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Nickel in Drinking-water

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

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Preface

One of the primary goals of WHO and its member states is that “all people, whatever their stage of development and their social and economic conditions, have the right to have access to an adequate supply of safe drinking water.” A major WHO function to achieve such goals is the responsibility “to propose ... regulations, and to make recommendations with respect to international health matters”

The first WHO document dealing specifically with public drinking-water quality was published in 1958 as *International Standards for Drinking-water*. It was subsequently revised in 1963 and in 1971 under the same title. In 1984–1985, the first edition of the WHO *Guidelines for Drinking-water Quality* (GDWQ) was published in three volumes: Volume 1, Recommendations; Volume 2, Health criteria and other supporting information; and Volume 3, Surveillance and control of community supplies. Second editions of these volumes were published in 1993, 1996 and 1997, respectively. Addenda to Volumes 1 and 2 of the second edition were published on selected chemicals in 1998 and on microbial aspects in 2002. The third edition of the GDWQ was published in 2004, the first addendum to the third edition was published in 2005, and the second addendum to the third edition was published in 2007.

The GDWQ are subject to a rolling revision process. Through this process, microbial, chemical and radiological aspects of drinking-water are subject to periodic review, and documentation related to aspects of protection and control of public drinking-water quality is accordingly prepared and updated.

Since the first edition of the GDWQ, WHO has published information on health criteria and other supporting information to the GDWQ, describing the approaches used in deriving guideline values and presenting critical reviews and evaluations of the effects on human health of the substances or contaminants of potential health concern in drinking-water. In the first and second editions, these constituted Volume 2 of the GDWQ. Since publication of the third edition, they comprise a series of free-standing monographs, including this one.

For each chemical contaminant or substance considered, a lead institution prepared a background document evaluating the risks for human health from exposure to the particular chemical in drinking-water. Institutions from Canada, Denmark, Finland, France, Germany, Italy, Japan, Netherlands, Norway, Poland, Sweden, United Kingdom and United States of America prepared the documents for the third edition and addenda.

Under the oversight of a group of coordinators, each of whom was responsible for a group of chemicals considered in the GDWQ, the draft health criteria documents were submitted to a number of scientific institutions and selected experts for peer review. Comments were taken into consideration by the coordinators and authors. The draft documents were also released to the public domain for comment and submitted for final evaluation by expert meetings.

During the preparation of background documents and at expert meetings, careful consideration was given to information available in previous risk assessments carried out by the International Programme on Chemical Safety, in its Environmental Health

Criteria monographs and Concise International Chemical Assessment Documents, the International Agency for Research on Cancer, the Joint FAO/WHO Meetings on Pesticide Residues and the Joint FAO/WHO Expert Committee on Food Additives (which evaluates contaminants such as lead, cadmium, nitrate and nitrite, in addition to food additives).

Further up-to-date information on the GDWQ and the process of their development is available on the WHO Internet site and in the current edition of the GDWQ.

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The work of the following working group coordinators was crucial in the development of this document and others contributing to the first addendum to the third edition:

Dr J. Cotruvo, J. Cotruvo Associates, USA (*Materials and chemicals*)
Mr J.K. Fawell, United Kingdom (*Naturally occurring and industrial contaminants*)
Ms M. Giddings, Health Canada (*Disinfectants and disinfection by-products*)
Mr P. Jackson, WRc-NSF, United Kingdom (*Chemicals – practical aspects*)
Prof. Y. Magara, Hokkaido University, Japan (*Analytical achievability*)
Dr E. Ohanian, Environmental Protection Agency, USA (*Disinfectants and disinfection by-products*)

The draft text was discussed at the Working Group Meeting for the second addendum to the third edition of the GDWQ, held on 15–19 May 2006. The final version of the document takes into consideration comments from both peer reviewers and the public. The input of those who provided comments and of participants in the meeting is gratefully acknowledged.

The WHO coordinator was Dr J. Bartram, Coordinator, Water, Sanitation and Health Programme, WHO Headquarters. Ms C. Vickers provided a liaison with the International Programme on Chemical Safety, WHO Headquarters. Mr Robert Bos, Water, Sanitation and Health Programme, WHO Headquarters, provided input on pesticides added to drinking-water for public health purposes.

Ms Penny Ward provided invaluable administrative support at the Working Group Meeting and throughout the review and publication process. Ms Marla Sheffer of Ottawa, Canada, was responsible for the scientific editing of the document.

Many individuals from various countries contributed to the development of the GDWQ. The efforts of all who contributed to the preparation of this document and in particular those who provided peer or public domain review comment are greatly appreciated.

Acronyms and abbreviations used in the text

DNA	deoxyribonucleic acid
EDTA	edetic acid; ethylenediaminetetraacetic acid
FAO	Food and Agriculture Organization of the United Nations
GDWQ	<i>Guidelines for Drinking-water Quality</i>
LOAEL	lowest-observed-adverse-effect level
NOAEL	no-observed-adverse-effect level
TDI	tolerable daily intake
USA	United States of America
WHO	World Health Organization

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1. GENERAL DESCRIPTION

1.1 Identity

Nickel 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%).

1.2 Physicochemical properties

<i>Property</i>	<i>Value</i>
Specific density	8.90 g/cm ³ at 25 °C
Melting point	1555 °C
Boiling point	2837 °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, 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 nickel 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).

1.3 Major uses and sources in drinking-water

The primary source of nickel in drinking-water is leaching from metals in contact with drinking-water, such as pipes and fittings. However, nickel may also be present in some groundwaters as a consequence of dissolution from nickel ore-bearing rocks.

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.

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, 2004).

1.4 Environmental fate

Nickel occurs predominantly as the ion $\text{Ni}(\text{H}_2\text{O})_6^{2+}$ in natural waters at pH 5–9 (IPCS, 1991). Complexes with ligands, such as OH^- , SO_4^{2-} , HCO_3^- , Cl^- , and NH_3 , are formed to a minor degree in this pH range. Nickel present as a consequence of leaching from nickel-plated fittings would be expected to be in a similar form. In assessing the hazard and potential risk from nickel in drinking-water, it is therefore

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appropriate to consider only data relating to water-soluble nickel salts, which will reflect the toxicity of the nickel ion.

2. ENVIRONMENTAL LEVELS AND HUMAN EXPOSURE

2.1 Air

Nickel 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 nickel (IARC, 1990).

2.2 Water

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/litre (urban areas) to 16.6 µg/litre (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/litre have been measured (RIVM, 1994).

In Canada, the median nickel level in drinking-water supplies was below the detection limit of 2 µg/litre; the maximum level observed was 69 µg/litre (Méranger et al., 1981). In drinking-water in the USA, 90% of all samples ($n = 2503$) contained ≤ 10 µg/litre, and 97% had nickel concentrations of ≤ 20 µg/litre (ATSDR, 1996).

In Europe, reported nickel concentrations in drinking-water were generally below 10 µg/litre (IPCS, 1991). Nickel levels below 1 µg/litre 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 are below 7 µg/litre (RIWA, 1994).

Increased nickel concentrations in groundwater and municipal tap water (100–2500 µg/litre) in polluted areas and areas in which natural nickel was mobilized have been reported (McNeely et al., 1972; Hopfer et al., 1989). Water left standing overnight in plumbing fittings plated with chromium on a base of nickel contained a nickel concentration up to 490 µg/litre, 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 nickel concentrations in groundwater wells in Arizona, USA. Mean nickel levels were 8–395 µg/litre; in some cases, nickel levels were in the range 1–5 mg/litre (Oakley & Korte, 1996).

Leaching of nickel from chromium–nickel 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 nickel is not of corrosive origin, but rather attributable to passive leaching of nickel ions from the surface of the pipes (Schwenk, 1992). Concentrations of nickel leaching from new stainless steel pipes used for drinking-water were up to 6 µg/litre (Nickel Development Institute, personal communication, 2004). This maximum concentration can be increased when the pipes are assembled with tinned copper and gunmetal fittings. Fittings such as taps, which are chromium-plated, release much higher concentrations, but these decrease significantly with time (EU, 2004).

Concentrations of nickel 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 nickel-plated elements; however, leaching decreases over time. Nickel concentrations in the range 100–400 µg/litre, with extreme values over 1000 µg/litre, have been reported (Rasmussen, 1983; Pedersen & Petersen, 1995; Berg et al., 2000; United Kingdom Drinking Water Inspectorate, 2002; EU, 2004).

Nickel concentrations in bottled mineral water will depend on the source and any treatment applied. Levels of nickel in a selection of bottled mineral waters were below the detection limit of 25 µg/litre (Allen et al., 1989).

2.3 Food

Since nickel is usually measured in food as total nickel, there is uncertainty as to the chemical form, although it is normally considered to be in the form of complex bound organic nickel, which may be less bioavailable than other forms (EU, 2004). Nickel 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 nickel (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 nickel 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 nickel 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 nickel concentrations in acid foodstuffs when new stainless steel pans were used.

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; 95% fractile, 0.27 mg) in Denmark

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(Fødevardirektoratet, 2000), and 0.16 mg in the USA (Myron et al., 1978). The dietary intake of nickel in a Canadian study ranged from 0.19 mg/day for 1- to 4-year-old children to 0.406 mg/day for 20- to 39-year-old males. The nickel intake for 20- to 39-year-old women was on average 0.275 mg/day (Dabeka & McKenzie, 1995). Dietary nickel intake by 0- to 12-month-old infants was on average 0.005 mg/kg of body weight per day (equal to 0.038 mg/day). Infants fed evaporated milk were exposed to 0.004 mg/kg of body weight per day, whereas infants fed soy-based formula were exposed to 0.010 mg/kg of body weight per day (Dabeka, 1989). Nickel is found in both human and cow's milk at concentrations reported to range from 0.001 to over 0.1 mg/litre, although concentrations in studies in the USA indicate levels in the region of 0.015 mg/kg (EU, 2004). 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 population group 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).

There is a great deal of concordance between the different studies of dietary intake, with the overall assessment that diet provides less than 0.2 mg/day.

2.4 Estimated total exposure and relative contribution of drinking-water

Food is the dominant source of nickel exposure in the non-smoking, non-occupationally exposed population. According to the 1981 United Kingdom Total Diet Study, the contribution from food is 0.22–0.23 mg/day per person. Later studies indicate that this is probably excessive, and 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 nickel) (MAFF, 1985). These figures are similar to those presented in the European risk assessment for nickel (EU, 2004). However, no account is taken of exposure from nickel-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 nickel concentrations in source water, particularly groundwater, are elevated or where there is significant input from nickel-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.

3. KINETICS AND METABOLISM IN LABORATORY ANIMALS AND HUMANS

3.1 Laboratory animals

Nickel is poorly absorbed from diets and is eliminated mainly in the faeces. Absorbed nickel is rapidly cleared from serum and excreted in urine (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 the intestinal mucosal cells (Tallkvist et al., 1994). In perfused rat jejunum, saturation of nickel uptake was observed at high concentrations of nickel chloride (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 that from food. After 24 h, 10–34% of a single oral dose of water-soluble nickel compounds (i.e., NiSO₄, NiCl₂, Ni(NO₃)₂) was absorbed, whereas less than 2% of a single oral dose of insoluble or scarcely soluble nickel compounds (i.e., NiO, Ni, Ni₃S₂, NiS) was absorbed. It is not known if the animals were fasted before treatment. The highest nickel concentrations were found in the kidneys and lungs, whereas nickel concentrations in the liver were low (Ishimatsu et al., 1995).

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 nickel in organs of rats orally exposed to nickel in drinking-water at concentrations of 100 mg/litre 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. Biliary excretion of nickel subcutaneously administered to rats as nickel chloride was less than 0.5% of the given dose (Marzouk & Sunderman, 1985).

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 nickel chloride to rats. The fetal organ with the highest nickel concentration was the urinary bladder (Sunderman et al., 1978).

A dose-dependent increase in nickel concentrations in rat milk was observed after a single subcutaneous injection of nickel chloride. The milk/plasma ratio was 0.02 (Dostal et al., 1989).

3.2 Humans

Following a 12-h fast, a volunteer ingested 20 µg of ⁶¹Ni-enriched nickel per kg of body weight as nickel nitrate in 1 litre of water. The serum nickel concentration peaked at 2 h at 34 µg/litre. 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 nickel dose (as nickel sulfate) added to drinking-water in 10 volunteers after a 12-h fast. Intestinal absorption was only 1% of the given dose when nickel as sulfate salt was added to scrambled eggs. The half-time for absorbed nickel averaged 28 ± 9 h (Sunderman et al., 1989). Plasma levels in fasting human subjects did not increase above fasting levels when 5 mg of nickel were 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 of body weight 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 ⁶¹Ni 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).

In studying a fatal case of nickel intoxication, the authors concluded that biliary excretion of nickel was of minor importance in humans (Grandjean et al., 1989).

According to the above studies, the daily amount of absorbed nickel in humans will be, on average, about 10 µg from food and about 5 µg or less from water.

Nickel has been detected in fetal tissues at levels similar to the levels found in adults (McNeely et al., 1972; Casey & Robinson, 1978).

Serum levels in the range 1.5–19 µg/litre were found in patients undergoing regular haemodialysis (Hopfer et al., 1989; Nixon et al., 1989). Significantly higher serum nickel levels were observed in non-occupationally exposed subjects from a heavily nickel-polluted area compared with levels in subjects living in a control area (nickel concentrations in tap water 109 ± 46 vs 0.6 ± 0.2 µg/litre; serum nickel levels 0.6 ± 0.3 vs 0.2 ± 0.2 µg/litre) (Hopfer et al., 1989). Tentative reference values for nickel in serum and urine have been proposed: 0.2 µg/litre or lower in serum, and 1–3 µg/litre in urine of healthy adults (Templeton et al., 1994b).

Nickel is also eliminated in the milk of lactating women. In studies reported in the USA, the nickel concentration in milk was in the region of 15 µg/kg (EU, 2004).

4. EFFECTS ON EXPERIMENTAL ANIMALS AND IN VITRO SYSTEMS

4.1 Acute exposure

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

4.2 Short-term exposure

Body weight gain, haemoglobin, and plasma alkaline phosphatase were significantly reduced in weanling rats exposed to nickel (as nickel acetate) at concentrations of 500 or 1000 mg/kg in the diet (equivalent to 25 or 50 mg/kg of body weight 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 of body weight per day).

In a 13-week study in which Sprague-Dawley rats were given 0, 44.7, 111.75, or 223.5 mg of nickel per litre in drinking-water as nickel sulfate (corresponding to 0, 4.5, 11.2, and 22.4 mg of nickel per kg of body weight 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/litre based on minor changes in body weight and relative weights of kidney and lung.

4.3 Long-term exposure

Rats (25 per sex per dose) were exposed to nickel (as nickel sulfate) in the diet at doses of 0, 100, 1000, or 2500 mg/kg (equivalent to 0, 5, 50, and 125 mg/kg of body weight per day) for 2 years (Ambrose et al., 1976). Growth was depressed in rats at 1000 and 2500 mg/kg of diet, but there were indications that decreased food consumption might explain the decreased body weight gains, particularly at 2500 mg/kg of diet. However, no statistical analysis seems to have been performed. Survival was overall very poor, especially in the control groups and the 2500 mg/kg of diet groups. In females at 1000 and 2500 mg/kg of diet, the 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. No histological or gross pathological findings related to nickel exposure were observed. The highest nickel concentrations were found in the kidneys. The NOAEL in this study was 5 mg/kg of body weight per day. However, the study does not meet current standards for long-term studies, mainly because of the low survival rate. The observed changes in organ weights in female rats might in part be due to changes in food and water consumption. Also, both gross and histopathological examinations of the animals were negative,

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although there were 20–30% changes in relative organ weights. It can thus not be excluded that the observed changes in relative organ weights were related to changes in food and/or water consumption rather than to a toxic effect of nickel.

Increased relative kidney weight was observed in rats exposed to nickel (as nickel sulfate) in drinking-water at a daily dose of about 7 mg/kg of body weight for up to 6 months (Vyskocil et al., 1994). There was an increased excretion of albumin in urine in females, but there were no changes in total protein, beta-2-microglobulin, *N*-acetyl-beta-D-glucosaminidase, or lactate dehydrogenase in urine due to nickel exposure.

In a 2-year study, dogs (three per sex per dose) were exposed to 0, 100, 1000, or 2500 mg of nickel per kg of diet (equivalent to 0, 2.5, 25, and 62.5 mg/kg of body weight 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 in this study was 25 mg/kg of body weight per day (Ambrose et al., 1976).

4.4 Reproductive and developmental toxicity

Intraperitoneal administration of nickel nitrate (12 mg of nickel per kg of body weight) to male mice resulted in reduced fertilizing capacity of spermatozoa; no effects were seen at 8 mg of nickel per kg of body weight (Jacquet & Mayence, 1982).

A reduced number of live pups and reduced body weights of fetuses were observed in rats exposed to single doses of nickel chloride (16 mg of nickel per kg of body weight) or nickel subsulfide (80 mg of nickel per kg of body weight) administered intramuscularly on day 8 and day 6, respectively. No congenital anomalies were found in the fetuses (Sunderman et al., 1978).

Velazquez & Poirer (1994) and ATSDR (1996) described a two-generation study in rats. Nickel chloride was administered in drinking-water at concentrations of 0, 50, 250, or 500 mg/litre (equal to 0, 7, 31, and 52 mg of nickel per kg of body weight per day) from 90 days before breeding. Along with changes in maternal body weight and liver weight at the 500 mg/litre dose level in the P₀ generation, there were also a dose-related decrease in live litter size and pup weight and increased neonatal mortality. In the F₁ generation, there was dose-related mortality between 3 and 7 weeks of age at the 250 and 500 mg/litre dose levels. For the F₁ matings, there were also dose-related decreases in live litter size and increased mortality per litter, but this was significant only in the high-dose group. Decreased food intake and water intake were observed in the exposed animals. Also, the room temperature was up to 6 °C higher than normal at certain times during gestation and the early postnatal days. Lower than normal levels of humidity were also recorded. Thus, the NOAEL in this study is considered to be 7 mg of nickel per kg of body weight per day; however, because of the problems referred to, it is difficult to make a direct association between the effects reported in this study and nickel exposure.

Female Long-Evans rats were exposed to nickel as nickel chloride for 11 weeks prior to mating and then during two successive gestation periods (G1 and G2) and lactation periods (L1 and L2) at concentrations of 0, 10, 50, or 250 mg/litre (equal to 0, 1.3, 6.8, and 31.6 mg of nickel per kg of body weight per day) in drinking-water (Smith et al., 1993). Dams drinking water containing nickel at 31.6 mg/kg of body weight per day consumed less liquid and more food per kg of body weight 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. It was noted that 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 of body weight per day represented the LOAEL in this study, although this is considered to be conservative, owing to 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, 2004). The range-finding and definitive studies for the rat two-generation reproduction study of nickel sulfate hexahydrate 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 utilizing small numbers of animals and nickel sulfate hexahydrate exposures of 0, 5, 15, 25, 50, 75, and 150 mg/kg of body weight per day. (Note that the lower 95% confidence limit for lethality from nickel sulfate hexahydrate is 170 mg/kg of body weight per day.) Lethality was observed at the 150 mg/kg of body weight per day exposure level.

The second part of the range-finding study (i.e., a one-generation reproductive toxicity study) utilized nickel sulfate hexahydrate exposures of 0, 10, 20, 30, 50, and 75 mg/kg of body weight 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 of body weight per day exposures and more questionable increases at the 10 and 20 mg/kg of body weight 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 of body weight per day level and was lower than historical controls at or above 30 mg/kg of body weight per day.

Based upon the results of the one-generation study, nickel sulfate hexahydrate exposure levels of 1, 2.5, 5.0, and 10 mg/kg of body weight 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 (F₀) 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 F₀ 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 F₀ animals during mating, during pregnancy, and through the weaning of their first-generation (F₁) offspring. At weaning, the administration of the substance was continued to F₁ offspring during their growth into adulthood, mating, and production of an F₂ generation and up until the F₂ 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 highest dose selected (10 mg/kg of body weight per day, or 2.2 mg of nickel per kg of body weight per day) was the LOAEL for adult and offspring rats for all the end-points studied, including the variable of post-implantation/perinatal lethality (SLI, 2000; EU, 2004), and the NOAEL was 5 mg/kg of body weight per day or 1.1 mg of nickel per kg of body weight per day.

In a three-generation study in rats at dietary levels of 250, 500, or 1000 mg of nickel (administered as nickel sulfate) per kg of diet (equivalent to 12.5, 25, or 50 mg/kg of body weight 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 nickel 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 nickel in drinking-water at 5 mg/litre, corresponding to 0.2 mg/kg of body weight per day (Schroeder & Mitchener, 1971).

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

4.5 Mutagenicity and related end-points

Nickel compounds are generally inactive in bacterial mutation assays but active in mammalian cell systems (IPCS, 1991). It was concluded that nickel-induced responses involved cell toxicity in all gene mutation studies using 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, nickel ions have been shown to potentiate the effects of other mutagenic agents, which 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 TERA (1999) and as part of the EU (2004) risk assessment. Most studies relate to water-soluble compounds, and the TERA (1999) review 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.”

4.6 Carcinogenicity

A number of studies on the carcinogenicity of nickel compounds in experimental animals are available (IARC, 1990; Aitio, 1995). Generally, tumours are induced at the site of administration of the nickel compound. For instance, several nickel compounds induce 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 nickel compounds. The incidence of tumours was not higher in rats exposed to drinking-water containing nickel at 5 mg/litre 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 nickel per kg of body weight 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 nickel. A similar 2-year study in dogs also revealed no increase in tumours (Ambrose et al., 1976).

4.7 Other effects

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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 nickel sulfate in drinking-water for 180 days. At the lowest dose (44 mg of nickel per kg of body weight per day), decreased thymus weight was observed, but there was no nickel-induced immunosuppression 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 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 nickel sulfate in drinking-water at doses of 0, 44, 108, or 150 mg of nickel per kg of body weight per day for 180 days (Dieter et al., 1988). The LOAEL in this study was 44 mg of nickel per kg of body weight per day.

5. EFFECTS ON HUMANS

5.1 Acute exposure

A 2½-year-old girl died after ingesting about 15 g of nickel sulfate 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 nickel sulfate and nickel chloride (1.63 g of nickel per litre). The nickel doses in persons who developed symptoms were estimated to range from 7 to 35 mg/kg of body weight. 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 hyperbilirubinaemia 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 nickel after intrarenal injection enhances 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 between 13 and 1340 µg/litre in persons with symptoms (Sunderman et al., 1988).

Seven hours after ingesting nickel sulfate in drinking-water (50 µg of nickel per kg of body weight), a 55-year-old man developed left homonymous haemianopsia, which lasted 2 h (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/litre and persisted for 3–13 h after dialysis.

5.2 Skin irritation and hypersensitivity

Allergic contact dermatitis is the most prevalent effect of nickel in the general population. A recent epidemiological investigation showed that 20% of young (15–34 years) Danish women and 10% of older (35–69 years) women were nickel-sensitized, compared with only 2–4% of Danish men (15–69 years) (Nielsen & Menné, 1992). The prevalence of nickel allergy was found to be 7–10% in previously published reports (Menné et al., 1989). EDTA reduced the number and severity of patch test reactions to nickel sulfate in nickel-sensitive subjects (Allenby & Goodwin, 1983).

Systemically induced flares of dermatitis are reported after oral challenge of nickel-sensitive women with 0.5–5.6 mg of nickel as nickel sulfate 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 persons 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; Gawkrödger et al., 1986).

After an oral dose of 1 mg of nickel, significantly higher levels of nickel were found in the urine of atopic patients (i.e., persons with a history of flexural dermatitis) compared with controls, indicating a higher gastrointestinal absorption of nickel in atopic persons (Hindsén et al., 1994). No such difference was found between nickel-allergic patients and controls. The small number of patients may explain these unexpected findings.

There are several reports on the effects of diets low or high in nickel, but it is still a matter of discussion 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 the period (i.e., days 0–11) and that the symptoms thus were nickel-induced. However, it should be noted that in some subjects the severity of the eczema (i.e., the number of vesicles in the palm of the hand) varied markedly between day 14 or 21 before the challenge period and the start of the challenge period.

Oral hyposensitization to nickel was reported after six weekly doses of 5 mg of nickel in a capsule (Sjöwall et al., 1978) and 0.1 mg of nickel sulfate daily for 3 years (Panzani et al., 1995). Cutaneous lesions were improved in eight patients with contact

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allergy to nickel after oral exposure to 5 mg of nickel weekly for 8 weeks (Bagot et al., 1995). Nickel in water (as nickel sulfate) was given to 25 nickel-sensitive women in daily doses of 0.01–0.04 mg/kg of body weight per day for 3 months after they had been challenged once with 2.24 mg of nickel (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 nickel in water (0.01–0.03 mg of nickel per kg of body weight per 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.

The LOAEL established after oral provocation of patients with empty stomachs was reported as 12 µg/kg of body weight (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 of body weight) was reported to result in a flare-up of dermatitis in an earlier patch test site in 2 of 10 nickel-sensitive patients. The dose of 12 µg/kg of body weight was considered to be the acute LOAEL in fasting patients on a 48-h diet with reduced nickel content. A cumulative LOAEL could be lower, but a LOAEL in non-fasting patients is probably higher because of reduced absorption of nickel ions when mixed in food.

5.3 Carcinogenicity

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

Inhalation is an important route of exposure to nickel and its salts in relation to health risks. IARC (1990) concluded that nickel compounds are carcinogenic to humans (Group 1), whereas metallic nickel is possibly carcinogenic to humans (Group 2B). However, there is a lack of evidence of a carcinogenic risk from oral exposure to nickel.

A number of subsequent epidemiological studies have also supported these earlier findings (TERA, 1999; EU, 2004), but there remain no data on oral exposure.

6. PRACTICAL ASPECTS

6.1 Analytical methods and analytical 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 0.5–100 µg/litre (ISO, 1986), whereas inductively coupled plasma atomic emission spectroscopy can be used for the determination of nickel with a limit of detection of about 10 µg/litre (ISO, 1996). A limit of detection of 0.1 µg/litre or better should be achievable using inductively coupled plasma mass spectrometry. The limit of detection is approximately 20 µg/litre by flame atomic absorption spectrometry, 15 µg/litre by inductively coupled plasma, 1 µg/litre by electrothermal atomic absorption spectrometry, and 1 µg/litre by inductively coupled plasma optical emission spectrometry. Alternatively, electrothermal atomic absorption spectrometry can be used.

6.2 Treatment and control methods and technical achievability

Nickel can be found in drinking-water as a consequence of its presence in alloys used in contact with drinking-water, chromium or nickel plating of fittings, or its presence in water sources, usually as a consequence of dissolution from naturally occurring nickel-bearing strata in groundwater. In the first two cases, control is by appropriate control of materials in contact with drinking-water or, in the second instance, education of consumers to flush chromium- or nickel-plated taps before using the water.

Conventional surface water treatment, comprising chemical coagulation, sedimentation, and filtration, can achieve 35–80% removal of nickel (Zemansky, 1974; Hunter et al., 1987; Duguet & Rizet, 1996). Better nickel 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 nickel removal (Welté, 2002). In a review of nickel removal, it was concluded that conventional coagulation, clarification, and granular activated carbon filtration can give nickel removals of 35–80%, depending on the speciation of the nickel. 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).

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

7. GUIDELINE VALUE

In a well conducted two-generation study on rats, a NOAEL of 1.1 mg of nickel per kg of body weight per day was identified for all the end-points studied, including the variable of post-implantation/perinatal lethality (SLI, 2000; EU, 2004). The

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application of an uncertainty factor of 100 (10 to account for interspecies variation and 10 to account for intraspecies variation) gives a TDI of 11 µg/kg of body weight. Data show that the exposure from food is moderate and that a higher exposure could be allowed from drinking-water in consideration of the circumstances when naturally elevated nickel is present. A health-based value of 70 µg/litre (rounded from 66 µg/litre) could be determined from this TDI by assuming a 60-kg adult drinking 2 litres of water per day and allocating 20% of the TDI to drinking-water.

The LOAEL established after provocation of fasted patients with an empty stomach is 12 µg/kg of body weight (Nielsen et al., 1999). Because this is based on a highly sensitive population, it is not necessary to include an additional uncertainty factor. Based on these data, the guideline value, to allow for nickel-sensitive individuals, can be calculated as 70 µg/litre (rounded value), assuming a 60-kg adult drinking 2 litres of water per day and allocating 20% of total daily intake to drinking-water. Although this is very close to the acute LOAEL established by Nielsen et al. (1999), the absorption from drinking-water is 10- to 40-fold higher than the absorption from food, and basing the total acceptable intake for oral challenge from studies using drinking-water on an empty stomach in fasted patients can be considered a worst-case scenario.

Based on consideration of both the animal and human data, assuming a 60-kg adult drinking 2 litres of water per day and making an allocation of 20% of the TDI to drinking-water in order to allow for circumstances where naturally elevated nickel occurs in drinking-water, the guideline value is 70 µg/litre. It must be emphasized that it is not appropriate to allow nickel concentrations to be increased to the guideline value from pollution or where cost-effective controls are available.

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