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**Nickel and Nickel Compounds:
Review of Toxicology and
Epidemiology with special
reference to Carcinogenesis**

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WITH SPECIAL REFERENCE TO CARCINOGENESIS

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REVIEW OF TOXICOLOGY AND EPIDEMIOLOGY
WITH SPECIAL REFERENCE TO CARCINOGENESIS

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Errata

In Table 7, p. 95, please insert/replace the
correct CAS N° for:

Nickel (IV) oxide 12035-36-8

Nickel subsulphide 12035-72-2

NICKEL AND NICKEL COMPOUNDS :
REVIEW OF TOXICOLOGY AND EPIDEMIOLOGY
WITH SPECIAL REFERENCE TO CARCINOGENESIS

A. SUMMARY

This report reviews the available data on the toxicology of nickel with particular reference to metabolism, animal carcinogenicity, mutagenicity and epidemiology. The physical and chemical properties of nickel and its compounds and methods of production from nickel-containing ores are briefly described. The use of nickel in its various forms in industry is recorded and an indication is given of the relative commercial importance of different nickel compounds.

Nickel carbonyl is acutely toxic by inhalation and soluble nickel salts may be harmful if ingested. Soluble and insoluble nickel compounds differ in their kinetic pattern and in their extra-cellular and intra-cellular bioavailability. The former are rapidly cleared from the body and enter cells only to a limited degree. The latter have a higher tendency to be retained at their site of deposition. They enter cells by phagocytosis (for which both particle size and surface charge are important) and achieve high bioavailability. Within the cell insoluble nickel particles may gradually and continuously release Ni^{2+} ions to their intra-cellular binding sites.

The most likely mechanism of interaction of nickel with cellular macromolecules is by forming a complex with chromosomal protein. Although there is some evidence of damage to DNA in in vitro systems with soluble and insoluble nickel compounds, there is no convincing experimental evidence of mutagenic activity of nickel compounds in vitro and in vivo.

Nickel subsulphide consistently produces local sarcomas when given parenterally by the intra-muscular and other routes to experimental animals. Other insoluble nickel compounds, but not soluble ones, also show this property which is not relevant to human risk assessment. To date nickel subsulphide is the only compound for which there is sufficient evidence of carcinogenicity by the production of lung tumours when given by inhalation.

There is sound epidemiological evidence that the process of nickel matte roasting resulted in cancers of the respiratory tract in exposed workers. Excess pulmonary and sinonasal cancers have been reported in workers engaged in an electrolytic refinery using the Hybinette process and in certain other processes involving the production of nickel sulphate. However because of mixed exposures there is insufficient evidence to indite conclusively any individual nickel compound as a proven human carcinogen.

The criteria for classifying carcinogenic substances in the E.E.C. are briefly described. These have been applied to nickel and its compounds in the light of the review of all the relevant data. The criteria do not allow the placement of any individual nickel compound in Category 1 (proven human carcinogen). However, mixed exposures from certain refining processes would warrant placement in Category 1 if processes were classifiable.

The various individual nickel compounds seem to fall into the following categories according to the criteria:

Category 2:

Nickel subsulphide (Ni_3S_2)

Category 3:

Nickel metal (powder)

Nickel (II) oxide (NiO)

No Classification:

Nickel metal (massive)

Nickel (III) oxide (Ni_2O_3)

Nickel (IV) oxide (NiO_2)

Nickel sulphide (NiS)

Nickel carbonyl ($\text{Ni}[\text{CO}]_4$)

Nickel sulphate ($\text{NiSO}_4 \cdot 7 \text{H}_2\text{O}$)

Nickel chloride (NiCl_2)
Nickel nitrate (NiNO_3)
Nickel hydroxide ($\text{Ni}[\text{OH}]_2$)
Nickel hydroxycarbonates
(nickel carbonate,
 $x \text{NiCO}_3 \cdot y \text{Ni}[\text{OH}]_2 \cdot z \text{H}_2\text{O}$)

B. INTRODUCTION

Nickel is a naturally occurring metal which is widely distributed in the environment. Historically it has been mined and refined in various parts of the world although currently the Sudbury Basin in Ontario, Canada is the main world source of nickel ore. Major western sites of nickel refining are in Canada, (Ontario, Manitoba, Saskatchewan), Wales, Norway, Finland, France (Le Havre and New Caledonia), and Australia. Nickel and some nickel compounds have a wide variety of industrial uses of which the most important commercially are stainless steel production, heat and corrosion-resistant nickel alloys, electroplating, battery manufacture and industrial catalysis. Nickel appears to be an essential trace element (Sunderman et al, 1972; Nielson and Ollerick, 1974; Underwood, 1976) and in nickel deficiency experiments growth retardation and increased mortality have been reported both in mothers and their offspring (Anke et al, 1980, 1983).

The toxicology of nickel and nickel compounds has been extensively reviewed (IARC 1976 and 1984; Brown and Sunderman, 1980; British Petroleum, 1984; Environmental Protection Agency, 1986; Fairhurst and Illing, 1987; U.S. Public Health Service, 1988). One nickel compound, nickel carbonyl, is acutely toxic both to man and animals when inhaled. Other nickel compounds have been shown to be acutely toxic when administered to laboratory animals experimentally but have rarely been associated with acute systemic effects in man (Fairhurst and Illing, 1987). In contrast nickel, both as metal and nickel salts, is a potent human skin sensitiser and nickel salts may also produce respiratory sensitisation.

The most important chronic effect which has been associated with certain forms of nickel is cancer of the respiratory tract. Observations on cases of the otherwise rare sinonasal cancer in workers at a nickel refinery at Clydach in South Wales in the 1920's and early 1930's first suggested an association between nickel and cancer in man (Bridge, 1932). These early case reports led to detailed epidemiology studies which clearly demonstrated excess sinonasal and lung cancer in workers commencing employment at the Clydach refinery before 1925, a time when very dusty working conditions prevailed. Epidemiology studies on nickel refinery workers in different parts of the world have confirmed the association

between certain nickel refining processes and excess sinonasal and lung cancer but to date it has not been possible to identify any specific form or forms of nickel responsible. The available evidence from epidemiology and experimental studies strongly suggests that the carcinogenic hazard may not be the same for all forms of nickel and this has implications for the classification of nickel and nickel compounds under the Sixth Amendment to the European Communities Council Directive 67/548/EEC and its adaptations.

In this report the toxicology of nickel and nickel compounds is reviewed with particular reference to metabolism, mutagenicity and carcinogenicity, but excluding work on sensitisation. In the light of the review, suggestions are made on classification.

C. PHYSICAL AND CHEMICAL PROPERTIES

Nickel is an element of Group VIII of Mendeleev's periodic table. It is a metal of the atomic number 28 and the atomic mass 58.71, which occurs naturally as 5 different isotopes : 58 (68.3%), 60 (26.1%), 61 (1.1%), 62 (3.6%) and 64 (0.9%). The metal in its massive form is silvery-white and lustrous. It is resistant to atmospheric corrosion, water, alkali and many organic compounds, but is slowly soluble in dilute non-oxidising mineral acids and quite rapidly in oxidising acids such as HNO_3 . It has ferromagnetic properties, although less marked than iron. Nickel is both malleable and ductile so that it is readily worked. It tarnishes when heated in air. Finely divided nickel can absorb fairly high amounts of hydrogen. It is used as a catalyst and is pyrophoric.

Nickel reacts on heating with boron, silicon, phosphorus, sulphur, and the halogens. The predominant valence is 2, but also 1, 3 and 4 occur.

The main groups of compounds are the following :

1. Oxides and Sulphides

The prevailing oxide is NiO , a green powder with the same crystalline structure as rock-salt. It turns black when deviating from stoichiometry, due to a defective structure. Values as high as $\text{NiO}_{1.32}$ have been reported.

Anhydrous higher oxides of nickel, e.g. Ni_2O_3 and NiO_2 have been stated to exist but have never been determined with sufficient certainty to be included in a phase diagram.

Hydrated forms of the higher nickel oxides are known and have industrial significance. Treating nickel solutions with alkali under oxidising conditions produces precipitates containing more oxygen than Ni(OH)_2 . On heating, the precipitates lose water down to $\text{Ni}_2\text{O}_3 \cdot \text{H}_2\text{O}$ at 138°C and then dissociate to NiO , oxygen and water.

Higher hydrated oxides can be produced by electrolytic oxidation. Thus a "black nickel hydroxide", thought to contain some tetravalent

nickel, can be produced by anodic oxidation of a nickel hydroxide slurry. This oxidised form is used in refining to separate cobalt hydroxide from solutions containing nickel and cobalt ions (Boldt, 1967).

In batteries tetravalent nickel also occurs in the active mass of nickel positive plates when these are charged. The equivalent of $\text{NiO}_{1.8}$ has been reported (Briggs et al, 1955).

To the best of our knowledge higher oxides of nickel in hydrated form are not sold as pure substances.

Nickel sulphides consist of NiS_2 (pyrite structure), Ni_3S_4 (spinel structure), and numerous metallic phases having compositions between NiS and Ni_3S_2 .

2. Salts

The water-free nickel halides are yellow (fluoride, chloride, bromide) or black (iodide). They crystallise from water as hexahydrates containing the green $[\text{Ni}(\text{OH}_2)_6]^{2+}$ ion.

The sulphate occurs as hexa- and heptahydrate. Most of the nickel salts are readily soluble in water.

3. Nickel-Carbonyl

Formed by reaction of carbon monoxide with finely divided nickel, the tetracarbonyl is a stable volatile liquid, tetrahedral in structure in the vapour and in the solid.

4. Nickel Complexes

Nickel forms complexes with many different ligands and a wide and interesting variety of coordination numbers and stereo chemistries. $\text{K}_2[\text{NiF}_6]$ for example is a strongly oxidising agent and liberates oxygen from water. The most well known complex is the red nickel

diacetyl dioxime, which can be precipitated from ammoniacal water solutions and can be used to separate nickel from cobalt.

The physical properties of the most important compounds addressed in this document are summarised in Table 1.

D. PRODUCTION

There are two main types of nickel-containing ores that are used in the production of nickel and nickel compounds. These are :-

a) Sulphide Ores

These consist principally of mixtures of pentlandite $[(Ni,Fe)_9S_8]$ and nickeliferrous pyrrhotite $[(Fe,Ni)_{1-x}S]$. They can contain appreciable amounts of other elements such as magnesium, copper and cobalt, and precious metals.

b) Laterite Ores

These ores are sometimes referred to as 'oxide ores' and are complex nickel-iron silicates. They can contain appreciable amounts of other elements such as magnesium and cobalt.

The distribution of deposits of the two ores around the world are shown in the map (Fig. 1). Of the total usage, approximately 80% is sulphide ore and 20% laterite ore.

The processes for extracting the nickel from these ores have evolved over the past 100-150 years. The main steps involved in the current multi-stage processes are given in Figures 2 and 3, and consist of high temperature roasting followed by electrolytic or carbonyl refining.

In early refining operations with sulphide ores, the high temperature (1800-1900°C) roasting by calcining and sintering was carried out on an impure nickel sulphide matte. Smelting was carried out at 1250°C. Nowadays the matte is mainly Ni_3S_2 . These early operations were very dusty. (Warner, 1984; Mastromatteo, 1986; Roberts et al, 1984). The dust appears to have been primarily a mixture of nickel subsulphide and nickel oxide created both by the initial grinding of the matte and by fine material being mixed with new feed for recirculation through the sintering process. From 1963 nickel matte roasting has been undertaken in enclosed fluid bed roasters.

The early refining processes also involved exposures to irritant gases (sulphur dioxide) and other materials such as the sulphides and oxides of copper, cobalt and arsenic and polynuclear aromatics (from the combustion of fuels). In other refineries exposure to both insoluble and soluble nickel compounds almost certainly occurred.

In modern refineries based on sulphide ores, exposures are now generally very low and comply with recognised hygiene standards. (See Appendix 4).

Less data is available on exposures in early laterite ore extraction processes but it is suggested they were lower than in the sulphide processes (Warner, 1984; Egedahl, 1984). Workers in the laterite processes were, however, exposed to a different range of compounds.

The major products from the overall extraction processes are :-

- (i) nickel metal (>95% Ni)
- (ii) ferronickel (20-50% Ni)
- (iii) nickel oxide (NiO)
- (iv) nickel salts (mainly sulphate and chloride)

In 1987 about 110,000 tonnes of such nickel and nickel compounds were produced in Western Europe with approximately a further 100,000 tonnes being imported. The total world supply in 1987 was 610,000 tonnes.

E. USE OF NICKEL AND NICKEL COMPOUNDS OF COMMERCIAL IMPORTANCE

In the early 1980's the nickel metal, ferronickel, nickel oxide and nickel salts from the refinery processes were used to produce the following materials :-

Product	%
Stainless steel	50%
Non-ferrous alloys (including coinage)	15%
Alloy steels	10%
Foundry alloys	10%
Electroplating	10%
Others (catalysts, batteries, pigments)	5%

Figure 4 summarises the main subsequent uses of these various nickel compounds and alloys.

In terms of individual chemical substances (i.e. non-alloys), those of major commercial importance are as follows :-

- Nickel metal : Sold as powder, briquettes, ingots, pellets and cathode. Present in some catalysts.
- Ferronickel : Sold mainly as ingots and shot.
- Nickel (II) oxide : Vary in colour from black (produced at 550°C) to green (produced at 1200°C). Most of the green material is sold to the stainless steel industry whereas most of the black is used in the production of nickel salts. Both forms are present in catalysts and pigments.
- Nickel sulphate : Sold mainly as the solid for electroplating.

- Nickel chloride : Sold mainly as the solid for electroplating.
- Nickel nitrate : Sold mainly as the solid for general chemical use.
- Nickel hydroxy carbonates: Of variable composition with the general formula $x \text{NiCO}_3 \cdot y \text{Ni(OH)}_2 \cdot z \text{H}_2\text{O}$. Quite often called nickel carbonate. Used in electroplating, catalysts and pigments.
- Nickel hydroxide : Used in the production of Ni-Cd batteries.
- Nickel titanium yellow : $(\text{Ti, Sb, Ni}) \text{O}_2$. Typical of a range of pigments used in enamels and ceramics or in the production of ferrites.

The following compounds are of little or no commercial significance but are referred to in the toxicological literature :-

- Nickel subsulphide : Important in refinery processes
(Ni_3S_2) but not commercially available.
- Nickel sulphide (NiS) : Of little commercial significance.
Available in crystalline or amorphous forms.
- Nickel carbonyl : Important in some refinery
(Ni(CO)_4) processes. Of small commercial significance.
- Nickel III oxide : Not available commercially.
(Ni_2O_3)
- Nickel IV oxide : Not available commercially.
(NiO_2)

F. GENERAL TOXICOLOGICAL PROFILE

1. Acute Toxicity

1.1. Experimental Data

Representative LD₅₀ and LC₅₀ values with signs of intoxication following exposure to a single dose of nickel metal or its relevant compounds, can be found in Table 2. From these data the toxicity ratings defined in the succeeding paragraphs have been derived using the EEC system for classification and labelling (EEC, 1983).

Not toxic, compounds with oral LD₅₀ values above 2000 mg/kg do not require classification for acute effects. These are the compounds of low water solubility, i.e. nickel metal, all forms of nickel oxides, both crystalline and amorphous, nickel subsulphide and nickel sulphide.

Harmful, if ingested: The more soluble compounds nickel hydroxide, nickel carbonate, nickel sulphate and its hexahydrated form, and nickel chloride.

Very toxic by inhalation: Nickel carbonyl. Kincaid et al (1953) have determined LC₅₀ values for a variety of species and different exposure times (Table 2).

1.2. Human Data

Data have been published by Daldrup et al (1982) for nickel sulphate, and by Sunderman et al (1988) for nickel sulphate and nickel chloride.

Daldrup et al (1982) reported on a fatal case of a 2 ½ year old girl, who had ingested an estimated dose of at least 5 grams of crystalline nickel sulphate. Four hours later she had a cardiac arrest; she died eight hours after ingestion of the nickel sulphate. Pathology revealed severe irritative changes in the