up of cutaneous reactions in some Ni-allergic patients (Christensen & Møller, 1975; Kaaber et al., 1978; Cronin et al., 1980; Veien et al., 1983; Hindsén et al., 2001; Gangemi et al., 2009). It should also be noted that on the other hand, experimental studies have also shown that repeated oral exposure to Ni may prevent diminish sensitization. Sjövall et al. (1987), Santucci et al. (1988), and Bonamonte et al. (2011) reported reduction of Ni contact dermatitis after oral exposure to soluble Ni over a longer period.

Systemically induced flares of dermatitis are reported after oral challenge of Ni-sensitive women with 0.5–5.6 mg of Ni as NiSO₄ administered in a lactose capsule (Veien, 1989). At the highest Ni dose (5.6 mg), there was a positive reaction in a majority of the subjects; at 0.5 mg, only a few persons responded with flares. Responses to oral doses of 0.4 or 2.5 mg of Ni did not exceed responses in subjects given placebos in double-blind studies (Joardan & King, 1979; Gawkrodger et al., 1986).

There are several reports on the effects of diets low or high in Ni, but it is still a matter of discussion whether naturally occurring Ni in food may worsen or maintain the hand eczema of Ni-sensitive patients, mainly because results from dietary depletion studies have been inconclusive (Veien & Menné, 1990). In a single-blind study, 12 Ni-sensitive women were challenged with a supplementary high-Ni diet (Nielsen et al., 1990). The authors concluded that hand eczema was aggravated during the period (i.e., Days 0–11) and that the symptoms were Ni-induced. However, in some subjects the severity of the eczema (i.e., the number of vesicles in the palm of the hand) varied markedly between Days 14 or 21 before the challenge period and the start of the challenge period.

Oral hyposensitization to Ni was reported after six weekly doses of 5 mg of Ni in a capsule (Sjöwall et al., 1978) and 0.1 ng of NiSO₄ daily for 3 years (Panzani et al., 1995). Cutaneous lesions were improved in eight patients with contact allergy to Ni after oral exposure to 5 mg of Ni weekly for 8 weeks (Bagot et al., 1995). Ni in water (as NiSO₄) was given to 25 Ni-sensitive women in daily doses of 0.01–0.04 mg/kg bw per day for 3 months after they had been challenged once with 2.24 mg of Ni (Santucci et al., 1988). In 18 women, flares occurred after the challenge dose, whereas only 3 out of 17 subjects had symptoms during the prolonged exposure period. Later, Santucci and co-workers (1994) gave increasing oral doses of Ni in water (0.01–0.03 mg of Ni per kg bw per day) to eight Ni-sensitive women for up to 178 days. A significant improvement in hand eczema was observed in all subjects after 1 month.

The LOAEL established after oral provocation of patients with empty stomachs was reported as 12 µg/kg bw (Nielsen et al., 1999). This figure was similar to the dose found in a study by Hindsén et al. (2001), where a total dose of 1 mg (17 µg/kg bw) was reported to result in a flare-up of dermatitis in an earlier patch test site in 2 of 10 Ni-sensitive patients. The dose of 12 µg/kg bw was considered to be the acute LOAEL in fasting patients on a 48-h diet with
reduced Ni content. A cumulative LOAEL could be lower, but a LOAEL in non-fasting patients is probably higher because of reduced absorption of Ni ions when mixed in food.

Jensen et al. (2006) performed a meta-analysis study on Ni exposure investigations to provide the best possible estimation of threshold doses of Ni that may cause systemic contact dermatitis in Ni sensitive patients. The authors identified 17 investigations to study the dose relationship of responses to oral exposure to Ni in Ni-sensitive individuals. There was clear indication of increasing reaction rate associated with increasing Ni dose. The results from the two most sensitive groups showed that 1% of these individuals may react with systemic contact dermatitis at normal daily Ni exposure from drinking-water and diet, i.e. 0.22–0.35 mg Ni. The EFSA CONTAM Panel noted difficulties with accepting this meta-analysis as a basis for deriving a health-based guidance value for acute exposure to Ni. The authors had excluded some studies which 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 has been used in the challenge).

The EFSA CONTAM Panel examined 17 studies reviewed by Jensen et al. (2006). Of these studies, the study by Jensen et al. (2003) showed effects at the lowest doses, with incidences of 1/10, 4/10, 4/10 and 7/10 at doses of 0, 0.3, 1, or 4 μg Ni per person, Jensen et al. (2003) investigated 40 Ni-sensitive individuals (39 female, 1 male) that were positive in patch testing to Ni. The patients were exposed to Ni sulfate hexahydrate (H₁₂NiO₁₀S) in lactose capsules as single bolus in the morning after a 12-hour fasting period. No other dietary intervention was conducted; hence each individual was exposed to Ni in the three dose groups or placebo (lactose) in the control group in addition to the Ni exposure from the normal diet in this study. Exposure from diet was not estimated and one day after the oral exposure the status of the skin area previously exposed to patch testing with Ni was scored for objective clinical responses.

5.4 Genotoxicity and carcinogenicity

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

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

6.0 EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO SYSTEMS

6.1 Acute exposure

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

### 6.2 Short-term exposure

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

In a 13-week study in which Sprague-Dawley rats were given 0, 44.7, 111.75, or 223.5 mg of Ni per litre in drinking-water as NiSO₄ (corresponding to 0, 4.5, 11.2, or 22.4 mg of Ni per kg bw per day), no apparent clinical signs of toxicity were observed. Final mean body weights were unaffected except for a decrease in the top dose group when 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). The EU (2004) risk assessment determined a NOAEL of 44.7 mg/L based on minor changes in body weight and relative weights of kidney and lung.

### 6.3 Long-term exposure

#### 6.3.1 Systemic effects

Rats (25 per sex per dose) were exposed to Ni (as NiSO₄) in the diet at doses of 0, 100, 1000, or 2500 mg/kg (equivalent to 0, 5, 50, or 125 mg/kg bw per day) for 2 years (Ambrose et al., 1976). Body weight was significantly reduced (more than 30% at highest dose) in rats at 1000 and 2500 mg/kg of diet, but there were indications that decreased food consumption might explain the decreased body weight, particularly at 2500 mg/kg of diet. Survival was overall very poor (survival rates: 62-72%), especially in the control and the 2500 mg/kg of diet groups in male. In females at 1000 and 2500 mg/kg of diet, mean relative liver weights were decreased by about 20% and the 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 Ni concentrations were found in the kidneys. The NOAEL was 5 mg/kg bw per day. However, the study does not meet current standards 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 0, 100, 1000, or 2500 mg of Ni per kg of diet (equivalent to 0, 2.5, 25, and 62.5 mg/kg bw per day). In the 2500 mg/kg of 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 per day (Ambrose et al., 1976). This study may have been confounded by palatability concerns, since all high-dose dogs vomited during the first 3 days.

Increased relative kidney weight was observed in rats exposed to Ni (as NiSO₄) in drinking-water at a daily dose of about 7 mg/kg bw for up to 6 months (Vyskocil et al., 1994). There was an increased excretion of albumin in urine in females without changes in total protein, beta-2-microglobulin, N-acetylbeta-D-glucosaminidase, or lactate dehydrogenase in urine.
6.3.2 Neurological effects

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

6.3.3 Reproductive and developmental effects

A reduced number of live pups and reduced fetal body weights were observed after rat dams received a single intramuscular dose of NiCl$_2$ (16 mg of Ni per kg bw) or NiS$_2$ (80 mg of Ni per kg bw) on Gestation Day 8 or 6, respectively. 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 0, 7, 31, and 52 mg of Ni per kg bw per day) from 90 days before breeding. Decreased food and water intake observed in the exposed animals were suggestive of 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 between 3 and 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 in this study was 7 mg of Ni per kg bw per 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 Ni as NiCl$_2$ for 11 weeks prior to mating and during two successive gestation (G1 and G2) and lactation periods (L1 and L2) at concentrations of 0, 10, 50, or 250 mg/L (equal to 0, 1.3, 6.8, or 31.6 mg of Ni per kg bw per day) in drinking-water (Smith et al., 1993). Dams drinking water containing Ni at 31.6 mg/kg bw per 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 (the increase at the middle dose in L2 approached statistical significance), with a dose-related response in both experimental segments. 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 per day represented the LOAEL, recognizing it to be 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 Ni (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 Ni in drinking-water and bioavailability problems with Ni in food. The range-finding study was designed in two parts. The first part was a dose–response probe utilizing small numbers of animals and H$_{12}$NiO$_{10}$S exposures of 0, 5, 15, 25, 50, 75, or 150 mg/kg bw per day. (Note that the lower 95% confidence limit for lethality from H$_{12}$NiO$_{10}$S is 170 mg/kg bw per day.) Lethality was observed at the 150 mg/kg bw per day exposure level.
The second part of the range-finding study (i.e., a one-generation reproductive toxicity study) utilized H$_{12}$NiO$_{10}$S exposures of 0, 10, 20, 30, 50, or 75 mg/kg bw per 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 per day exposures and more questionable increases at the 10 and 20 mg/kg bw per 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 per day level and was lower than historical controls at or above 30 mg/kg bw per day.

Based upon 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 per 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 in order to elicit any possible adverse effects on spermatogenesis by the test substance. Females of the F$_0$ generation were dosed during growth and for several complete estrous cycles in order to elicit any possible adverse effects on estrus by the test substance. The test substance was administered to F$_0$ animals during mating, 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 up 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 indicate that the NOAEL was 5 mg/kg bw per day or 1.1 mg of Ni per kg bw per day in adult and offspring based on the effects observed at the highest dose of 10 mg/kg bw per day or 2.2 mg of Ni per kg bw per day), including the variable of postimplantation/perinatal lethality (SLI, 2000; EU, 2008).

In a three-generation study in rats at dietary levels of 250, 500, or 1000 mg of Ni (administered as NiSO$_4$) per kg of diet (equivalent to 12.5, 25, or 50 mg/kg bw per 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 of 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 Ni dose, but no statistical analysis of the results is presented. Decreased weanling body weight is a clear-cut effect in the 1000 mg/kg of 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 small-scale three-generation study in rats administered Ni in drinking-water at 5 mg/L, corresponding to 0.2 mg/kg bw per day (Schroeder & Mitchener, 1971).

Alterations in milk composition were observed in lactating rats exposed to four daily subcutaneous injections of Ni at doses of 3–6 mg/kg bw (Dostal et al., 1989). Liver weights were decreased in pups whose dams received 6 mg of Ni per kg bw. These findings may explain the effects seen on litter size and body weights of the pups in 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 per day for 3, 6, 9 or 12 weeks, the authors reported significant morphometric changes in the histology of the testis. However, there are a number of uncertainties regarding this study which would require confirmation (Toman et al., 2012).

### 6.3.4 Genotoxicity and carcinogenicity

Ni compounds are generally inactive in bacterial mutation assays but active in mammalian cell systems (IPCS, 1991). However, it was concluded that Ni-induced responses was 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 are reported in mammalian systems, including human cell systems. Chromosomal aberrations occur in all chromosomes but with preference for the heterochromatic centromeric regions (IPCS, 1991; Rossman, 1994).

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

The genotoxicity of Ni compounds has been reviewed by TERA (1999) and as part of the EU (2004) risk assessment. Most studies relate to water-soluble compounds, and TERA (1999) concluded that “evidence for genotoxicity is mixed, although water soluble Ni 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 on the carcinogenicity of Ni compounds in experimental animals are available (IARC, 1990; Aitio, 1995). Generally, tumours are induced at the site of administration of the Ni compound. For instance, several Ni 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).

There are only a limited number of studies on carcinogenic effects after oral exposure to Ni compounds. The incidence of tumours was not higher in rats exposed to drinking-water containing Ni at 5 mg/L during their lifetime compared with control rats (Schroeder et al., 1974). As well, no difference in tumour incidence was observed in a lifetime study in rats exposed to 5, 50, or 125 mg of Ni per kg bw per day in the feed compared with controls (Ambrose et al., 1976). Owing to the high death rate and lack of information on cause of death, this study is of minor value in evaluating carcinogenicity after oral exposure to Ni. 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 10, 30 or 50 mg/kg bw per day of NiSO$_4$ (6H$_2$O) 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).

### 6.4 Mode of action

Ni can cross-link amino acids to DNA, lead to formation of reactive oxygen species (ROS),
and mimic hypoxia. These changes may activate some signaling pathways, subsequent transcription factors and eventually alter gene expression and cellular metabolism (Forgács et al., 2012). The mechanisms of Ni genotoxicity including epigenetic modifications are complex (EFSA, 2015).

Interactions of metal ions with proteins and the role for immune responses have been reviewed by Martin et al. (2006). There is evidence that the combination of Ni with circulating or tissue protein gives rise to antigen specific responses, and thus Ni 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 Ni-specific T lymphocytes. Contact sensitivity is either expressed as Type I or Type IV hypersensitivity, mediated by reagins and allergen-specific T lymphocytes, expressing in a wide range of cutaneous eruptions following dermal or systemic exposure. An alternative, but not mutually exclusive, hypothesis is that this metal interferes with the antigen recognition step of the immune response, i.e. binding to MHC and or MHC-bound peptides and T cell receptors leading to the activation of Ni-specific T cells (EFSA, 2015).

6.5 Other effects

With respect to the immunological system, Ni 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 Ni (IPCS, 1991). Dose-related decreased spleen proliferative response to lipopolysaccharide was observed in mice exposed to NiSO₄ in drinking-water for 180 days. At the lowest dose (44 mg of Ni per kg bw per day), decreased thymus weight was observed, but there was no Ni-induced immunosuppression NK cell activity or response to T-cell mitogens.

Parenteral administration of Ni to rabbits, chickens, and rats and oral administration of Ni to rabbits induce hyperglycaemia and reduce the levels of prolactin releasing factor in rats (IPCS, 1991).

The myeloid system was affected (i.e., decrease in bone marrow cellularity and dose-related reductions in the bone marrow proliferative response) when mice were exposed to NiSO₄ in drinking-water at doses of 0, 44, 108, or 150 mg of Ni per kg bw per day for 180 days (Dieter et al., 1988). The LOAEL in this study was 44 mg of Ni per kg bw per day.

7.0 OVERALL DATABASE AND QUALITY OF EVIDENCE

7.1 Summary of health effects

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

In humans, oral exposure to Ni was associated with effects on the gastrointestinal, haematological, neurological and immune system. Gastrointestinal and neurological symptoms were the most reported effects after acute exposure. Exposure through skin or by inhalation may lead to Ni sensitization. Whereas oral exposure to Ni is not known to lead to sensitization, oral absorption of Ni is able to elicit eczematous flare-up reactions in the skin in Ni-sensitized individuals.

In experimental animals, oral ingestion of soluble Ni salts resulted in a wide range of adverse
effects including nephrotoxicity/hepatotoxicity and metabolic effects. Ni can cross the placental barrier and affect the developing embryo or fetus. Pre- and perinatal mortality were increased in the offspring of pregnant rats ingesting Ni salts. These adverse effects occur at the lowest doses. However, the results of reported human studies do not support the association of effects on reproduction or developmental with oral exposure to Ni (EFSA, 2015).

As for evaluation of the allergic effects by Ni exposure, it has been reported that individuals sensitised to Ni through dermal contact and who have allergic contact dermatitis may develop eczematous flare-up reactions in the skin (systemic contact dermatitis, SCD) from single oral exposure to Ni salts. Several studies analysing SCD elicited in Ni-sensitive humans after acute oral exposure to Ni were identified as suitable for dose response analysis using the BMD approach. The EFSA CONTAM Panel selected a lowest BMDL_{10} (10% extra risk Benchmark Dose, 95% Lower Confidence Limit) of 80 μg Ni/day from the dose-response analysis of the Jansen et al. (2003) study.

7.2 Quality of evidence

Several kinetic studies in humans and experimental animals indicate that oral absorption of soluble Ni species is more efficient when administered in drinking-water or other beverages under fasting conditions, than via solid food. There is uncertainty in the systemic absorption rate of the key studies identified for the derivation of the acute and chronic reference values, in which Ni was administered via gavage using an aqueous solution as vehicle in the rat, or via lactose capsules under fasting conditions in human volunteer studies.

From the identified chronic exposure studies, it is appropriate to calculate the BMDL_{10} values for reproductive and developmental toxicity based on data from a well conducted two-generation study in rats using of post-implantation loss in the F₀/F₁ generation per litter as the most suitable endpoint (SLI, 2000; EFSA, 2015). It was noted that this endpoint 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 of the offspring (presence or absence of an effect occurring between implantation and birth).

Observations in humans showed toxicity of Ni at very high doses resulting after accidental or intended oral, occupational or other intoxication. However, epidemiological data from well conducted studies on human dietary exposure to Ni have been rare and were negative or inconclusive. This is in contrast to studies on humans who were primarily exposed to Ni via inhalation during occupation which could be used to classify Ni as carcinogenic to humans causing cancer of the lung and nasal cavity.

8.0 PRACTICAL ASPECTS

8.1 Analytical methods and achievability

The two most commonly used analytical methods for Ni in water are atomic absorption spectrometry and inductively coupled plasma atomic emission spectrometry. Flame atomic absorption spectrometry is suitable in the range of 0.5–100 μg/L (ISO, 1986), whereas inductively coupled plasma atomic emission spectroscopy can be used for the determination of Ni with a limit of detection of about 10 μg/L (ISO, 1996). A limit of detection of 0.1 μg/L or better should be achievable using inductively coupled plasma mass spectrometry. The limit of detection is approximately 20 μg/L by flame atomic absorption spectrometry, 15 μg/L by inductively coupled plasma, 1 μg/L by electrothermal atomic absorption spectrometry, and 1 μg/L by inductively coupled plasma optical emission spectrometry. Alternatively,
electrothermal atomic absorption spectrometry can be used.

8.2 Source control

Ni can be found in drinking-water due to its presence in alloys used in drinking-water contact applications, through Ni plating of pipe fittings, or its presence in water sources, usually as a consequence of dissolution from naturally occurring Ni-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. In the latter instance, consumers should flush chromium- or Ni-plated taps before using the water, particularly after periods of stagnation.

8.3 Treatment methods and performance

Conventional surface water treatment, comprising chemical coagulation, sedimentation, and filtration, can achieve 35–80% removal of Ni (Zemansky, 1974; Hunter et al., 1987; Duguet & Rizet, 1996). Better Ni removal occurs with waters containing high concentrations of suspended solids; for waters low in solids, the addition of powdered activated carbon can be used to enhance Ni removal (Welté, 2002). In a review of Ni removal, it was concluded that conventional coagulation, clarification, and granular activated carbon filtration can give Ni removals of 35–80%, depending on the speciation of the Ni. Increasing pH and the presence of high turbidity both favour Ni removal. The optimum pH for removal on activated carbon was reported to be pH 8 (Duguet & Rizet, 1996). However, other studies have reported that Ni is rather poorly adsorbed on activated carbon (Seco et al., 1997).

In the case of groundwaters, effective removal of Ni can be achieved using chelating ion-exchange resins (Stetter et al., 2002). Various adsorbents could potentially be used to remove Ni from groundwaters (Duguet & Rizet, 1996; Welté, 2002).

9.0 CONCLUSION

9.1 Derivation of the Health-based Value and/or final Guideline Value

EFSA identified reproductive and developmental toxicity as the critical effect for the risk characterization of chronic oral exposure to Ni. EFSA (2015) derived a BMDL$_{10}$ of 0.28 mg Ni/kg bw based on the incidence of litters with post-implantation loss in rat dams. This benchmark dose modelling was performed on a dose range finding one-generation study, on a subsequent full two-generation study and on the combination of the data from the two studies (SLI, 2000). The EFSA CONTAM Panel noted that the use of combined data from both individual studies provided the most robust results.

The well-conducted two-generation study in rats is a key study for derivation of a Guideline Value (GV), due to inadequate quantitative data available from human studies of chronic or reproductive/developmental effects. The BMDL$_{10}$ of 0.28 mg Ni/kg bw estimated by EFSA (SLI, 2000; EFSA 2015) can serve as the basis of the GV derivation. The application of an uncertainty factor of 100 (10 to account for interspecies differences and 10 to account for intraspecies variation) gives a TDI of 2.8 µg/kg bw per day. Data show that the exposure from food is moderate and that a higher relative source contribution could be allowed from drinking-water in circumstances when naturally elevated Ni is present. Data also indicate that a mean of 27% of the administered Ni dose is absorbed when exposure occurs via drinking-water versus a mean of 0.7% when exposure occurs via food, which support that Ni absorption from foods is more than 10-fold less than from drinking-water. Based on the differential absorption rates between food and drinking-water, the upper bound exposure
level of 14 μg Ni /kg bw per day from food estimated by EFSA corresponds to 1.4 μg/kg bw per day of systemic exposure via drinking-water, which corresponds to about 50% of the TDI for chronic toxicity. Therefore, an allocation factor of 50% will be applied to the TDI to derive the GV for drinking-water. The GV of 40 μg/L (1.4 μg/kg bw per day x 60 kg bw/2L) is protective of chronic systemic toxicity.

For acute toxicity, the systemic contact dermatitis (SCD) elicited in Ni-sensitive humans after exposure to Ni through water is the most sensitive and critical effect. Most of studies had small sample sizes and were case-control or volunteer studies with Ni-sensitive patients orally exposure to Ni ranging from 0.3 to 5 mg. These human studies support a dose-related response after low-dose exposures. The available evidence from case-control reports supports 0.3 mg/day as the LOAEL, based on the Jensen (2003) study, and the corresponding BMDL₁₀ of 0.08 mg/day estimated by EFSA (2015) is an appropriate point-of-departure for the derivation of a GV protective of SCD in humans. Considering that the point-of-departure is lower than all reported doses range, and that a sensitized population is tested under conditions that maximize absorption, no additional uncertainty factor was needed. The SCD patients were also exposed to Ni via foods at presumably typical exposure levels in most of the SCD studies. Thus, the induction of SCD was attributed to the additional Ni intake via drinking-water. A similar approach for deriving the point of departure for Ni reference dose in addition to Ni in food was proposed for protection of the SCD patients (Haber et.al., 2017). Therefore, no allocation factor is necessary for derivation of the health based GV for SCD effects. A GV of 40 μg/L can be derived from the BMDL₁₀ of 0.08 mg/day assuming water consumption of 2 L per day. Considering that the SCD elicited in the Jansen et al. study (2003) was associated with a bolus exposure compared to the intermittent nature of a drinking-water exposure scenario, the GV of 40 μg/L is conservative.

The GV of 40 μg/L is the same whether based on the most sensitive adverse effect from experimental animal studies or based on SCD in Ni-sensitive patients.

9.2 Considerations in applying the Guideline or Health-based Value

The GV estimation is based on the most sensitive effects of reproductive and developmental toxicity in rats. No related toxicological effects were demonstrated in human studies. From the point of view of protection of the chronic health effects, the GV of 40 μg/L would be prophylactic. However, there is little information about daily Ni consumption in humans, especially in Ni-sensitive patients. Furthermore, the study used for the acute GV derivation did not consider the contribution of the dietary exposure in the estimation of the Ni doses tested in human volunteers. Assuming that systemic absorption via drinking-water is at least 10 times more than that via food, very low levels of Ni in drinking-water may cause SCD in Ni-sensitive patients, such as those with SCD via Ni exposure from daily food intake. As the major source of Ni in drinking-water results from leaching from stainless steel devices or materials used in water supply systems, flushing the tap before drinking is recommended for Ni-sensitive patients.

10.0 APPENDICES

10.1 REFERENCES


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