Contaminants in soil: updated collation of toxicological data and intake values for humans

Nickel

Better Regulation science programme
Science report: SC050021/ Tox 8
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Steve Killeen

Head of Science
Executive summary

This report, one of a number on the assessment of risks to human health from contaminants in soil, presents key data and expert opinions on the toxicology and intake of nickel. It provides an update to an earlier report by the Department for Environment, Food and Rural Affairs (Defra) and the Environment Agency published in March 2002.

The report is based on findings identified in a series of literature searches, the latest of which was undertaken in November 2008. These findings, together with evaluations of national, European and international expert groups, are used to recommend health criteria values (HCVs) and estimate mean daily intakes (MDIs) for nickel in the UK.

Chemical overview

Nickel exists in nature primarily in oxidation state +2 as nickel salts, but its many uses in metal form mean that human exposure to nickel in oxidation state 0 is common. Water-soluble nickel salts include the chloride and sulphate, while less-soluble nickel compounds include sulphide and oxide compounds. Nickel occurs in environmental media largely due to anthropogenic activity.

Pharmacokinetics

On inhalation, absorption of soluble nickel compounds may be extensive (up to 100%), while absorption of insoluble compounds and metallic nickel is much lower. Similarly, following oral exposure, soluble nickel compounds are more extensively absorbed than are insoluble compounds. For example, rats absorbed about 10–34% of soluble nickel salts on gavage administration, compared with about 1–2% of insoluble nickel compounds and metal. The medium influences the extent of absorption, with humans absorbing nearly 30% soluble nickel sulphate from water compared with only 1% when it was given in food. The dermal absorption of nickel is low. Absorbed nickel is transported by the blood as protein complexes and distributed to the tissues, notably the kidneys, lungs and liver. Absorbed nickel is excreted primarily in the urine.

Toxicity

Nickel is a potent skin sensitisier, and as many as 1–4% of men and 8–20% of women in the general population may be nickel-sensitive. The threshold for initial induction of sensitisation is unknown. Oral ingestion of nickel can also produce skin sensitisation reactions in individuals who have been previously sensitised to nickel. Sensitised individuals have experienced skin reactions following ingestion of about 0.5–0.7 mg of nickel. In a volunteer study, an acute oral dose of 12 µg kg⁻¹ bw on an empty stomach induced hand eczema in women with an established skin sensitivity to nickel.

The other main concern for oral exposure to nickel is its developmental toxicity potential, which has been observed in experimental animal studies. In a two-generation rat study, a wide range of developmental effects were observed at doses of 2.2 mg nickel kg⁻¹ bw day⁻¹.

The respiratory system is the primary site of toxicity of inhaled nickel in both humans and laboratory animals. Effects seen in occupationally exposed workers include chronic bronchitis, emphysema, reduced vital capacity and asthma. Respiratory effects were seen in rodents chronically exposed to nickel sulphate at 60 µg m⁻³.

There is adequate evidence from occupational studies that soluble nickel salts and the mixture of sulphides and oxides present in nickel refinery dust are also carcinogenic to the lungs and/or nasal tissues in humans. Lifetime inhalation of nickel subsulphide or nickel oxide also led to lung tumours in rats, while a similar study on metallic nickel
found increases in adrenal gland tumours but not respiratory tract cancers. Nickel sulphate showed no carcinogenic activity in lifetime studies in rats or mice exposed by inhalation, or in rats treated by gavage or via the diet. There is some evidence that occupational exposure to nickel compounds can induce chromosome aberrations, and nickel salts (especially the sulphate and chloride) have shown activity in a range of in vivo and in vitro screening tests for genotoxicity. Although the evidence is not clear, several expert groups have therefore assumed that the genotoxic character displayed by nickel could play a role in tumour development and, consequently, there might not be a threshold for the carcinogenicity of inhaled nickel. Other expert groups, however, have concluded that there will be a threshold. For oral exposure, nickel compounds tested thus far have shown no carcinogenic potential.

**Health Criteria Values and risk assessment**

For oral exposure, a tolerable daily intake (TDI\textsubscript{oral}) of 12 µg kg\textsuperscript{-1} bw day\textsuperscript{-1} is proposed, based on the developmental effects seen in animals and the skin hypersensitivity reactions in humans.

For inhalation exposure, an HCV based on carcinogenicity or on non-cancer effects would in each case be approximately 0.006 µg kg\textsuperscript{-1} bw day\textsuperscript{-1}. This value is recommended here as an inhalation tolerable daily intake (TDI\textsubscript{inh}) for use in deriving SGVs.

Both oral and dermal exposure to nickel can cause hypersensitivity reactions of the skin. This should therefore be considered in a risk assessment where there is exposure via both routes. Inhalation exposure might also be expected to contribute to these effects, but only to a minimal extent at the TDI\textsubscript{inh}. Oral and dermal exposures do not cause the effects on the respiratory system that are the critical effects for inhalation exposure.

**Mean daily intakes from non-soil sources**

The adult mean daily intake of nickel from food and drinking-water (MDI\textsubscript{oral}) is estimated to be 130 µg day\textsuperscript{-1}. The adult mean daily intake of nickel from inhalation of ambient air (MDI\textsubscript{inh}) is estimated to be 0.06 µg day\textsuperscript{-1}.

**HCV and MDI values for nickel**

<table>
<thead>
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<th>Oral</th>
<th>Inhalation</th>
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<tr>
<td>MDI</td>
<td>µg day\textsuperscript{-1}</td>
<td>130</td>
<td>0.06</td>
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<tr>
<td>MDI for 70-kg adult</td>
<td>µg kg\textsuperscript{-1} bw day\textsuperscript{-1}</td>
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<td>MDI for 20-kg child</td>
<td>µg kg\textsuperscript{-1} bw day\textsuperscript{-1}</td>
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<tr>
<td>TDI</td>
<td>µg kg\textsuperscript{-1} bw day\textsuperscript{-1}</td>
<td>12</td>
<td>0.006</td>
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\textsuperscript{a} See Environment Agency (2009a) for details of MDI conversion factors.

**Summary of changes to HCV recommendations**

The TDI\textsubscript{inh} of 0.006 µg kg\textsuperscript{-1} bw day\textsuperscript{-1} is the same as was proposed in the previous report published in 2002. The TDI\textsubscript{oral} recommended in the 2002 TOX report was based on the then WHO TDI of 5 µg kg\textsuperscript{-1} bw day\textsuperscript{-1}. WHO has since revised its TDI to 12 µg kg\textsuperscript{-1} bw day\textsuperscript{-1}. The TDI\textsubscript{oral} recommended in this report is in line with the WHO revision.
Acknowledgements

This document was initially written in 1997 by RPS Group plc. It was updated by TNO BIBRA International Ltd in 2002 and published. The 2002 report was updated in 2009 with the assistance of bibra toxicology advice & consulting.

The Environment Agency is also grateful for the valuable inputs from various government agencies and departments, particularly the Health Protection Agency and Food Standards Agency. It would also like to thank the Medical Research Council’s Institute for Environment and Health for peer reviewing the original document written by RPS Group plc.
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1 Introduction

1.1 Update to R&D Publication TOX 8

This report presents key data and expert opinion on the human toxicology and non-soil intakes of nickel. It updates and replaces R&D Publication TOX 8 published in 2002 (Defra and Environment Agency, 2002), taking into account:

- updates to the toxicological framework document that describes how the human toxicity of chemical soil contaminants is assessed (Environment Agency, 2009a)
- further review of the scientific literature on the toxicology of nickel and the findings and opinion of national, European, and international expert groups up to November 2008 (see Appendix).

1.2 Background

The main purpose of this report is to provide technical guidance to regulators and their advisors in support of the statutory regimes addressing land contamination, particularly Part 2A of the Environmental Protection Act 1990 and development control under the Town and Country Planning Acts.

Part 2A defines the term contaminated land according to whether or not it poses a significant risk to human health and/or the environment.

In relation to health effects not attributable to radioactivity, it considers land to be contaminated land where it:

“... appears to the local authority in whose area the land is situated to be in such a condition by reason of substances in, on or under the land that (a) significant harm [to human health] is being caused or there is a significant possibility of such harm being caused.”

Statutory guidance (Defra, 2006) explains that significant harm to a person would include such health effects as death, disease, serious injury, genetic mutation, birth defects or the impairment of reproductive function. The definition of significant harm therefore encompasses a broad range of possible health outcomes from chemical exposure.

Land contamination is a material consideration within the planning regime. A planning authority has to consider the potential implications of contamination both when it is developing structure or local plans (or unitary development plans) and when it is considering applications for planning permission. Planning Policy Statement 23: Planning and Pollution Control (PPS 23) (ODPM, 2004) explains the relationship between planning and Part 2A. In the granting of planning permission for new development including permission to carry out remediation, PPS 23 states that remediation must remove unacceptable risk to human health and make the site suitable for its intended use. As a minimum, after carrying out a development and

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1 For the purpose of the Statutory Guidance, disease is taken to mean an unhealthy condition of the body or part of it and can include, for example, cancer, mental dysfunction, liver dysfunction or extensive skin ailments.
2

commencement of its use, the land should not be capable of being determined as contaminated land under Part 2A.

1.3 Advice on using this report

This report reviews the key toxicological literature and expert opinion on health effects arising from exposure to nickel. It has been prepared by the Environment Agency with the support of the Health Protection Agency (HPA) and the Food Standards Agency (FSA).

This report recommends one or more Health Criteria Values (HCVs) for use in assessing the risks to health from long-term human exposure to nickel in soil. HCVs are an important part of the risk assessment process. They are used subsequently in the derivation of Soil Guideline Values (SGVs), which are scientifically-based generic assessment criteria used to simplify the screening of land contamination (Defra and Environment Agency, 2004). HCVs can also be used to derive site-specific assessment criteria for soil as part of any Detailed Quantitative Risk Assessment.

The HCVs set out in this report represent levels of minimal or tolerable risk from long-term human exposure to chemicals in soil. They represent a baseline and health protective position to minimise risks of significant harm. They do not represent thresholds above which there is an unacceptable intake or a significant possibility of significant harm in the context of Part 2A, but they can be a useful starting point for such an assessment (Defra, 2008). Science alone cannot answer the question of whether or not a given possibility of significant harm is significant, since what is either significant or unacceptable is a matter of socio-political judgment and the law entrusts decisions on this to the enforcing authorities (Defra, 2008).

In the context of Part 2A, an assessor using the HCVs in this report can conclude that (Defra, 2008):

- human exposure at or below the HCV is unlikely to represent a significant possibility of significant harm;
- human exposure above the HCV might represent a significant possibility of significant harm – with the significance linked to the margin of exceedance, the duration and frequency of exposure, and other factors that the enforcing authority may wish to take into account.

The information presented in this report is intended for technical professionals familiar with assessment of the risks posed to human health by land contamination. It should be read in conjunction with Science Report SC050021/SR2 Human Health Toxicological Assessment of Contaminants in Soil (Environment Agency, 2009a), which introduces and describes the terms and general technical approaches used in this review of nickel.

Although HCVs are an important quantitative tool for judging the health risks associated with a particular level of human exposure, they should not be used in isolation from the rest of the information presented in this report. Further understanding of the mechanisms of toxicity and the range of potential health effects are important to assessing the risks posed by nickel at any level of exposure both individually and when combined with other chemicals present.

The remainder of this report is separated into the following sections:

Section 2 provides a short overview of the chemistry of nickel, its main uses and its behaviour in the environment with particular reference to soils.
Section 3 presents information obtained from the literature search on the toxicity of nickel (pharmacokinetics, acute toxicity, repeated dose toxicity, reproductive and developmental toxicity, genotoxicity and carcinogenicity).

Section 4 summarises evidence of the effects of nickel deficiency.

Section 5 sets out the HCVs derived by various expert groups worldwide.

Section 6 provides estimates of exposure to background levels of nickel in food and water, air and other sources.

Section 7 presents the conclusions drawn from the literature review including the recommendations for HCVs.
2 Chemical overview

In its elemental form, nickel (CAS No. 7440-02-0) is a hard, lustrous, silvery-white transition metal (ATSDR, 2005). However, its powder is reactive in air and may spontaneously ignite (ATSDR, 2005). Nickel is resistant to corrosion by water and air under ambient conditions and combines readily with other metals including iron, copper, chromium and zinc to form alloys (ATSDR, 2005; Kabata-Pendias and Mukherjee, 2007).

Nickel occurs naturally in the environment although rarely in its elemental form (EC-JRC, 2005a). Nickel forms compounds in various oxidation states although the most important is the +2 oxidation state (divalent), with the -1, +3 and +4 states being encountered less frequently (ATSDR, 2005). It forms divalent salts with virtually every anion and has an extensive aqueous chemistry based on the green coloured hexahydrate ion, \([\text{Ni(H}_2\text{O)}_6]^{2+}\). Nickel also forms organometallic complexes, including nickel carbonyl, but these are generally not very stable (Greenwood and Earnshaw, 1997).

The primary uses of nickel metal are in the production of alloys including stainless steel, in nickel plating, in the manufacture of nickel containing products such as batteries and welding electrodes, and in the production of chemicals containing nickel including nickel sulphate, nickel chloride, and in catalysts (EC-JRC, 2005a). Nickel alloys and platings are commonly found in transport vehicles, tools, electrical and household goods, jewellery and coins (IPCS, 1991).

Nickel occurs naturally in soils as a result of the weathering of the parent rock (McGrath, 1995). Anthropogenic activity has resulted in the widespread atmospheric deposition of nickel from the burning of oil and coal and the incineration of wastes and sewage sludge (IPCS, 1991; McGrath, 1995; Klein and Costa, 2007).

The soil chemistry of nickel is based on the divalent cation (McGrath, 1995). Above pH 8, the hydroxy complex is also a major species in soil solution, whilst in acid soils nickel sulphate and nickel hydrogen phosphate are important, depending on the levels of sulphate and phosphate present (McGrath, 1995). In surface and sludge amended soils, nickel may be increasingly bound to organic matter, a part of which forms easily soluble chelates (Kabata-Pendias and Mukherjee, 2007). In the presence of fulvic and humic acids, these complexes are much more mobile and may be more important than the hydrated divalent cation in soil solution chemistry (ATSDR, 2005).

The predominant salts of nickel for which epidemiology data or animal toxicity data are available include the soluble chloride (NiCl\(_2\)) and sulphate (NiSO\(_4\)) (which have been used in nickel plating) and the insoluble subsulphide (Ni\(_3\)S\(_2\)) (an intermediate in the refining of some nickel ores) and oxide (NiO) (used in stainless steel and alloy production).
3  Toxicity

3.1  Literature sources

Major reviews of the toxicology of nickel have been published by:

- European Commission (EC, 2001; CSTEE, 2001; EC-JRC, 2005a, 2005b, 2005c, 2005d, 2005e);
- World Health Organization (WHO, 2000, 2006a, 2006b, 2007);
- International Programme on Chemical Safety (IPCS, 1991);
- International Agency for Research on Cancer (IARC, 1990, 1999);

This section is largely based on the major conclusions of these reviews. Those studies used in deriving HCVs receive particular attention in this report. In general, the primary literature has not been consulted.

3.2  Pharmacokinetics

3.2.1  Absorption

Nickel and its inorganic compounds can be absorbed in humans via the gastrointestinal tract and respiratory passages. Dermal absorption is poor, but, nonetheless, important in the pathogenesis of skin sensitisation (see Section 3.4.2). Absorption depends on the quantities administered and on the physical-chemical characteristics of the nickel compound. Soluble nickel compounds dissociate readily in the aqueous environment of biological membranes, thus facilitating their transport as metal ions. Conversely, insoluble nickel compounds are relatively poorly absorbed (IPCS, 1991; EC-JRC, 2005a; WHO, 2006b).

As with all particles, the deposition pattern of inhaled nickel particles in the lung – and hence the potential for, and the mechanism of, absorption – is related to particle size, with larger particles depositing in the upper airways while smaller particles pass deeper into the lungs (ATSDR, 2005). Limited rodent data have shown 50–80% absorption of inhaled soluble nickel salts and suggest absorption may be as high as 97–99% (EC-JRC, 2005e). Absorption of insoluble salts and metallic nickel would be expected to be more limited, e.g. about 6% for the metal (EC-JRC, 2005a). Urinary nickel concentrations were found to be higher in workers exposed to the soluble nickel chloride and sulphate than in those exposed to the less soluble nickel oxide and subsulphide, again indicating a greater systemic absorption of the soluble salts (ATSDR, 2005).

Draft EU risk assessments for nickel chloride and nickel sulphate have concluded that their inhalation absorption should be considered complete for particles with an aerodynamic diameter less than 5 µm. Pulmonary absorption of larger particles will be negligible, but as these particles will be cleared from the lungs via mucociliary action and swallowed, absorption from the gastrointestinal tract will occur (EC-JRC, 2005b, 2005e).
In a human study, about 27% of nickel sulphate given in drinking-water was absorbed, markedly higher than the 1% absorption when it was given with food (Sunderman et al., 1989; IPCS, 1991; WHO, 2006b). In rats, 10–34% of an oral dose of water-soluble nickel compounds (nickel sulphate, chloride and nitrate) was absorbed compared with less than 1–2% of insoluble or scarcely soluble compounds (nickel metal, oxide, sulphide and subsulphide) (Ishimatsu et al., 1995; WHO, 2006b). The Danish Environmental Protection Agency has concluded that it is appropriate in risk assessments on nickel sulphate, nickel chloride, nickel nitrate and nickel carbonate to use oral absorption values of 5% and 30% in non-fasting and fasting people respectively (Andersen et al., 2006).

3.2.2 Distribution, metabolism and excretion

Experiments have shown that metallic nickel can become oxidised to nickel ions in sweat (and thence be absorbed across the skin) (Larese et al., 2007).

On entry into the bloodstream, nickel ions are rapidly distributed throughout the body. In human serum, nickel is present as a complex associated with albumin (34%), another complex associated with a nickel-metalloprotein (26%), and as ultrafiltrable material (40%). In rodents, a primary site of elevated tissue levels is the kidney. In addition, elevated concentrations are often found in the lungs (including after oral dosing) and liver (EC-JRC, 2005a). Human and rodent studies have demonstrated transfer across the placenta (IPCS, 1991; EC-JRC, 2005a).

Unabsorbed ingested nickel is eliminated in the faeces. Nickel absorbed into the bloodstream is rapidly cleared from serum and excreted in the urine (IPCS, 1991; EC-JRC, 2005a; WHO, 2007). In humans, nickel excreted in the urine following oral intake of soluble nickel compounds accounts for 20–30% of the dose when the nickel compound is administered in drinking-water to fasting subjects compared with 1–5% when administered together with food or in close proximity to a meal, reflecting the different extent of absorption from food and water (EC-JRC, 2005a). Following an oral dose in mice, less than 1% of the dose remained unexcreted after five days (Nielsen et al., 1993).

3.3 Acute toxicity

3.3.1 Inhalation

Data on the acute inhalation toxicity of nickel compounds in humans are limited. An adult died from respiratory distress 13 days after a 90-minute exposure to metallic nickel particles at an estimated concentration of 382 mg m⁻³. Post-mortem examination revealed alveolar wall damage and oedema, and marked renal tubular necrosis (ATSDR, 2005; WHO, 2006b).

Nickel carbonyl (which is not likely to be present in soil) appears to be exceptionally toxic by inhalation. Local effects in the lungs following inhalation exposure include haemorrhage, oedema and cellular derangement. Other effects include frontal headache, vertigo, nausea, vomiting, insomnia, and irritability. The liver, kidneys, adrenal glands, spleen, and brain are also affected (IPCS, 1991; WHO, 2006b).

Nickel oxide is a suspected cause of metal fume fever. Symptoms typically appear 4–12 hours after inhaling high (unspecified) concentrations of respirable nickel oxide particles and include a sweet or metallic taste in the mouth, throat irritation, cough,
dyspnoea, malaise, fatigue, myalgias (muscle pains) and arthralgias (joint pains). Fever develops later, associated with profuse sweating and shaking chills. The syndrome may last for 24–48 hours (Kelleher et al., 2000).

3.3.2 Oral

A two-year-old child died from heart failure after ingesting about 570 mg kg\(^{-1}\) bodyweight (bw) nickel as nickel sulphate (Daldrup et al., 1983). The oral exposure of 22 workers to nickel (estimated doses 7–35 mg kg\(^{-1}\) bw) via contaminated drinking-water resulted in reports of nausea, vomiting, diarrhoea, giddiness, lassitude, headache and shortness of breath for periods ranging from a few hours up to two days. Elevated urinary albumin suggested mild, transient kidney toxicity (Sunderman et al., 1988). Gastrointestinal distress, muscular pain and a temporary increase in blood reticulocytes, serum bilirubin and urine albumin were recorded in humans following ingestion of nickel compounds (Daldrup et al., 1983). Single oral doses of nickel can also exacerbate allergic dermatitis in nickel-sensitive individuals (discussed further in Section 3.4.2).

In rats, the acute oral toxicity of the metal and insoluble salts (e.g. the oxides and sulphides) is low, with LD\(_{50}\) values exceeding 5,000 mg kg\(^{-1}\) bw. The slightly soluble carbonate and hydroxide have LD\(_{50}\) values of about 1,000–1,600 mg kg\(^{-1}\) bw (as does the soluble nitrate), while the soluble chloride, sulphate and acetate are more toxic, with values in the range 175–529 mg kg\(^{-1}\) bw (EC-JRC, 2005a).

3.4 Repeated dose toxicity

3.4.1 General toxicity

**Inhalation**

The respiratory system is the primary site of toxicity of inhaled nickel and its compounds. Non-cancer respiratory effects in nickel-exposed workers have included chronic bronchitis, emphysema, reduced vital capacity, chronic rhinitis, sinusitis, nasal separations and asthma. Interpretation of many of the available studies has been complicated by exposure to other toxic agents and irritants such as arsenic, chromium, iron, lead and uranium (IPCS, 1991).

Dose-related changes in the respiratory tract, including increases in alveolar proteinosis, histiocytosis, chronic inflammation and bronchiolar-alveolar hyperplasia, occurred in rats exposed to atmospheres containing metallic nickel powder. The rats were treated for six hours daily, five days per week for two years, followed by a six-month period without exposure. The lesions were seen in all treatment groups including those exposed to the lowest tested concentration of 0.1 mg m\(^{-3}\) (Oller et al., 2008). Similar effects were seen in the preliminary 13-week study at 1 mg m\(^{-3}\), again the lowest concentration tested (WIL, 2003).

Inhalation studies, conducted under the US National Toxicology Program (NTP), are available on certain nickel salts. Exposure of rats and mice for six hours per day, five days per week, for 16 or 90 days resulted in atrophy of olfactory nasal epithelium, chronic active inflammation in the lungs, fibrosis and increased lung weight. These effects occurred at nickel concentrations of 0.06 mg m\(^{-3}\) as nickel sulphate, 0.11 mg m\(^{-3}\)
as nickel subsulphide and 0.4 mg m\(^{-3}\) as nickel oxide. Rats seemed more sensitive than mice and, for both species, the toxicity was related directly to the compound’s solubility (i.e. greater solubility was related to greater toxicity) (NTP, 1996a, 1996b, 1996c; EC-JRC, 2005a).

The corresponding two-year NTP studies found lung effects in both species even at the lowest tested nickel concentrations of 0.5 and 0.11 mg m\(^{-3}\) in the case of nickel oxide and nickel subsulphide respectively (NTP, 1996a, 1996b). Nickel sulphate produced clear lung toxicity (inflammation, fibrosis and increased weight) at 0.06 mg m\(^{-3}\) and above. There were no statistically significant effects at 0.03 mg m\(^{-3}\) after two years but, at 7 and 15-month interim sacrifices, mild lung changes and increased lung weights were seen (NTP, 1996c). The latter findings were the basis of the differing opinions of expert groups over whether the lowest tested concentration of 0.03 mg m\(^{-3}\) could be described as a no-observed adverse effect level (NOAEL) (see Section 5).

**Oral**

In a two-year feeding study, rats (25 per sex per group) were given 0, 5, 50 or 125 mg nickel kg\(^{-1}\) bw day\(^{-1}\) in the diet as nickel sulphate. There was a significant reduction in bodyweight at 50 mg kg\(^{-1}\) bw day\(^{-1}\) and above, with the females being more affected than the males. Female rats at the two highest doses demonstrated significantly higher relative heart weight and lower relative liver weight. No histopathological abnormalities were detected and 5 mg nickel kg\(^{-1}\) bw day\(^{-1}\) was considered to be the NOAEL. Survival at two years was poor, particularly in the controls, which raises some doubts about the sensitivity of the study (Ambrose et al., 1976). Nonetheless, a similar NOAEL of 4.5 mg nickel kg\(^{-1}\) bw day\(^{-1}\) was seen in a rat study where nickel sulphate was given in the drinking-water for 13 weeks. At higher doses (11.2 mg kg\(^{-1}\) bw day\(^{-1}\) and above), there were slight changes in bodyweight and weights of the lungs and kidneys (Obone et al., 1999). Similarly, a 90-day rat gavage study with nickel chloride found 5 mg nickel kg\(^{-1}\) bw day\(^{-1}\) to be a NOAEL. At doses of 35 and 100 mg kg\(^{-1}\) bw day\(^{-1}\) there were effects on bodyweight, on organ weight (kidney, liver and spleen) and on the nervous system (ABC, 1986).

### 3.4.2 Hypersensitivity

Nickel and its water-soluble salts are potent skin sensitisers (i.e. able to cause allergic reaction) in humans (USEPA, 1996; WHO, 2006b). The prevalence tends to be higher in young women than any other segment of the population, which is probably the result of higher rates of ear and other types of body piercing rather than increased susceptibility to sensitisation (ATSDR, 2005). For example, patch-testing in the general population in the US found that about 8–10% of women and 1–2% of men demonstrate sensitivity to nickel (USEPA, 1996). WHO reported prevalence figures of 2% in males and 11% in females (WHO, 2000). In Denmark, prevalence figures were 2–4% in men compared with 10–20% in women (Nielsen and Menné, 1992). The overall prevalence of nickel-sensitivity in the UK is around 7–10% (EVM, 2003). Close to one-third of UK female dermatitis patients were sensitive to nickel (McDonagh et al., 1992).

The most common cause of nickel dermatitis is metallic jewellery – in particular, watches and earrings, though other nickel-containing items such as buttons and zips have also been implicated. There is now a European Directive (EC, 1994; Delescluse and Dinet, 1994) and UK Statutory Instrument (TSO, 2005) restricting the use of nickel in products that may come into direct and extended contact with the skin, with the aim of reducing the prevalence of nickel sensitivity. Accessories of nickel that are plated
with another metal are similarly restricted. For these products, it must be demonstrated that the liberation of nickel is less than 0.5 µg cm⁻² week⁻¹.

An attempt to identify the threshold concentration for elicitation of existing nickel-induced allergic dermatitis looked closely at the skin responses of 51 patients with proven dermal sensitivity to nickel. “None reacted with definite allergic reactions to 100 ppm [nickel] or below” applied as a nickel chloride solution (Menné and Calvín, 1993). When 92 nickel-allergic patients were patch-tested with serial dilutions of nickel sulphate, minimal reactions were elicited in 5, 4 and 0 patients exposed to 0.26, 0.05 and 0.026 µg cm⁻² skin respectively (Uter et al., 1995).

A number of dermatologists have reported that the ingestion of nickel salts can elicit allergic dermatitis in those who have already been sensitised from previous dermal contact with nickel (IPCS, 1991; USEPA, 1991b; ATSDR, 2005; EC-JRC, 2005a; WHO, 2007). Studies suggest that a large proportion of dermatitis patients with patch-test sensitivity to nickel suffer an exacerbation of their skin condition when given nickel at doses in the range 0.5–2.5 mg day⁻¹ (8–35 µg kg⁻¹ bw day⁻¹). However, the studies often involved only small numbers of patients and lacked placebo-treated controls. These factors, and the fluctuating nature of the disease, make it difficult to judge whether the observed effects are truly nickel-induced.

In a study in which fasted female volunteers with confirmed sensitivity to dermal nickel received oral doses, the lowest-observed adverse effect level (LOAEL) was 12 µg kg⁻¹ bw (Nielsen et al., 1999). A similar dose of 1 mg (17 µg kg⁻¹ bw) resulted in a flare-up of dermatitis at an earlier patch test site in two of 10 nickel-sensitive patients (Hindsén et al., 2001). WHO considered that a dose of 12 µg kg⁻¹ bw was the acute LOAEL in fasting patients on a 48-hour diet with reduced nickel content. WHO considered that a cumulative LOAEL for repeated exposure could be lower, but that a LOAEL in non-fasting patients would probably be higher due to lower absorption of nickel ions when mixed in food (WHO, 2007).

Nickel sulphate is a recognised sensitiser of the respiratory tract, inducing asthma in exposed workers. There are also reports of metallic nickel having a similar potential (EC-JRC, 2005a).

### 3.5 Reproductive and developmental toxicity

#### 3.5.1 Humans

WHO (2006b) noted the lack of data on nickel-induced reproductive/developmental effects in humans. Two epidemiological studies have been undertaken in Russian females exposed occupationally. The first (Chashschin et al., 1994) reported reproductive effects in females working in a nickel refinery where the average nickel concentrations were 0.13–0.2 mg m⁻³. Spontaneous abortions were found in 16% of nickel-exposed workers compared with 9% of unexposed construction workers, and structural malformations were reported in 17% of live births of nickel-exposed mothers compared with about 6% of the construction worker mothers. In a more recent study of almost 23,000 children, of which over 5,100 were born to mothers employed within a nickel refinery complex, maternal occupational exposure to nickel was unrelated to musculoskeletal defects in the offspring. Expert judgement was applied to work histories to allow comparisons of three exposure categories – background, low and high nickel exposure (Vaktskjold et al., 2008).
3.5.2 Experimental animals

A number of laboratory animal studies, using a variety of different routes of administration, have demonstrated reproductive toxicity or foetotoxicity following nickel exposure (Fairhurst and Illing, 1987; Coogan et al., 1989; USEPA, 1991a, 1996; ATSDR, 2005; WHO, 2006b, 2007). Serious developmental effects have also been reported in animals exposed to soluble nickel compounds. Stillbirth and post-implantation/perinatal lethality were consistently seen in several studies involving nickel chloride or nickel sulphate exposure prior to mating and during gestation and lactation (Sunderman et al., 1978; Lu et al., 1979; Smith et al., 1993; Kakela et al., 1999). Decreased pup survival was observed when nickel-exposed male rats were mated with unexposed females (Kakela et al., 1999). Increases in the incidences of foetal malformations were seen when pregnant mice were treated with nickel chloride (Lu et al., 1979) and nickel carbonyl has produced embryotoxic and teratogenic effects in rats and hamsters (Sunderman et al., 1978, 1979, 1980).

In a study in which male mice were administered nickel sulphate by gavage at 5 or 10 mg kg\(^{-1}\) bw\(^{-1}\) day\(^{-1}\), five days per week, for 35 days, reduced testes weight, decreases in testicular enzyme activities and increases in sperm abnormalities (and possibly some mild pathological changes in the testes) were reported at the lower dose. Testes injury and reductions in sperm count and motility were clearly present at the higher dose (Pandey et al., 1999).

In a two-generation rat study, addition of nickel chloride to the drinking-water to supply 52 mg nickel kg\(^{-1}\) bw\(^{-1}\) day\(^{-1}\) was toxic to the parents and reduced the number of live pups per litter and increased pup mortality. There were inconclusive indications of the same effects on pups at the two lowest tested doses, 7.3 and 30.8 mg kg\(^{-1}\) bw day\(^{-1}\), doses that were not toxic to the adult animals (RTI, 1987). An increased incidence of perinatal mortality was seen when nickel chloride was given in the drinking-water of female rats for 11 weeks prior to mating and during two successive gestation and lactation periods. This occurred even at the lowest tested dose of 1.3 mg nickel kg\(^{-1}\) bw day\(^{-1}\) in the second litter, a dose that did not produce signs of maternal toxicity. The absence of a clear dose–response (the perinatal mortality was seen in the low- and high-dose but not in the mid-dose animals) precluded any confident conclusion on NOAEL (Smith et al., 1993). A limited three-generation rat study reported an increased neonatal mortality in the offspring of rats given drinking-water containing 5 mg L\(^{-1}\) of nickel (which would have provided a dose of around 0.5 mg kg\(^{-1}\) bw day\(^{-1}\)) (Schroeder and Mitchener, 1971).

In another two-generation study in rats, a NOAEL of 1.1 mg nickel kg\(^{-1}\) bw day\(^{-1}\) (5 mg nickel sulphate hexahydrate kg\(^{-1}\) bw day\(^{-1}\)) was established. The F\(_0\) rats were dosed by daily gavage over at least one spermatogenesis cycle (males) and several oestrus cycles (females), during mating, pregnancy and up to weaning of the F\(_1\) rats. The F\(_1\) rats received similar treatment until the F\(_2\) animals were weaned. At 2.2 mg nickel kg\(^{-1}\) bw day\(^{-1}\), a wide range of endpoints of developmental toxicity were affected (SLI, 2000a). In a one-generation study carried out at the same laboratory, increased post-implantation loss and pup mortality occurred in rats given nickel sulphate hexahydrate at the lowest tested dose of 2.2 mg nickel kg\(^{-1}\) bw day\(^{-1}\) (SLI, 2000b). A study by Ambrose et al. (1976), which involved the administration of nickel sulphate in the diet of rats (at 12.5 mg nickel kg\(^{-1}\) bw day\(^{-1}\)), also included an examination of reproductive toxicity in that three generations of animals were exposed. There was a higher incidence of stillborn offspring in the first generation. The results, which did not clearly define a NOAEL, have been described as equivocal, and the investigators' statistical analysis of their data has been criticised (USEPA, 1996).

Maternal weight gain and foetal weight were reduced when rats were exposed by inhalation to nickel oxide throughout pregnancy. The lowest concentration at which
effects were seen was described as 1.6 mg m$^{-3}$, but it is unclear whether this was expressed as nickel oxide or nickel. A concentration of 1.6 mg m$^{-3}$ nickel oxide would equate to 1.2 mg nickel m$^{-3}$ (Weischer et al., 1980).

3.6 Genotoxicity

3.6.1 Humans

Slight increases in chromosomal aberrations (mainly gaps), but not chromosomal breaks or sister chromatid exchanges, have been seen in blood cells of nickel refinery workers (Waksvik and Boysen, 1982; Deng et al., 1983, 1988; Waksvik et al., 1984; Decheng et al., 1987) and in workers exposed to nickel oxide at a chemical plant (Senft et al., 1992).

3.6.2 Experimental animals and in vitro

In laboratory animals, nickel salts (mainly the sulphate and chloride) have induced DNA damage, chromosome aberrations and possibly micronuclei in various tissues following oral or inhalation exposure, or intraperitoneal injection (EC-JRC, 2005a, 2005b, 2005c). However, a recent study found no evidence of micronuclei induction in the bone marrow of rats given nickel sulphate by repeated gavage administration (Oller and Erxson, 2007). In a comprehensive study in rats exposed to the sulphate or the subsulphide by inhalation, DNA strand breaks were induced in the lungs and persisted even after a 13-week recovery period. There was no evidence of oxidative DNA damage, suggesting that the genotoxicity was not secondary to inflammation or apoptosis (Benson et al., 2002). Comet assay DNA damage was also reported in the blood of mice given an acute oral dose of nickel chloride (Danadevi et al., 2004).

Nickel compounds (notably the soluble salts) have consistently induced chromosome aberrations, micronuclei, sister chromatid exchanges, gene mutation, DNA adducts, DNA damage and cell transformation in mammalian cells in culture, but were generally inactive in bacterial mutagenicity tests (IARC, 1990; IPCS, 1991; WHO, 2000, 2007; EC-JRC, 2005a, 2005b, 2005c). Nickel metal induced DNA damage, gene mutations and cell transformation in mammalian cells in culture (EC-JRC, 2005a).

3.7 Carcinogenicity

3.7.1 Expert group overviews

A number of expert groups have published reviews on nickel carcinogenesis (IARC, 1987, 1990; Sunderman, 1989; Doll, 1990; IPCS, 1991; USEPA, 1991a, 1991b, 1996; EC-JRC, 2005a, 2005b, 2005c, 2005d, 2005e), and this section is based largely on these reviews.

The International Agency for Research on Cancer (IARC) has concluded that “nickel compounds are carcinogenic to humans” (Group 1) and that (based on induction of lung tumours in rats after intratracheal instillation) “metallic nickel is possibly carcinogenic to humans” (Group 2B) (IARC, 1987, 1990). IARC considered that there was sufficient evidence in humans for the carcinogenicity of nickel sulphate and of the

A more recent IARC evaluation of surgical implants concluded that there was sufficient evidence of carcinogenicity in laboratory animals for implants of metallic nickel and for nickel alloy powder (Group 2B) (IARC, 1999).

The US Environmental Protection Agency has classified “nickel refinery dust” and nickel subsulphide as known human carcinogens (Group A) (USEPA, 1991b, 1991c), and nickel carbonyl as a “probable human carcinogen” (Group B2) because of its ability to induce a low incidence of lung tumours in rats exposed by inhalation (USEPA, 1991d).

An EU draft Risk Assessment Report (RAR) concluded that “it is reasonable to assume that all nickel compounds that can create nickel ions inside or outside the cell are carcinogenic to humans following exposure by inhalation” (EC-JRC, 2005a). A European Commission Group of Specialised Experts has concluded that nickel sulphate and chloride should be considered as human carcinogens, based on sufficient evidence (for the sulphate) for lung cancer and more limited data on nasal cancer. It also recommended that, for classification purposes, the nitrate and carbonate should also be considered to have this potential (EC, 2004). The draft RAR concluded that the “experimental evidence for carcinogenicity following oral exposure suggests that this effect does not occur with soluble nickel salts, although the data is limited” (EC-JRC, 2005a).

Although the genotoxicity data demonstrate nickel is an in vivo genotoxin, uncertainty remains concerning its likely mode of carcinogenic action. A WHO Task Group noted in 2005 that “The parameters responsible for the carcinogenic activity of nickel compounds have not yet been clearly identified”. Reactive oxygen species leading to DNA damage, inhibition of DNA repair, and alteration of DNA methylation are all features of nickel’s biological profile that could also be influential in the development of tumours (WHO, 2006b). In 2008, the UK Expert Panel on Air Quality Standards concluded that, based on plausible mechanisms, there is likely to be a threshold to nickel’s inhalation carcinogenicity (see Section 5.3) (EPAQS, 2008).

3.7.2 Humans

Nickel-induced cancer of the lungs and nasal passages has been recorded in workers in the nickel refinery and processing industries of Canada, USA, Wales and Norway.

Evidence of a carcinogenic action seems strongest for “soluble nickel”, particularly nickel sulphate, and also for nickel subsulphide and nickel oxide (IARC, 1990; IPCS, 1991; WHO, 2000; EC-JRC, 2005a). Based on studies of the exposure–response of the lung cancer seen in workers at Kristiansand, Norway (Andersen, 1992; Andersen et al., 1996), the incremental unit risk for nickel was estimated by a WHO Working Group to be $3.8 \times 10^{-4}$ for each $\mu$g m$^{-3}$ of exposure (WHO, 2000) (see Section 5.5).

3.7.3 Experimental animals

Inhalation

IARC (1990) reported that inhalation studies in rats showed that nickel subsulphide induced benign and malignant lung tumours, but did not conclusively demonstrate any carcinogenic potential of metallic nickel. A few lung tumours were observed in rats
exposed by inhalation to nickel carbonyl. The direct administration of the oxide and metallic nickel into the trachea induced malignant lung tumours in rats (IARC, 1990).

In US NTP carcinogenicity studies using the inhalation route, lung tumours (adenomas and carcinomas) were induced by insoluble nickel salts (nickel subsulphide and nickel oxide) in rats. In mice, there was equivocal evidence of carcinogenicity for the oxide but no evidence for the subsulphide (NTP, 1996a, 1996b). No evidence of carcinogenic activity was seen with soluble nickel sulphate in either species (NTP, 1996c).

In more recent studies, no increase in tumours of the respiratory tissues was seen in rats exposed to metallic nickel powder for two years followed by a six-month period without exposure. Although there were dose-related increases in adrenal gland tumours, the investigators suggested these might have been a secondary consequence of nickel-induced lung toxicity (NiPERA, 2008; Oller et al., 2008) (see Section 3.4.1).

Oral

No evidence of carcinogenic potential was seen for nickel sulphate hexahydrate in two lifetime oral rat studies. In the more recent study, nickel was given at up to 11 mg kg\(^{-1}\) bw day\(^{-1}\) by gavage for two years (CRL, 2005; Heim et al., 2007). The earlier study involved administration via the diet at up to 125 mg nickel kg\(^{-1}\) bw day\(^{-1}\) (Ambrose et al., 1976), but poor survival of the animals meant that the experiment would have had a reduced power to detect an effect. Long-term studies where nickel (acetate) was given at 5 parts per million (ppm) in the drinking-water of rats and mice (equivalent to doses of about 0.5 and 2 mg kg\(^{-1}\) bw day\(^{-1}\) respectively) did not detect any treatment-related tumours (Schroeder et al., 1964; Schroeder and Mitchener, 1971, 1975).

3.8 Summary

The major endpoints of concern associated with exposure to nickel and its compounds are skin sensitisation, respiratory toxicity, carcinogenicity and developmental toxicity.

Nickel and its water-soluble salts are potent skin sensitisers. Within the general population as many as 8–20% of women and 1–4% of men may be nickel-sensitive. The threshold for sensitisation has not been determined. However, previously sensitised individuals have been shown to have skin reactions following dermal application of as little as 0.05 µg cm\(^{-2}\) skin in patch tests or ingestion of about 0.5–0.7 mg (about 8–12 µg kg\(^{-1}\) bw).

Inhalation of nickel and its compounds leads to adverse effects on the respiratory system, but the data in humans are inadequate to define the dose–response. Subchronic and chronic studies in rodents have found respiratory effects (such as inflammation, fibrosis and increased lung weight) at nickel concentrations of 0.4–0.5 mg m\(^{-3}\) as nickel oxide, 0.11 mg m\(^{-3}\) as nickel subsulphide, and 0.06 mg m\(^{-3}\) (and possibly 0.03 mg m\(^{-3}\)) as nickel sulphate.

There is adequate evidence that soluble nickel salts (sulphate and chloride) and the mixture of sulphides and oxides present in refinery dust are carcinogenic to the lungs and/or nasal tissues in humans exposed occupationally, but there is no convincing evidence for a similar potential for metallic nickel. Lifetime inhalation of nickel subsulphide or nickel oxide led to lung tumours in rats, while a similar study on metallic nickel found increases in adrenal gland tumours (thought to be secondary to lung toxicity) but no respiratory tract cancers. Nickel sulphate showed no carcinogenic activity in lifetime studies in rats or mice exposed by inhalation, nor in rats treated by gavage or via the diet.
Thus, while the experimental animal data on non-carcinogenic effects of inhaled nickel compounds indicate that toxicity may be related to solubility, the animal carcinogenicity data indicate that nickel compounds of lower solubility may be of equal or greater concern. In considering the overall risks posed by nickel, it does not seem appropriate to differentiate between the more soluble and less soluble compounds based on the data available.

There is some evidence that occupational exposure to nickel compounds can induce chromosome aberrations in the blood. In laboratory animals, nickel salts – especially the sulphate and chloride – have induced DNA damage, chromosome aberrations and possibly micronuclei in various tissues following oral or inhalation exposure or intraperitoneal injection. Nickel compounds, although generally inactive in bacterial mutagenicity tests, have consistently induced chromosome damage (aberrations and micronuclei), sister chromatid exchanges, gene mutations, DNA adducts, DNA damage and cell transformation in mammalian cells in culture. Despite this clear evidence of genotoxic potential, there is as yet no confident understanding of nickel's mode of carcinogenic action.

Laboratory animal studies have demonstrated foetotoxicity due to exposure to nickel compounds. In a drinking-water study on nickel chloride, perinatal mortality was increased following administration of 1.3 mg nickel kg$^{-1}$ bw day$^{-1}$ (the lowest dose used) to female rats, starting 11 weeks prior to mating and continuing until two successive litters had been raised. A study where nickel sulphate was administered to both sexes in a two-generation rat study established a NOAEL of 1.1 mg nickel kg$^{-1}$ bw day$^{-1}$. Foetal weight was reduced when rats were exposed by inhalation to nickel oxide at 1.2 mg nickel m$^{-3}$ throughout pregnancy, though this exposure was also associated with maternal toxicity.
4 Essentaility and deficiency

Nickel has not been established as essential for humans, but reports of nickel deficiency in several other species (e.g. rats, chicks, cows and goats) suggest that it may indeed have a functional role in animals. Nickel deficiency is manifested primarily in the liver. Effects include “abnormal cellular morphology, oxidative metabolism, and increases and decreases in lipid levels. Decreases in growth and haemoglobin concentration and impaired glucose metabolism have also been observed.” Nickel dietary recommendations have not been established for humans (ATSDR, 2005).

Nickel deficiency is unlikely to be a practical problem in humans due to its presence in foodstuffs (Anke et al., 1984).
5 Derivation of Health Criteria Values

5.1 UK Expert Group on Vitamins and Minerals

The UK Expert Group on Vitamins and Minerals (EVM) was established in 1998 to advise on safe levels of intakes of vitamins and minerals in food supplements and fortified foods, and the resulting report was published in May 2003 (EVM, 2003). The group was unable to set either a Safe Upper Level\(^2\) or a Guidance Level\(^3\) of intake for nickel because some 7–10% of the UK population are reportedly nickel-sensitive and there was uncertainty over the lowest intakes that can cause flare-ups. It appeared that amounts as low as 0.5–0.7 mg (about 7–12 µg kg\(^{-1}\) bw) may be able to trigger reactions, especially if taken on an empty stomach (Nielsen et al., 1990, 1999).

For non-sensitised individuals, it was considered that a total intake of 4.3 µg kg\(^{-1}\) bw day\(^{-1}\) (equivalent to 0.3 mg nickel day\(^{-1}\) for a 70-kg adult) would not be expected to have toxic effects. This was derived from a LOAEL of 1.3 mg kg\(^{-1}\) bw day\(^{-1}\) for perinatal mortality in a rat study (Smith et al., 1993) by applying a total UF of 300, comprising 3 to extrapolate from a LOAEL to a NOAEL, and two factors of 10 for inter- and intra-species variations (EVM, 2003).

5.2 UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment

The UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) was asked in 2003 to comment on results of the UK Food Standards Agency 2000 Total Diet Study (TDS) and to assess if levels of nickel in the diet posed a risk to human health. Mean estimates of nickel intake were below the WHO TDI (at that time, 5 µg kg\(^{-1}\) bw day\(^{-1}\)) for all age subgroups. Estimated “high-level” intakes\(^4\) exceeded this TDI figure by 6% for the 4–18 year-olds subgroup and by 44% for toddlers aged 1.5–4.5 years (COT, 2004). COT concluded that current dietary exposures to nickel were unlikely to be of any toxicological concern for consumers on the grounds that the WHO TDI derivation from a two-year rat oral study on nickel sulphate (Ambrose et al., 1976) had incorporated a large UF (1,000), that toddlers are less likely to have been sensitised to nickel, and that population exposures to nickel have been decreasing over 25 years (COT, 2004).

A similar conclusion was reached in relation to the results of the 2006 Total Diet Study (FSA, 2009). The benchmarks for comparison were again the old WHO TDI (5 µg kg\(^{-1}\) bw day\(^{-1}\)) and the dose that EVM considered would be without toxic effects in non-sensitised individuals (4.3 µg kg\(^{-1}\) bw day\(^{-1}\); see Section 5.1). Dietary exposure estimates were similar to those of the 2000 study. Estimates of high-level intake by toddlers and young people (4–18 years old) exceeded the EVM and (old) WHO figures.

\(^{2}\) A Safe Upper Level (SUL) represents an intake that can be consumed daily over a lifetime without significant risk to health on the basis of available evidence.

\(^{3}\) A Guidance Level is an approximate indication of a level that would not be expected to cause adverse effects, but has been derived from limited data.

\(^{4}\) High level consumers are those whose intakes are at the 97.5\(^{th}\) percentile level of their class.
However, the previous COT observation that toddlers are less likely than adults to be sensitised and are therefore not considered to be a sensitive subgroup was repeated, as was the conclusion that dietary nickel exposures are unlikely to be of toxicological concern (FSA, 2009).

5.3 UK Expert Panel on Air Quality Standards

The UK Expert Panel on Air Quality Standards (EPAQS) has recommended in a 2008 consultation document (EPAQS, 2008) that an airborne concentration of all nickel compounds (measured as nickel) of 0.02 µg m\(^{-3}\) (annual mean) should protect against the short- and long-term effects of inhaled nickel.

In its consideration of nickel’s carcinogenic potential upon inhalation, EPAQS stated it is “plausible that a non-genotoxic mechanism, based on the formation of oxygen radicals and consequent sustained cell proliferation due to repair of oxidative damage, could account for the lung tumours seen. If this is the active mechanism then there is likely to be a threshold of effect.” It also concluded that nasal cancer appears to be confined to occupational exposures.

Based on the epidemiological data on respiratory tract tumours associated with occupational nickel exposure, EPAQS concluded that 0.02 mg m\(^{-3}\) could be taken as a LOAEL in humans. An uncertainty factor (UF) of 1,000 was applied to derive the proposed guideline. The UF comprised of three factors of 10 to account for extrapolation of a LOAEL to a NOAEL, extrapolation of occupational exposure to lifetime exposure, and to allow for susceptible groups within the population (EPAQS, 2008).

EPAQS also presented a derivation based on the inflammatory response seen in experimental animals exposed to nickel via inhalation. A LOAEL of 0.06 mg m\(^{-3}\) was identified from the results of the NTP studies of nickel sulphate hexahydrate (NTP, 1996c). A factor of 5 was considered adequate for extrapolation of this LOAEL to a NOAEL. A factor of 6 was then applied to convert from the experimental exposure (six hours per day, five days per week) to continuous exposure, before an UF of 100 was applied (10 each for inter- and intraspecies variability) to produce a value of 0.02 µg m\(^{-3}\). As less than 50% of atmospheric nickel is present as soluble salts and EPAQS considered the NOAEL for the insoluble compounds to be an order of magnitude higher, this value was doubled to 0.04 µg m\(^{-3}\). As this was similar to but slightly greater than the concentration derived based on carcinogenic effects in humans, the lower value of 0.02 µg m\(^{-3}\) was adopted by the Panel.

5.4 WHO guidelines for drinking-water quality

A review by the World Health Organization (WHO) in 2004 acknowledged IARC’s conclusions relating to the carcinogenicity of inhaled nickel compounds (and possibly metallic nickel). However, WHO noted the lack of evidence for a carcinogenic risk from oral exposure to nickel and concluded that allergic contact dermatitis is the most prevalent effect of nickel in the general population.

The WHO drinking-water guideline gives the tolerable daily intake (TDI) as 12 µg kg\(^{-1}\) bw day\(^{-1}\) (WHO, 2006a). This was derived from the LOAEL (also 12 µg kg\(^{-1}\) bw) established after oral provocation tests in fasted, nickel-sensitive patients (Nielsen et al., 1999). As nickel absorption on an empty stomach is 10- to 40-fold higher than with food, it was considered that deriving a total acceptable intake from a study on fasted patients represented a worst-case scenario. Because this was a highly sensitive
population, it was not felt necessary to include any additional UFs (WHO, 2006a, 2007).

The supporting background document was revised in 2007 (WHO, 2007) in preparation for the development of the fourth edition of the WHO guidelines for drinking-water quality. This document gives more emphasis to a “well-conducted” two-generation rat study with a NOAEL of 1.1 mg nickel kg\(^{-1}\) bw day\(^{-1}\) (SLI, 2000a) and presents a TDI figure of 11 µg kg\(^{-1}\) bw day\(^{-1}\), derived by applying UFs of 10 each for inter- and intraspecies variations to this NOAEL. The human study of Nielsen \textit{et al.} (1999) was mentioned but seemingly mainly as a corroborating study.

In each case, these (very similar) TDIs, resulted in a (rounded) guideline value for nickel in drinking-water of 70 µg L\(^{-1}\), based on a 60-kg adult drinking two litres of water per day and allocating 20% of the TDI to drinking-water (WHO, 2006a, 2007).

5.5 WHO air quality guidelines for Europe

A WHO Working Group concluded in 1996 that the key criterion for assessing the risk of inhaled nickel is its carcinogenic potential and that “no safe level for nickel compounds can be recommended” (WHO, 2000). The guideline for nickel was therefore expressed as an estimate of unit risk, defined as “the additional lifetime cancer risk occurring in a hypothetical population in which all individuals are exposed continuously from birth throughout their lifetimes to a concentration of 1 µg m\(^{-3}\) of the agent in the air they breathe”. Based on studies of the exposure–response of the lung cancer seen in workers at Kristiansand, Norway (Andersen, 1992; Andersen \textit{et al.}, 1996), the incremental unit risk for nickel was estimated to be \(3.8 \times 10^{-4}\) for each µg m\(^{-3}\) of exposure. The concentration corresponding to an excess lifetime risk of 1 in 100,000 was said to be about 25 ng m\(^{-3}\) (0.025 µg m\(^{-3}\)) (WHO, 2000).

This risk estimate was very similar to WHO’s previous evaluation, which had generated a “conservative estimate” for nickel’s unit cancer risk of about \(4 \times 10^{-4}\) for each µg m\(^{-3}\) (WHO, 1987). This was based on the geometric mean of the three risk estimates of the cancer experience of refinery workers from Clydach, Wales (Doll \textit{et al.}, 1977), Copper Cliff, Ontario, Canada (Chovil \textit{et al.}, 1981) and Kristiansand, Norway (Magnus \textit{et al.}, 1982).

5.6 EU draft Risk Assessment Reports

Draft EU Risk Assessment Reports (RARs) are available for nickel and four of its highest volume compounds (EC-JRC, 2005a, 2005b, 2005c, 2005d, 2005e). Although HCVs were not derived, critical NOAELs and LOAELs for assessing risks of various endpoints were proposed.

For dermal exposure, an empirical dermal dose level of 0.5 µg nickel cm\(^{-2}\) week\(^{-1}\) was suggested to prevent induction of sensitisation after direct and prolonged contact in a substantial proportion of a non-sensitised population. On the basis of the available data it was not possible to set a threshold for elicitation in existing nickel-sensitised individuals, but it was estimated that a release rate of 0.5 µg nickel cm\(^{-2}\) week\(^{-1}\) could prevent elicitation in approximately 70% of the nickel-allergic population.

The Rapporteur considered that it was not possible to establish a NOAEL for oral challenge (i.e. testing for allergic reaction) in patients with nickel dermatitis, but the LOAEL established after provocation of patients with an empty stomach was 12 µg kg\(^{-1}\) bw (Nielsen \textit{et al.}, 1999). It was suggested that, since this was an acute test, a
cumulative LOAEL might be lower, but a LOAEL in non-fasting patients would probably be higher (EC-JRC, 2005a).

From studies on the sulphate or chloride, an oral NOAEL of 2.2 mg nickel kg\(^{-1}\) bw day\(^{-1}\) for fertility and effects on male sex organs and a NOAEL of 1.1 mg kg\(^{-1}\) bw day\(^{-1}\) for developmental toxicity were reported (SLI, 2000a). By inhalation, a no-observed adverse effect concentration (NOAEC) of 0.45 mg nickel m\(^{-3}\) was seen for fertility and effects on male sex organs (Dunnick et al., 1989; NTP, 1996c). Route-to-route extrapolation of the oral NOAEL of 1.1 mg kg\(^{-1}\) bw day\(^{-1}\) (SLI, 2000a) for nickel sulphate was used to propose a NOAEC of 0.28 mg nickel m\(^{-3}\) for developmental toxicity.\(^5\)

Concluding that there is no concern for carcinogenicity by the oral route of exposure, a two-year rat gavage study on nickel sulphate hexahydrate was used to derive an oral NOAEL of 2.2 mg nickel kg\(^{-1}\) bw day\(^{-1}\) (CRL, 2005). Concern over the genotoxic potential of nickel on inhalation exposure led the inhalation carcinogenicity risk characterisation to be carried out using a non-threshold approach. The Rapporteur adopted the WHO unit risk figure of 3.8 \(\times\) 10\(^{-4}\) per µg m\(^{-3}\) of exposure to determine an HT25 value\(^6\) of 188 µg kg\(^{-1}\) bw day\(^{-1}\) (EC-JRC, 2005a, 2005b, 2005c, 2005d, 2005e).

The EU Scientific Committee on Health and Environmental Risks (SCHER) evaluated the draft RARs and, in general, agreed with the conclusions reached. However, while accepting the conclusion that oral exposure to nickel is not associated with a carcinogenic risk, SCHER recommended that the conclusion needs to be viewed with caution since nickel ions are the active species responsible for tumour induction and nickel ions may also be absorbed after oral exposure to nickel salts (SCHER, 2006, 2008).

### 5.7 EU Scientific Committee for Toxicity, Ecotoxicity and the Environment

In 2001, the EU Scientific Committee for Toxicity, Ecotoxicity and the Environment (CSTEE) issued an opinion on the human health risks posed by nickel in ambient air (CSTEE, 2001). The key experimental finding for non-cancer effects was considered to be the increased lung weights seen in a long-term (two-year) rat study involving repeated daily inhalation exposure at a nickel concentration of 60 µg m\(^{-3}\) (as nickel sulphate) (NTP, 1996c). A UF of 10 was used to convert this LOAEL to a NOAEL\(^7\), a factor of 6 to convert from intermittent to continuous exposure, and two factors of 10 to take account of inter- and intra-species variability. The application of the total UF of 6,000 to the 60 µg m\(^{-3}\) dose produced a figure of 10 ng m\(^{-3}\). As soluble nickel does not constitute more than 50 per cent of the total nickel compounds in ambient air (and soluble nickel was thought to be the main cause of the non-tumour pathology), CSTEE concluded that the limit value to protect against non-cancer effects should be 20 ng m\(^{-3}\) (0.02 µg m\(^{-3}\)).

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\(^5\) 1.1 mg kg\(^{-1}\) bw day\(^{-1}\) with an assumed 5% absorption gave an estimated internal dose of 0.055 mg kg\(^{-1}\) bw day\(^{-1}\). This was multiplied by 70-kg bodyweight and divided by an inhalation rate of 13.9 m\(^3\) day\(^{-1}\) to produce the estimated NOAEC of 0.277 mg Ni m\(^{-3}\) (EC-JRC, 2005e).

\(^6\) Defined by EC-JRC (2005b) as the lifetime dose that theoretically will cause cancer in 25% of the exposed population.

\(^7\) CSTEE was not convinced that the lowest tested inhalation concentration of 30 µg m\(^{-3}\) in the NTP study was a NOAEL because there were indications of chronic active inflammation and increased lung weights in the rats sacrificed at months 7 and 15 (five males and five females per time point).
Based on an overall evaluation of the epidemiological and experimental data, CSTEE found that there was “sufficient evidence for classifying soluble nickel compounds as known human carcinogens and that a genotoxic component in the mode of action is probable”. The Committee “does not support the application of a threshold approach for assessing the carcinogenic risks associated with exposure to ambient nickel compounds”. It considered the WHO recommendation on unit risk of $3.8 \times 10^{-4}$ for each $\mu g \ m^{-3}$ of exposure – based on the study of Andersen et al. (1996) – was valid, but emphasised that the estimate was conservative and that there were considerable differences in cancer potency among the different nickel species in ambient air. CSTEE noted that the unit risk corresponds to concentrations of 25 and 2.5 ng m$^{-3}$ for increased lifetime cancer risks of 1 in 100,000 and 1 in 1,000,000 respectively, concluding “that the limit value of 20 ng m$^{-3}$ proposed for non-cancer effects, also is likely to provide reasonable protection of the general population to the carcinogenic effects of nickel compounds in ambient air” (CSTEE, 2001).

5.8 EC Working Group on Arsenic, Cadmium and Nickel Compounds

An EC Working Group was charged with the derivation of a Limit Value for nickel (an atmospheric concentration that could be used in European Community regulations on air quality). A “final version” of its report, dated November 2000, was published in 2001.

The critical study identified for non-cancer health effects was one in which rats were exposed by inhalation to nickel sulphate for two years (NTP, 1996c). As there was uncertainty over whether the lowest nickel exposure concentration (30 $\mu g \ m^{-3}$) was in fact a NOAEL for respiratory system effects, the Working Group chose 60 $\mu g \ m^{-3}$ as an unequivocal LOAEL. This LOAEL was converted to a NOAEL by applying a UF of 10. A factor of 6 was used to convert to a continuous exposure equivalent, and an UF of 100 was then applied to account for inter- and intra-species variations, resulting in a non-cancer limit value of 10 ng nickel m$^{-3}$ (0.01 $\mu g \ m^{-3}$) (EC, 2001). The Working Group acknowledged a California Environmental Protection Agency (CalEPA) limit value of 50 ng m$^{-3}$, derived by assuming 30 $\mu g \ m^{-3}$ was the study NOAEL (and applying factors of 5.6 to convert to continuous exposure and about 100 to account for inter- and intra-species variations) (OEHHA, 2000) and the derivation by an industry group of a limit value of 50–160 ng m$^{-3}$, in which the NOAEL was also regarded as 30 $\mu g \ m^{-3}$ (and applying factors of 6 to convert to continuous exposure, 10 for intra-species variation and 3–10 for inter-species variation). Overall the EC Working Group proposed a limit value for non-cancer effects in the range of 10–50 ng nickel m$^{-3}$ (0.01–0.05 $\mu g \ m^{-3}$) as an annual mean (EC, 2001).

The Working Group concluded that the available information was not sufficient to permit a clear classification of nickel compounds as being non-genotoxic carcinogens and regarded a non-threshold approach as appropriate for cancer risk assessment. It noted estimated unit risk figures (expressed per $\mu g \ m^{-3}$ of exposure) derived by other groups of: $2.4 \times 10^{-4}$ (and a derived value of $4.8 \times 10^{-4}$ for nickel subsulphide) (USEPA, 1991b, 1991c); $2.5 \times 10^{-4}$ (and derived values of $4.0 \times 10^{-5}$ for nickel oxide and $3.0 \times 10^{-4}$ for nickel subsulphide) (Lepicard et al., 1997); and $3.8 \times 10^{-4}$ (WHO, 2000). For a 1 in 1,000,000 excess lifetime risk, these equate to exposures in the range of 2.6–4 ng m$^{-3}$ (EC, 2001); (exposures equating to a 1 in 100,000 excess lifetime cancer risk would be 26–40 ng m$^{-3}$ or 0.026–0.04 $\mu g \ m^{-3}$). The Working Group noted that these

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8 See footnote to Section 5.7.

9 From the Centre d’Etude sur l’Evaluation de la Protection dans le domaine Nucléaire (CEPN).
values may overestimate the true risk by about one order of magnitude— one reason being because nickel refinery workers might be exposed to different nickel species than individuals in the public at large. It was concluded that a limit value in the range 10–50 ng m\(^{-3}\) \((0.01–0.05 \, \mu g \, m^{-3})\) as derived from non-cancer effects can be judged compatible with the aim of limiting the excess lifetime cancer risk to not more than one in a million. The majority of the Working Group proposed a limit value at the lower end of this range as an annual mean of total airborne nickel (EC, 2001).

5.9 EU Scientific Panel on Dietetic Products, Nutrition and Allergies

In relation to possible food supplement use of nickel salts, the Scientific Panel on Dietetic Products, Nutrition and Allergies of the European Food Safety Authority (EFSA) was unable in 2005 to establish a tolerable upper intake level for nickel (EFSA, 2005).

EFSA was concerned that perinatal mortality had been reported to increase in rats, even at the lowest administered oral nickel dose level of 1.3 mg kg\(^{-1}\) bw \(\text{day}^{-1}\) (Smith et al., 1993) and that only very limited data were available on carcinogenicity by the oral route. Moreover, oral doses as low as 8 \(\mu g \, kg^{-1} \, \text{bw} \, \text{day}^{-1}\) had been reported to aggravate hand eczema in nickel-sensitised individuals (Nielsen et al., 1990). Average intakes from food are about 2.5 \(\mu g \, kg^{-1} \, \text{bw} \, \text{day}^{-1}\), and consumption of food with high nickel content and additional exposure from first-run drinking-water and kitchen utensils could therefore result in an intake that is above the dose able to elicit a skin reaction in sensitised subjects. Any additional nickel intake from supplements would further increase the risk (EFSA, 2005).

5.10 US Environmental Protection Agency

In a 1991 cancer risk assessment, USEPA used the lung cancer incidence in refinery workers in Huntington, West Virginia (Enterline and Marsh, 1982), Copper Cliff, Ontario (Chovil et al., 1981), Clydach, Wales (Peto et al., 1984), and Kristiansand, Norway (Magnus et al., 1982), to estimate an inhalation unit risk (USEPA, 1991b). Using both the relative risk and additive models, the mid-point of the range of the estimates was \(2.4 \times 10^{-4}\) for each \(\mu g \, m^{-3}\) of refinery dust (USEPA, 1991b). As the refinery dusts were roughly 50 per cent nickel subsulphide, the incremental unit risk due to a lifetime exposure to nickel subsulphide was taken to be twice this value, or \(4.8 \times 10^{-4}\) for each \(\mu g \, m^{-3}\) (USEPA, 1991c). A comprehensive review of new toxicological studies published up to June 2006 carried out by a USEPA contractor (USEPA, 2006) did not identify any new data that would be useful in revising the 1991 assessment (USEPA, 1991b).

In a 1996 assessment, USEPA recommended an oral Reference Dose (RfD)\(^{10}\) for soluble nickel salts of 20 \(\mu g \, kg^{-1} \, \text{bw} \, \text{day}^{-1}\), based primarily upon the long-term rat feeding study of Ambrose et al. (1976). A UF of 300 was applied to the NOAEL of 5 mg nickel kg\(^{-1}\) bw \(\text{day}^{-1}\). This was composed of factors of 10 each to allow for inter- and intra-species variations, and an additional factor of 3 because of inadequacies in the available reproductive studies (USEPA, 1991a, 1996).  

\(^{10}\) The RfD is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily population exposure that is likely to be without an appreciable risk of deleterious, non-carcinogenic effects during a lifetime.
None of the human studies of hypersensitivity "were considered adequate to serve as the basis for a quantitative risk assessment". The RfD was believed to be set at a level that would not induce initial sensitisation to nickel, although individuals who have previously developed nickel "hypersensitivity (e.g. from a dermal exposure) may not be fully protected" (USEPA, 1996).

5.11 US Agency for Toxic Substances and Disease Registry

In 2005, the US Agency for Toxic Substances and Disease Registry (ATSDR) recommended a Minimal Risk Level (MRL) of 0.09 µg m⁻³ for chronic inhalation exposure to nickel. This was based upon the findings of a two-year inhalation study of nickel sulphate in rats (NTP, 1996c). The lowest tested exposure concentration of 0.03 mg nickel m⁻³, which was considered to be a NOAEL, was converted first to continuous exposure \((\times 6/24 \times 5/7)\), and then to a ‘human equivalent concentration’ (HEC) by the introduction of a factor of 0.506 for extrapolating from particle deposition in the pulmonary region of rats to deposition in humans. A UF of 30 – comprising a factor of 3 for extrapolation from laboratory animals to humans and a factor of 10 for human variability – was applied to the HEC of 0.0027 mg m⁻³ to arrive at the MRL of 0.09 µg m⁻³. By definition, an MRL is only concerned with non-cancer endpoints and therefore no account was taken of nickel’s ability to produce respiratory tract cancers on inhalation (ATSDR, 2005).

In 2005, ATSDR considered it inappropriate to derive an MRL for oral exposure to nickel. The threshold oral dose for dermatitis in nickel-sensitised individuals was regarded as about 10 µg kg⁻¹ bw (Nielsen et al., 1990; Jensen et al., 2003). The application of UFs to this lowest observed effect level, because of concern about protecting sensitive individuals, would bring the oral MRL to below the normal dietary intake of about 2 µg kg⁻¹ bw day⁻¹ (ATSDR, 2005).

5.12 Dutch National Institute for Public Health and the Environment

The Dutch National Institute for Public Health and the Environment (RIVM) has proposed a TDI and a Tolerable Concentration in Air (TCA) for nickel (RIVM, 2001). Its 2000 assessment noted that "it is clear that inhalation exposure of nickel leads to tumours in the lungs and the nasal area" [in humans]. It was also acknowledged that nickel’s “clastogenic properties have been demonstrated in humans”. Despite this, RIVM stated that “[m]utagenicity data, however, did not demonstrate genotoxic properties, and the mechanism of toxic action suggests a cytotoxic effect. Thus a TDI for nickel can be proposed on the basis of a NOAEL and extrapolation factors”. It retained its earlier oral TDI of 50 µg kg⁻¹ bw day⁻¹, which had been based on the application of an UF of 100 (presumably to take account of inter- and intraspecies variations) to a NOAEL of 5 mg kg⁻¹ bw day⁻¹ in a two-year rat feeding study on nickel sulphate (Ambrose et al., 1976).

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11 An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse non-cancer health effects over a specified duration of exposure.

12 The TCA is the concentration of a substance in the atmosphere that any human individual can be exposed to during a full lifetime without significant health risk.
RIVM recommended a TCA of 0.05 µg m\(^{-3}\). Its foundation was a rat NOAEC of 30 µg m\(^{-3}\) – presumably from the two-year inhalation study on nickel sulphate (NTP, 1996c) – converted to an equivalent of 5 µg m\(^{-3}\) for continuous exposure. The TCA arose from the division of this continuous concentration by the two standard UFs of 10 each for inter- and intra-species variations.

5.13 Discussion

5.13.1 Inhalation

Nickel compounds are established carcinogens in humans by the inhalation route, tumours of the respiratory tract being a consequence of occupational exposure to both soluble and insoluble nickel salts.

The assessment of inhalation exposure by expert groups has tended to centre on the elucidation of cancer risk. The lack of any confident knowledge of the detailed mechanism of the induced cancers has meant that several expert groups have adopted the assumption that nickel’s genotoxicity might be critical in the development of the tumours and thus there might be no dose threshold for the cancer risk. For example, CSTEE concluded in a 2001 opinion that a genotoxic component in the carcinogenicity of inhaled soluble nickel compounds was probable. The Committee therefore did not support a threshold approach (CSTEE, 2001).

These expert group assessments of inhalation cancer risk have relied primarily on the cancer pattern observed in exposed workers to estimate the low-dose cancer risks. From the epidemiological data available in 1991, USEPA modelling procedures yielded a lifetime cancer risk of \(2.4 \times 10^{-4}\) for each µg m\(^{-3}\) of nickel exposure (USEPA, 1991b). The corresponding value derived by WHO in 1996, relying on epidemiological reports published in 1992 and 1996, was \(3.8 \times 10^{-4}\) for µg m\(^{-3}\) (WHO, 2000) – a value supported by CSTEE (2001) and the draft EU RARs (EC-JRC, 2005a, 2005b, 2005c, 2005d, 2005e). On this basis, the concentration of nickel producing an excess lifetime cancer risk of 1 in 100,000 would be about 0.025 µg m\(^{-3}\) (25 ng m\(^{-3}\)). This was further supported by a number of cancer risk estimates (including those of WHO and USEPA) cited by a European Commission Working Group in 2000, which together indicated that lifetime exposures of 26–40 ng m\(^{-3}\) would produce a 1 in 100,000 excess lifetime cancer risk (EC, 2001).

In contrast to these assessments, a non-genotoxic, threshold mechanism is implied in EPAQS 2008 draft assessment (EPAQS, 2008). EPAQS concluded that 20 µg m\(^{-3}\) could be taken as the LOAEL for respiratory tumours in humans. An UF of 1,000 (10 for use of a LOAEL and 10 each for inter- and intraspecies variability) was applied to derive the proposed guideline of 0.02 µg m\(^{-3}\).

RIVM’s 2000 derivation of a TCA was similarly based on the assumption that nickel’s inhalation carcinogenicity would exhibit a dose threshold (RIVM, 2001). RIVM instead derived its TCA of 0.05 µg m\(^{-3}\) by applying an UF of 100 (and exposure duration conversions) to the NOAEC of 30 µg m\(^{-3}\) for non-tumour lung pathology reported in a two-year inhalation study in rats (NTP, 1996c).

The chronic inhalation MRL of 0.09 µg m\(^{-3}\) derived by ATSDR in 2005 was also based on this same NOAEC (albeit with a lower UF for possible inter-species differences). (An ATSDR MRL is intended to protect against “non-cancer health effects” only.) CSTEE also used the two-year rat study to estimate a non-cancer inhalation guideline value (to supplement its cancer risk estimate from the occupational epidemiology). CSTEE had doubts over the validity of the NOAEC of 30 µg m\(^{-3}\) in the rat study and thus preferred
to base its derivation of a non-cancer HCV on the unequivocal LOAEC of 60 µg m⁻³. After conversion to an equivalent for continuous exposure, it applied a UF of 1,000, which included a factor of 10 for the use of a LOAEC rather than a NOAEC, to generate a figure of 0.01 µg m⁻³. Because only half of the nickel in the ambient air is likely to be soluble nickel (the presumed main cause of the non-tumour lung abnormalities), this was doubled to produce a non-cancer inhalation HCV of 0.02 µg m⁻³ (CSTEE, 2001).

The WHO assessment based on potential non-threshold carcinogenicity (and an excess lifetime cancer risk of 1 in 100,000), the EPAQS assessment based on the assumption of a threshold to nickel’s carcinogenicity, and the CSTEE assessment based on non-cancer effects each resulted in an atmospheric concentration of approximately 0.02 µg m⁻³. This value is selected here for derivation of an inhalation TDI (TDI_{inh}). Based on the default 70-kg adult inhaling 20 m³ of air per day, the TDI_{inh} is (after rounding) 0.006 µg kg⁻¹ bw day⁻¹. This is of an approximately similar order to the exposures arising from current atmospheric concentrations of nickel (see Section 6).

5.13.2 Oral

Although not all the expert groups have explicitly concluded that there is no carcinogenic concern from ingested nickel, none of those evaluating oral exposure to nickel concluded that it should be assessed as a non-threshold carcinogen.

A long-term oral feeding study in rats on nickel sulphate (Ambrose et al., 1976) is the foundation of two expert group derivations of oral health-based guidance values. Both USEPA and RIVM agreed that the study NOAEL was 5 mg kg⁻¹ bw day⁻¹. RIVM in 2000 applied a UF of 100 to generate a TDI of 50 µg kg⁻¹ bw, whereas USEPA used an overall UF of 300, its extra conservatism arising from an additional factor of 3 for database inadequacies, in the generation of an oral RfD of 20 µg kg⁻¹ bw day⁻¹ set in 1996.

In the general population, 8–20% of women and 1–4% of men may be nickel-sensitive and recent expert group reviews have focused on orally-induced sensitisation reactions as a critical feature in their derivations of oral HCVs. An oral NOAEL for eliciting skin reactions in nickel-sensitised individuals has not been established, but it is now generally accepted that an acute dose of about 8–12 µg kg⁻¹ bw can elicit reactions in a proportion of these highly sensitive subjects (USEPA, 1996; EVM, 2003; ATSDR, 2005; EC-JRC, 2005a, 2005b, 2005c, 2005d, 2005e; EFSA, 2005; WHO, 2006a, 2007).

In 2004, WHO derived a TDI of 12 µg kg⁻¹ bw day⁻¹ for nickel from the results of a study where an acute oral dose at this level induced hand eczema in nickel-sensitised volunteers who had fasted prior to the administration of the nickel salt (Nielsen et al., 1999). Although this dose level was a LOAEL in these patients, WHO felt that deriving a TDI from this study represented a worst-case scenario because nickel absorption from the empty stomach is likely to be 10- to 40-fold higher than from food. The draft EU RARs on nickel and several of its salts agreed that an acute LOAEL in non-fasting patients is probably higher because of reduced absorption of nickel ions when mixed in food, but noted that a LOAEL after repeated exposure may be lower (EC-JRC, 2005a, 2005b, 2005c, 2005d, 2005e).

In a 2007 revision of the background document to its drinking-water guideline, WHO derived an almost identical TDI (of 11 µg kg⁻¹ bw day⁻¹) by applying a UF of 100 (to account for inter- and intra-species variations) to a NOAEL of 1.1 mg kg⁻¹ bw day⁻¹ for developmental effects seen in a well-conducted two-generation rat reproduction study (SLI, 2000a; WHO, 2006a, 2007).
The current WHO TDI of 12 µg kg\(^{-1}\) bw day\(^{-1}\) is recommended here as the TDI\(_{\text{oral}}\). It should be noted that a minority of those who have been pre-sensitised to nickel may suffer an exacerbation of their skin condition as a result of the ingestion of nickel at the TDI\(_{\text{oral}}\).

### 5.13.3 Risk assessment considerations

The critical effects of ingested nickel are developmental effects on the offspring of females exposed during pregnancy and dermal effects in those sensitised to nickel. As it has been suggested that young children are less likely than adults to be sensitised to nickel (COT, 2004), it could be argued that, for oral exposure to nickel, the critical receptor is a woman of child-bearing age. This argument would seem to be strengthened if the recent introduction of legislative restrictions on the use of nickel (TSO, 2005) reduces the prevalence of nickel hypersensitisation in the UK population – perhaps initially in children.

However, a study of sensitisation in American infants (Bruckner et al. 2000) indicates that sensitisation may be prevalent in children. In addition, the effect which the EU Directive on nickel will have on the prevalence of nickel hypersensitisation in the UK population is unclear. In view of the uncertainties, and the greater exposure of infants and children to soil contaminants compared to adults (on a per bodyweight basis), the available data do not provide sufficient basis for departing from the default child critical receptor in deriving screening level SGVs for the residential and allotment scenarios.

Oral exposure does not contribute to the local effects seen in the lung following inhalation. Inhalation exposures may therefore be considered separately for their effects on the respiratory system (the critical effect on which the TDI\(_{\text{inh}}\) is based).

Both oral and dermal exposure to nickel can cause hypersensitivity reactions of the skin and both exposures should be assessed together. Inhaled nickel may be absorbed into the systemic circulation as well as causing local effects. Therefore inhalation exposures may be included, along with oral and dermal exposures, in the derivation of SGVs based on the TDI\(_{\text{oral}}\). However, because the recommended TDI\(_{\text{inh}}\) is orders of magnitude lower than the TDI\(_{\text{oral}}\), exposure via inhalation will make a negligible contribution to the systemic load for the standard land-use scenarios.
6 Background intake

6.1 Food

Dietary exposure to nickel for the general UK population in the 2000 FSA Total Diet Study was estimated as 1.5 µg kg\(^{-1}\) bw day\(^{-1}\) for an average adult consumer and 2.9 µg kg\(^{-1}\) bw day\(^{-1}\) for a high-level consumer (at the 97.5th percentile). Estimated intakes were higher for young people aged 4–18 years (mean 2.6, high-level 5.3 µg kg\(^{-1}\) bw day\(^{-1}\)) and toddlers aged 1.5–4.5 years (mean 3.9, high-level 7.2 µg kg\(^{-1}\) bw day\(^{-1}\)). The “population dietary exposure” was 130 µg day\(^{-1}\) (estimated using upper bound mean concentrations for each food group together with national consumption figures), which would equate to about 1.9 µg kg\(^{-1}\) bw day\(^{-1}\) for a 70-kg adult (FSA, 2004).

The results of the 2006 TDS give dietary exposure estimates of 1.5–1.6 µg kg\(^{-1}\) bw day\(^{-1}\) for an average adult consumer and 3.0–3.1 µg kg\(^{-1}\) bw day\(^{-1}\) for a high-level consumer. Again, estimated intakes were higher for young people aged 4–18 years (mean 2.6–3.1, high-level 5.3–5.8 µg kg\(^{-1}\) bw day\(^{-1}\)) and toddlers aged 1.5–4.5 years (mean 4.2–4.9, high-level 7.5–8.3 µg kg\(^{-1}\) bw day\(^{-1}\)). The “population dietary exposure” was 127–129 µg day\(^{-1}\) (the average consumption of the population, estimated from national consumption figures and corresponding upper and lower bound mean concentrations in each food group), which would equate to about 1.8 µg kg\(^{-1}\) bw day\(^{-1}\) for a 70-kg adult (FSA, 2009).

6.2 Water

Reported nickel concentrations in water vary widely. As laid down by Schedule 1 of The Water Supply (Water Quality) Regulations (SI 2000, No. 3184), the UK drinking-water limit (Prescribed Concentration or Value) for nickel is 20 µg L\(^{-1}\) (TSO, 2000).

Concentrations can be substantially increased by acid rain in polluted areas, by leaching from chromium–nickel stainless steel pipework or due to release from nickel-plated elements in electric kettles (EC-JRC, 2005a; WHO, 2007). However, kettles with exposed elements are becoming less common in the UK and data indicate that, while notably increased levels of nickel in water may transiently result from initial leaching from a new kettle, levels rapidly decrease with repeated use of the kettle (COT, 2007).

The Drinking Water Inspectorate (DWI) collects data on nickel concentrations in drinking-water, obtained from sampling at domestic taps in England and Wales. A summary of this data is shown in Table 6.1. Based on the mean concentrations and using the default adult drinking-water consumption rate of two litres per day, the mean daily intake (MDI) of nickel from drinking-water is concluded to be less than 4 µg day\(^{-1}\).
Table 6.1  Summary of 2004–2007 levels of nickel in samples of drinking-water in England and Wales (Marsden, 2009)

<table>
<thead>
<tr>
<th>Year</th>
<th>No. samples</th>
<th>Concentration (μg L⁻¹)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Min</td>
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<tr>
<td>2004</td>
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<td>2005</td>
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<td>0.001</td>
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<tr>
<td>2006</td>
<td>15,000</td>
<td>0.001</td>
</tr>
<tr>
<td>2007</td>
<td>12,856</td>
<td>0.001</td>
</tr>
</tbody>
</table>

6.3 Air

Concentrations of nickel in air measured at UK rural monitoring sites declined by about 80% between 1972 and 2001 as a result of decreasing emissions (EPAQS, 2008). A 1993 paper reported typical nickel concentrations in UK urban air as 10–15 ng m⁻³, with concentrations in rural air about half these values (QUARG, 1993). In 2005, annual mean nickel concentrations in UK air were in the range of 0.3–1.5 ng m⁻³ at rural locations, 1.9–4.5 ng m⁻³ at urban locations and 2.3–19.6 ng m⁻³ at sites close to metal industries (EPAQS, 2008).

6.4 Other sources

A cigarette contains 1–3 µg of nickel, of which about 10–20% is released into mainstream smoke and can be inhaled. This indicates that 2–12 µg of nickel are inhaled for each pack of 20 cigarettes smoked (ATSDR, 2005). Very similar values for mainstream smoke of 0.04–0.58 µg nickel per cigarette have been reported elsewhere (IARC, 1990). This represents an extra daily intake of about 1–12 µg for a 20 cigarettes per day smoker, up to 60 times that inhaled by a non-smoking urban adult.

6.5 Estimation of mean daily intakes

Based on the population dietary exposure estimates of the 2000 and 2006 Total Diet Studies (130 and 127–129 µg day⁻¹ respectively), and a mean concentration of nickel in UK drinking-water of about 2 µg L⁻¹ with the default assumption that an adult consumes two litres of water per day, the adult oral mean daily intake (MDIoral) of nickel from food and drinking-water combined is estimated to be approximately 130 µg day⁻¹.

Based on the 2005 UK air monitoring data, an overall national average atmospheric nickel concentration of about 3 ng m⁻³ seems reasonable. Based on the default 70-kg adult inhaling 20 m³ of air per day, this is equivalent to an adult inhalation mean daily intake (MDIinh) from ambient air of 60 ng day⁻¹ (0.06 µg day⁻¹).
7 Conclusions

Both soluble and insoluble nickel salts are proven respiratory tract carcinogens by inhalation in the workplace. It is uncertain whether the genotoxic potential of nickel salts plays a key role in the development of the tumours and, if so, whether the underlying mechanism might nonetheless be expected to demonstrate a threshold.

Irrespective of whether the inhalation HCV is derived based on non-threshold carcinogenicity, threshold carcinogenicity, or non-cancer effects, the resultant value would in each case be approximately 0.006 µg kg$^{-1}$ bw day$^{-1}$ (6 ng kg$^{-1}$ bw day$^{-1}$). This value is recommended here as a TDI$_{inh}$ for use in deriving SGVs. The recommendation of a TDI reflects the fact that non-cancer effects are critical to the derivation, as well as being consistent with the EPAQS view that there may be a threshold for the mechanism of carcinogenicity.

Recent expert group evaluations of tolerable oral exposures have focused increasingly on preventing elicitation of skin reactions in pre-sensitised people. In a volunteer study, an acute oral dose of 12 µg kg$^{-1}$ bw induced hand eczema in women with an established skin sensitivity to nickel. This study represented a worst-case scenario; therefore, this dose of 12 µg kg$^{-1}$ bw day$^{-1}$ is recommended here as the TDI$_{oral}$. This value is also supported by the results of a reproduction study in experimental animals in which adverse effects on foetal development were seen – a TDI$_{oral}$ derived from these animal data would be 11 µg kg$^{-1}$ bw day$^{-1}$.

Table 7.1 summarises the HCV and MDI values recommended for nickel.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Units</th>
<th>Oral</th>
<th>Inhalation</th>
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<tr>
<td>MDI</td>
<td>µg day$^{-1}$</td>
<td>130</td>
<td>0.06</td>
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<td>MDI for 70-kg adult</td>
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<td>1.9</td>
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<td>MDI for 20-kg child</td>
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<td>4.8$^a$</td>
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<td>TDI</td>
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<td>12</td>
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$^a$ See Environment Agency (2009a) for details of MDI conversion factors.

Oral exposure does not contribute to the local effects seen in the lung following inhalation. Inhalation exposures may therefore be considered separately for their effects on the respiratory system (the critical effect on which the TDI$_{inh}$ is based).

Both oral and dermal exposure to nickel can cause hypersensitivity reactions of the skin and both exposures should be assessed together. Inhaled nickel may be absorbed into the systemic circulation as well as causing local effects. Therefore inhalation exposures may be included, along with oral and dermal exposures, in the derivation of SGVs based on the TDI$_{oral}$. However, because the recommended TDI$_{inh}$ is orders of magnitude lower than the TDI$_{oral}$, exposure via inhalation will make a negligible contribution to the systemic load for the standard land-use scenarios.
References


List of abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALARP</td>
<td>as low as reasonably practicable</td>
</tr>
<tr>
<td>ATSDR</td>
<td>Agency for Toxic Substances and Disease Registry [USA]</td>
</tr>
<tr>
<td>bw</td>
<td>bodyweight</td>
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<tr>
<td>CEPN</td>
<td>Centre d’Etude sur l’Evaluation de la Protection dans le domaine Nucléaire</td>
</tr>
<tr>
<td>CLEA</td>
<td>Contaminated Land Exposure Assessment</td>
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<tr>
<td>COT</td>
<td>Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment [UK]</td>
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<td>CSTEE</td>
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<td>Department for Environment, Food and Rural Affairs [UK]</td>
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<td>EFSA</td>
<td>European Food Safety Authority</td>
</tr>
<tr>
<td>EVM</td>
<td>Expert Group on Vitamins and Minerals [UK]</td>
</tr>
<tr>
<td>FSA</td>
<td>Food Standards Agency [UK]</td>
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<tr>
<td>HCV</td>
<td>Health Criteria Value</td>
</tr>
<tr>
<td>HEC</td>
<td>human equivalent concentration</td>
</tr>
<tr>
<td>HPA</td>
<td>Health Protection Agency [UK]</td>
</tr>
<tr>
<td>IARC</td>
<td>International Agency for Research on Cancer</td>
</tr>
<tr>
<td>IPCS</td>
<td>International Programme on Chemical Safety</td>
</tr>
<tr>
<td>LOAEC</td>
<td>lowest-observed adverse effect concentration</td>
</tr>
<tr>
<td>LOAEL</td>
<td>lowest-observed adverse effect level</td>
</tr>
<tr>
<td>MAFF</td>
<td>Ministry for Agriculture, Fisheries and Food [UK]</td>
</tr>
<tr>
<td>MDI</td>
<td>mean daily intake</td>
</tr>
<tr>
<td>MOS</td>
<td>Margin of Safety</td>
</tr>
<tr>
<td>MRL</td>
<td>Minimal Risk Level</td>
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<tr>
<td>NOAEC</td>
<td>no-observed adverse effect concentration</td>
</tr>
<tr>
<td>NOAEL</td>
<td>no-observed adverse effect level</td>
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<tr>
<td>NTP</td>
<td>National Toxicology Program [USA]</td>
</tr>
<tr>
<td>ppm</td>
<td>parts per million</td>
</tr>
<tr>
<td>RAR</td>
<td>Risk Assessment Report [EU]</td>
</tr>
<tr>
<td>Acronym</td>
<td>Description</td>
</tr>
<tr>
<td>---------</td>
<td>-------------</td>
</tr>
<tr>
<td>RfD</td>
<td>Reference Dose</td>
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<tr>
<td>RIVM</td>
<td>National Institute for Public Health and the Environment [The Netherlands]</td>
</tr>
<tr>
<td>SCHER</td>
<td>Scientific Committee on Health and Environmental Risks [EU]</td>
</tr>
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<td>SGV</td>
<td>Soil Guideline Value</td>
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<tr>
<td>SUL</td>
<td>Safe Upper Limit</td>
</tr>
<tr>
<td>TCA</td>
<td>Tolerable Concentration in Air</td>
</tr>
<tr>
<td>TDI</td>
<td>tolerable daily intake</td>
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<tr>
<td>TDS</td>
<td>Total Diet Study [FSA]</td>
</tr>
<tr>
<td>UF</td>
<td>uncertainty factor</td>
</tr>
<tr>
<td>USEPA</td>
<td>US Environmental Protection Agency</td>
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<tr>
<td>WHO</td>
<td>World Health Organization</td>
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Appendix – Literature search

The literature search that formed the basis of this update report was undertaken in November 2008 using a proprietary database – the TRACE database developed and managed by bibra toxicology advice & consulting. The database was searched for expert group reviews and evaluations of nickel. It was also searched for primary reports published during 2004–2008 to ensure consideration of critical data that might not have been assessed by the expert groups.

TRACE includes information from peer-reviewed toxicology and nutrition journals as well as secondary sources (websites, official publications and evaluations by authoritative groups) including:

- UK government agency (Defra, the Environment Agency, FSA and HPA) and advisory committee (COT, COM, COC, ACAF, ACNFP and ACP) reports and evaluations
- EU Risk Assessment Reports
- EU expert committees (EU scientific committees, EFSA scientific panels)
- WHO/IPCS reports and evaluations (including CICADs and EHCs, and IARC, JECFA and JMPR monographs), and the WHO Air Quality and Drinking-Water Quality Guidelines
- OECD SIDS dossiers/SIARS
- US government agency reports and evaluations (EPA, ATSDR, FDA, NTP, OSHA, NCEA, CFSAN, CERHR, NIEHS and OEHHA)
- Health Canada, RIVM and DFG assessments and reports
- ECETOC, ACGIH, BG Chemie and DFG reports and monographs
- IUCLID data sets
- NICNAS Priority Existing Chemical Assessments
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The Environment Agency. Out there, making your environment a better place.