

## Risk Assessment

## Nickel

### General information

#### Chemistry

Nickel is an abundant metallic element which can exist in valency states of 0, +1, +2 and +3 and form a variety of compounds. Within this risk assessment, the word nickel refers to ionic nickel, unless specific compounds are stated.

#### Natural occurrence

Nickel and nickel compounds are found in soil, water, animals and plants.

#### Occurrence in food, food supplements and medicines

Nickel is present in a variety of foods particularly pulses, oats (0.18 mg/kg in miscellaneous cereals) and nuts (1.77 mg/kg). Lower levels of nickel are present in drinking water. Nickel is present in a few multi-mineral food supplements at levels of approximately 0.005 mg/daily dose. The average intake of nickel in the UK is 0.13 mg/day from food, and 0.02-0.04 mg/day from drinking water.

#### Other sources of exposure

Nickel-plated objects, such as jewellery, coins and nickel-containing implants, are sources of internal and dermal exposure.

#### Recommended amounts

COMA was unable to set recommended amounts for nickel intake.

#### Analysis of tissue levels and nickel status

Markers for nickel status have not been established. Nickel may be analysed in serum.

#### Brief overview of non-nutritional beneficial effects

No non-nutritional beneficial effects of nickel have been clearly identified.

#### Function

Nickel is present in a number of enzymes in plants and microorganisms. In humans, nickel influences iron absorption and metabolism, and may be an essential component of the haemopoietic process.

## Deficiency

Nickel deficiency has not been observed in humans. In animals deficiency is associated with disturbances such as reduced growth, impaired reproductive function and reduced haematopoiesis.

## Interactions

It has been suggested that high levels of nickel may impair absorption or utilisation of iron when iron status is low. It has been hypothesised (on the basis of their chemistry and biology and limited *in vitro* studies) that magnesium and nickel may interact, but no toxic effects have been observed to result from such interaction *in vivo*.

## Absorption and bioavailability

Absorption of nickel takes place in the small intestine via a carrier-mediated mechanism but passive diffusion may also occur. In a fasting state, the fraction of nickel salts absorbed after ingestion as a solution is between 20-25%. However absorption of nickel from solution can be reduced to less than 1% when ingested with food, ascorbic acid, milk, tea, coffee and orange juice.

## Distribution and metabolism

Nickel binds to albumin, histidine and  $\alpha_2$  macroglobulin, and is distributed widely throughout the tissues. The highest nickel levels are found in the bone, lung, kidney, liver and endocrine glands. Nickel is also found in breast milk, saliva, nails and hair. Transplacental transfer of nickel has been demonstrated in rodents.

## Excretion

Absorbed nickel is excreted in the urine predominantly in the form of low molecular weight complexes. Non-absorbed nickel is eliminated via the faeces together with a fraction of absorbed nickel that is excreted in the bile. Nickel is also eliminated in sweat.

# Toxicity

## Human data

Acute nickel exposure is associated with a variety of clinical symptoms and signs which include gastrointestinal disturbances (nausea, vomiting, abdominal discomfort and diarrhoea), visual disturbance (temporary left homonymous hemianopia), headache, giddiness, wheezing and cough.

Chronic inhalation of nickel and its compounds is associated with an increased risk of lung cancer.

Trials investigating nickel sensitisation are reviewed below. No additional data have been identified.

## Animal data

Nickel has moderate to low acute toxicity. In laboratory animals, long-term exposure to nickel is associated with adverse effects on haematological parameters, decreased body weights and changes in organ weights. These effects are generally produced at doses greater than 5 to 10 mg/kg bw/day.

In reproductive toxicity studies, nickel is associated with an increase in perinatal mortality. Abnormal embryonic development has been reported following high doses of nickel chloride given by intra-peritoneal injection, which were also associated with maternal toxicity.

## Carcinogenicity and genotoxicity

In animal studies, orally administered nickel was not found to be carcinogenic. Nickel compounds cause chromosome aberrations in cultured cells *in vitro* but are generally negative or weakly positive in *in vitro* bacterial mutation assays. Chromosome aberrations have been observed *in vivo* in both humans and laboratory animals following exposure to nickel by inhalation and nickel is carcinogenic by this route.

## Vulnerable groups

Approximately 7-10% of the population (predominately women) are affected by nickel allergic dermatitis. There is evidence suggesting that nickel ingestion may contribute to the exacerbation of eczema in sensitised individuals.

Iron-deficient individuals may be vulnerable to increased intestinal absorption of nickel, and thus to nickel sensitisation and adverse effects on haematopoiesis.

## Genetic variations

No genetic variations that influence adverse reactions to nickel have been identified.

## Mechanism of toxicity

Gastrointestinal effects are thought to be due to irritation rather than to specific toxicity. The chemical structure of the nickel atom is conducive to formation of antigens by binding to peptides or proteins, hence its strong sensitising potential. Nickel is thought to bind to histone proteins, generating potentially DNA damaging oxygen radicals through a redox cycling process. The interaction is dependent on the delivery of ionic nickel to target sites. Other mechanisms explaining the carcinogenicity of nickel following inhalation, such as inhibition of DNA repair, interference with cell signalling, calcium metabolism and transcription factors, have been suggested. The carcinogenic effects following inhalation are not relevant to low level oral exposure to nickel.

## Dose-response characterisation

The lowest reported oral dose associated with acute effects in humans was 0.05 mg/kg bw (1.2 mg in a 60 kg adult).

The dose response associated with sensitisation is difficult to define since sensitised subjects differ widely in their sensitivity, so that even a very small exposure could theoretically trigger a response in some individuals. Doses as low as 0.6 mg have resulted in exacerbation of eczema in sensitised individuals.

Adverse effects are produced in laboratory animals, at doses above 5 to 10 mg/kg bw/day, although some studies have reported effects at lower doses.

## Studies of particular importance in the risk assessment

(For full review see <http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers> or the enclosed CD).

### Human studies

*Christensen and Moller, 1975*

This was a double-blind crossover study on the provocation of eczema. 12 patients were given a placebo or nickel sulphate challenge. Oral nickel sulphate (5.6 mg nickel) provoked a reaction in 9/12 sensitised subjects. The test was repeated with the reversed medication on a later occasion. The placebo did not provoke a response.

*Kaaber et al., 1978*

Seventeen out of 28 patients with chronic nickel dermatitis experienced aggravation of symptoms when given a 2.5 mg oral dose of nickel, but no effect with placebo. Dermatitis improved in 9 of the 17 patients when they were put on a low nickel diet for 6 weeks and worsened when the normal diet was resumed. The nickel content of the diet was not measured but nickel excretion was measured in 14 of the patients and was found to decrease, indicating that nickel in the normal diet can contribute to dermatitis.

*Gawkrodger et al., 1986*

In a double blind crossover study, an oral dose of 5.6 mg (but not 0.4 mg or 2.5 mg) nickel produced a reaction in nickel-sensitised subjects more frequently than the placebo.

*Nielsen et al., 1990*

In a single-blind cross-over study, 12 nickel sensitive subjects were given a supplementary high nickel diet for 4 days. The additional dose of nickel was 0.49 mg by analysis, this dose was lower than doses used in other oral challenge studies where reactions were not provoked. Hand eczema was exacerbated in 10/12 patients.

*Menne and Maibach, 1991*

Following a review of 12 published nickel challenge studies (1975-1988) using a variety of designs, the authors concluded that a dose-response existed for exposure to oral nickel and the exacerbation of dermatitis. Thus, a minority of nickel sensitive subjects would react to doses of < 1.25 mg but the majority will react to oral doses of 5.5 mg nickel.

*Nielsen et al., 1999*

Eight non-allergic volunteers were given nickel in drinking water, followed by scrambled egg meals at different time intervals. When the nickel was ingested 30-60 minutes before the meal, peak serum nickel levels were reached 1 hour after water intake and were thirteen fold higher than when the nickel was ingested with the meal. Where the nickel and meal were taken together, a delayed peak in serum levels occurred 3 hours after ingestion. Nine out of 20 nickel-sensitised patients with vesicular hand eczema of the pompholyx type, developed flare-up of symptoms 12 hours after ingesting as little as 0.012 mg/kg body weight nickel in solution (0.003 mg/mL), on a empty stomach, with abstinence from food maintained for a further 4 hours. The dose given can be estimated to be equivalent to 0.720 mg in a 60 kg adult. Twenty age-matched non nickel-sensitive controls, with similar hand eczema symptoms, exhibited no exacerbation following oral nickel challenge. The dermatologists assessing the symptoms were not informed of the status of the patients.

### **Animal studies**

*Ambrose et al., 1976*

Groups of 25 rats of each sex were fed nickel, as nickel sulphate hexahydrate, in the diet for 2 years. The doses were estimated to be 0, 5, 50 or 125 mg/kg bw/day. Decreased body weights, significantly increased heart and decreased liver weights were observed in both the mid and top dose groups. Analyses of blood, urine and tissue histology revealed no significant effects, but few data were reported. Poor survival of animals from the control and all dose groups was a major limitation of this study.

Groups of 3 beagle dogs of each sex were fed diets containing nickel, as nickel sulphate hexahydrate, for 2 years. The doses were estimated to be 0, 3, 29 or 70 mg/kg bw/day. In the highest dose group, decreased body weights and increased kidney and liver weights were observed. No significant haematological effects were observed, and histological changes were seen only in the high dose group.

In a 3 generation rat study, groups of 20 rats of each sex were fed diets containing nickel, as nickel sulphate hexahydrate, for 11 weeks prior to breeding of three generations (F<sub>0</sub>, F<sub>1</sub>, F<sub>2</sub>), throughout pregnancy and lactation. The doses were estimated to be 5, 25 or 50 mg/kg bw/day nickel. No effects on fertility, gestation, viability or lactation were observed. An increased number of stillborn rats was apparent in all treatment groups of the F<sub>1</sub> generation but not in the F<sub>2</sub> and F<sub>3</sub> generations. The number of siblings per litter and siblings weaned decreased as the dose of nickel increased. Body weights were markedly reduced in the offspring of the dams exposed to 50 mg/kg nickel. No statistical analysis was reported.

*Smith et al., 1993*

Groups of 34 female rats were given nickel chloride in drinking water for 11 weeks prior to breeding and throughout 2 gestation (G1 and G2) and lactation (L1 and (L2) periods. The average doses provided by the water were estimated to be 1.33, 6.8 or 31.8 mg/kg bw/day nickel. No overt toxicity was reported. There was a dose-related increase in pups born dead or dying shortly after birth. This was significant at top dose at G1 and all doses at G2. Body weight gain was reduced in dams in the mid and top dose group in G1. Reproductive performance was unaffected by treatment. Although it is of unusual design, this was a well-conducted and reported study.

## Exposure assessment

Total exposure/intake:

Food	Mean: 0.13 mg/day (1997 TDS) 97.5th percentile: 0.21 mg/day
Water	0.04 mg/day (maximum) from water (NAS/NRC)
Supplements	up to 0.005 mg/day (Annex 4; OTC, 2001).

Estimated maximum intake:  $0.21 + 0.04 + 0.005 = 0.26$  mg/day

No potential high intake groups have been identified.

## Risk assessment

The carcinogenicity of nickel compounds which occurs through inhalation mainly as a result of occupational exposure does not appear to be relevant to oral exposure from low levels in food, although data are lacking in this area.

In animals, nickel caused a decrease in bodyweight in dogs and an increase in kidney weight at a dose of 70 mg/kg bw/day. In reproductive toxicity studies in rats, nickel was shown not to affect reproduction at doses up to 50 mg/kg bw/day. However, there was an increase in the number of pups stillborn or dying shortly after birth with the numbers stillborn increasing as dose increased from 5 to 50 mg/kg bw/day. At 50 mg/kg bw/day, there was a significant decrease in body weight of the pups.

The key toxic endpoint for nickel in humans is the aggravation of nickel sensitisation, for which a threshold is unclear but which is possible at the levels of nickel found in food. It is also possible that oral intakes of nickel as low as 0.49 mg (Nielsen, 1990) could trigger symptoms, particularly in the fasting state. Although certain sensitised subjects will be aware that exposure to nickel may be responsible for their dermatological symptoms, other subjects may only be aware that they are unable to tolerate certain jewellery. They also may not be aware that their dermal symptoms could be aggravated by food.

### ESTABLISHMENT OF GUIDANCE LEVEL

Nickel is a potent skin sensitiser, with 7-10% of the UK population reportedly affected. Dietary nickel can cause flare-ups of dermatitis and while there is some discussion about the levels at which this effect occurs, it appears that levels as low as 0.49 to 0.72 mg may be able to trigger a reaction, particularly if taken on an empty stomach.

In animals, nickel has fairly non-specific toxic effects, but appears to be associated with increased perinatal mortality in multi-generation studies. Using the LOAEL of 1.3 mg/kg bw/day derived from the study by Smith *et al.* (1993) and applying the conventional uncertainty factors of 3 for LOAEL to NOAEL extrapolation, 10 for inter-species variation and 10 for intra-individual variation, indicates that total nickel intake of 0.0043 mg/kg bw/day would not be expected to have effects in non-sensitised individuals (equivalent to 0.26 mg/day in a 60 kg adult).

Prevalence of nickel sensitivity is high and many individuals may not be aware that they are sensitised. Furthermore, the absorption of nickel is greater when taken on an empty stomach and in the absence of food, as may occur with supplements. It is therefore not possible to set a safe upper level or guidance for supplemental intake of nickel. UK dietary intake of nickel in food is not expected to result in harmful effects.

## References

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