Technical Report

No 33

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

February 1989

ISSN-0773-8072-33

Technical Report

N° 33

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

ISSN - 0773 - 8072 - 33

Brussels, February 1989

NICKEL AND NICKEL COMPOUNDS :

REVIEW OF TOXICOLOGY AND EPIDEMIOLOGY

WITH SPECIAL REFERENCE TO CARCINOGENESIS

ECETOC Technical Report No. 33

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

CONTENTS

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

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

Errata

In Table 7, p. 95, please inserr/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 ($Ni[CO]_4$)
Nickel sulphate ($NiSO_4.7\ H_2O$)

Nickel chloride ($NiCl_2$)
Nickel nitrate ($NiNO_3$)
Nickel hydroxide ($Ni[OH]_2$)
Nickel hydroxycarbonates
(nickel carbonate,
x $NiCO_3$.y $Ni[OH]_2$.z H_2O)

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 toxiciology 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 $NiO_{1.32}$ 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 $Ni_2O_3.H_2O$ 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 $NiO_{1.8}$ 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 $[Ni(OH_2)_6]^{2+}$ 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. $K_2[NiF_6]$ 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 $NiCO_3$.y $Ni(OH)_2$.z H_2O. Quite often called nickel carbonate. Used in electroplating, catalysts and pigments.
Nickel hydroxide	:	Used in the production of Ni-Cd batteries.
Nickel titanium yellow	:	(Ti, Sb, Ni) 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 (Ni_3S_2)	:	Important in refinery processes but not commercially available.
Nickel sulphide (NiS)	:	Of little commercial significance. Available in crystalline or amorphous forms.
Nickel carbonyl ($Ni(CO)_4$)	:	Important in some refinery processes. Of small commercial significance.
Nickel III oxide (Ni_2O_3)	:	Not available commercially.
Nickel IV oxide (NiO_2)	:	Not available commercially.

F. GENERAL TOXICOLOGICAL PROFILE

1. Acute Toxicity

1.1. Experimental Data

Representative LD_{50} and LC_{50} 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 LD_{50} 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 LC_{50} 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

gastrointestinal tract. This case can be considered as confirmation of the experimental data indicating the classification "harmful" for nickel sulphate.

Sunderman et al (1988) described an acute nickel intoxication in 32 electroplating workers who accidentally ingested an aqueous solution of nickel sulphate and nickel chloride. The nickel concentration of this solution was 1.63 g/l, the total dose in workers with signs of intoxication were estimated to range from 0.5-2.5 grams. Signs developed promptly, and encompassed nausea, vomiting, abdominal discomfort, diarrhoea, giddiness, lassitude, headache, cough and shortness of breath. These signs typically lasted a few hours, and persisted at most two days.

Nausea, vomiting, weakness and headache were the predominant signs of acute nickel intoxication in a group of 23 patients undergoing haemodialysis for renal disease (Webster et al 1980). Nickel had leached from a nickel-plated stainless steel water heater contaminating the dialysate. The dose and form of nickel causing these signs, reported to be within 2-3 hours to onset of exposure, lasting for 3-13 hours, and disappearing in 48 hours, was not indicated.

2. Short-term toxicity (Fairhurst and Illing, 1987, unless otherwise stated)

Exposures to any of the nickel compounds mentioned below, whether via the oral or the inhalation route, can affect bodyweight gain (Table 3). In a comparative 12-day inhalation study in rats and mice, the amount of nickel in the lungs at the end of exposure varied in relation to the water solubility of the compounds: the burden did not increase with concentration for the soluble sulphate but did for the insoluble oxide and the subsulphide. Toxicity ranking according to mortality indicated the highest toxicity for the soluble sulphate, followed by subsulphide, whereas nickel oxide, which has an even lower solubility, was the least toxic after repeated exposure (Dunnick et al, 1988).

2.1. Nickel (II) Oxide

Inhalation exposure of rats and mice to nickel oxide (calcined at 1350°C) at a range of concentrations from 0 to 10 mg NiO/m^3 for 6 hours per day, 5 days per week for 13 weeks produced inflammation in the lung. In rats this was seen at exposures of 2.5 mg/m^3 and over but in mice only at 10 mg/m^3. Alveolar macrophage hyperplasia and perivascular lymphocytic inflitrates occurred in rats exposed to 1.2 mg/m^3 and in mice at 2.5 mg/m^3 or greater (Hobbs et al, 1988).

2.2. Nickel Carbonate

Insufficient data available.

2.3. Nickel Sulphate

Exposure of rats via the oral route at doses of 100 mg/kg/day for 20 days caused decreased bodyweight gain, elevated blood glucose levels and reduced serum proteins (Table 3).

Inhalation exposure of rats and mice to aerosols of nickel sulphate hexahydrate, 6 hours per day for 12 days, at a range of concentrations from 0 to 60 mg/m^3 resulted in exposure related mortality in rats at 15 mg/m^3 and in mice at 7 mg/m^3 or greater. Treatment related inflammatory lesions in the lung and nasal lesions, including degeneration of the respiratory and atrophy of the olfactory epithelium, were seen at exposure as low as 3.5 mg/m^3 (Benson et al, 1988a).

In a further experiment rats and mice were exposed to nickel sulphate hexahydrate, 6 hours per day, 5 days per week for 13 weeks at concentrations of 0 to 2.0 mg Ni/m^3. Pneumonic changes occurred in the lungs and atrophy of the olfactory epithelium in the nose in both species, at concentrations near the TLV of 0.1 mg Ni/m^3 (see Appendix 4) (Benson et al, 1988b).

2.4. Nickel Chloride

Oral administration via the drinking water to rats at dose levels of 0, 2.5, 5 and 10 ppm Ni for 28 days resulted in reduced bodyweight gain and elevated serum glucose at all dose levels (see Table 3).

2.5. Nickel Subsulphide

Inhalation exposure of rats and mice to aerosols of nickel subsulphide for 6 hours per day for 12 days at a range of concentrations from 0 to 10 mg/m^3 resulted in mortalities at the highest dose which were associated with necrotising pneumonia. Emphysema developed in rats and fibrosis in mice exposed to 5 mg/m^3. Degeneration of the respiratory and atrophy of the olfactory epithelium occurred in the nose in rats exposed to concentrations of 0.6 mg/m^3 an mice exposed to 1.2 mg/m^3 and over. Nickel lung burdens increased linearly with exposure concentrations (Benson et al, 1987).

2.6. Nickel Carbonyl

Because of the high acute toxicity of nickel carbonyl little short term toxicity data is available. One study in 3 different species with repeated exposures indicated development of partial tolerance to sublethal concentrations (Kincaid et al, 1953).

3. Summary

1. Soluble nickel salts are harmful by ingestion. The most prominent signs of intoxication are nausea, diarrhoea, giddiness and headache; in addition, ataxia was observed in animals. Limited pathological evidence indicates an irritative action on the mucous membranes.

2. The degree of acute inhalational toxicity of nickel carbonyl varies with species; this compound should be classified as very toxic.

3. Repeated inhalational exposure to nickel and its compounds, can be considered to cause irritative changes of the respiratory tract, even at concentrations near the relevant recommended occupational exposure limit. Prolonged exposure to higher concentrations may cause lung fibrosis.

G. METABOLISM - TOXICOKINETICS - INTRACELLULAR AVAILABILITY

1. Introduction

Soluble and insoluble nickel compounds differ markedly in their metabolic and kinetic behaviour. Solubility in body fluids (which in particular for Ni_3S_2 may be considerably higher than aqueous solubility [Andersen et al, 1980; Kuehn and Sunderman, 1982]) is the main determinant for absorption from the site of exposure, intracellular bioavailability and persistence in the tissue.

$Ni(CO)_4$ is only briefly mentioned in this chapter since its metabolism and toxicological profile is unique. It is soluble in lipids and therefore easily penetrates the alveolar membranes, enters the central nervous system and displays a high acute CNS toxicity. After termination of exposure it is fairly rapidly removed from the body due to its volatility.

In some of the papers reviewed the content of Ni or Ni^{2+} in body fluids or tissue was analytically measured, while its associated counter-ion(s) and its solubility or the physical form of the exposure were neglected or less well described. In such cases the evaluation of a study can be difficult.

For some plants and animals nickel is a vital requirement (Anke et al, 1983) and there is some evidence that nickel is an essential trace element in several species (Sunderman et al, 1972; Nielson and Ollerich, 1974; Anke et al, 1983). It was not possible to induce a clear nickel deficiency in several animal experiments (Sunderman et al, 1972, 1975), the problem being the difficulty of providing a nickel-free environment whilst avoiding deficiencies of other essential trace elements (Anke et al, 1980). The first enzyme considered to be a nickel metalloenzyme was urease (Fishbein et al, 1976). Many more enzymes are activated or inhibited by Ni^{2+} ions (Sunderman et al, 1975).

2. Absorption and Tissue Bioavailability

Nickel and nickel compounds may enter the body via the following routes :

- *oral* intake (from food and drinking water or by accidental ingestion),
- *inhalation* (occupational dust or aerosol exposure, tobacco smoke and environmental dust pollution),
- *percutaneous* absorption (probably unimportant for systemic effects, but the usual route of exposure for the development of contact dermatitis),
- *parenteral* uptake (possible from medical devices and fluids; artificial route in animal experiments).

2.1 Nickel Levels in Body Fluids

The absorption of nickel from the site of contact and the entrance of soluble forms of nickel into the systemic circulation may be measured via the whole blood, serum or plasma or urinary levels, all of which give similar information (Nomoto and Sunderman, 1970). Urinary levels are more frequently used and correlate well with systemic absorption into the circulation.

In non-occupationally exposed man, the mean concentrations of nickel in whole blood and serum are in the range of 1 - 5 µg/l and in urine < 10 µg/l (Christiensen and Lagesson, 1980; Sunderman, 1977; Mushak, 1980; Zober et al, 1984). Levels were extensively reviewed in relation to exposure and health risks (Sunderman et al, 1986) but should be used to assess these only with great caution (see also 2.3). Serum concentrations are similar in other species (Hendel and Sunderman, 1972; Mushak, 1980).

In human and rabbit blood, nickel is bound to several fractions : (a) an ultrafiltrable histidine complex, (b) albumin and (c) metalloprotein (= "nickeloplasmin", which in rabbits is an alpha-macro-globulin and in humans is a 9.5 S alpha-glycoprotein

(Nomoto et al, 1971; v. Soestbergen and Sunderman, 1972; Hendel and Sunderman, 1972; Sunderman et al, 1972; Sarcar, 1984; Scott and Bradwell, 1984).

Nickel levels are unaffected by age, sex and pregnancy (McNeely et al, 1971; Zober et al, 1984), but may be considerably increased in certain disease states, like cerebral or myocardial ischaemia, and decreased in others, e.g. hepatic diseases (McNeely et al, 1971; Sunderman et al, 1972).

Average total body burden has been estimated by Bennet (1984) as 0.5 mg for an adult person; other authors have calculated 5 and 10 mg, respectively (Sumino et al, 1975; Schroeder et al, 1962).

2.2 Oral Route

The human average daily dietary intake is in the range of 100 to 800 µg/person per day (Schroeder et al, 1962; Clemente et al, 1980; Smart and Sherlock, 1987). Nielsen and Flyvholm (1983) estimate nickel intake from the average Danish diet to be approximately 150 µg/day, occasionally reaching approximately 900 µg/day with some foods. One to ten per cent of the ingested amount is systemically absorbed and enters the circulation (Horak and Sunderman, 1973; Mushak, 1980; EPA, 1986; Bennet, 1984).

According to Schroeder et al (1962) there appears to be a mechanism which is probably non-specific, that limits intestinal absorption.

After oral intake of 5.6 mg soluble nickel per person (as 25 mg $NiSO_4$. 6 H_2O) serum levels rose to about 25 - 40 g/l within about 2.5 hours. They returned to normal (1 - 5 g/l) within 1 - 2 days (Christensen and Lagesson, 1981). Serum nickel levels were similarly elevated when 5 mg Ni (22.4 mg $NiSO_4$. 6 H_2O) in water were consumed by fasting persons; when this amount was ingested with meals, nickel levels in serum did not increase. EDTA added to the the diet suppressed serum nickel to below fasting baseline

levels (Solomons et al, 1982), while thiuram disulphide medication or iron deficiency may increase intestinal absorption.

It is also known that elevated nickel intake in some diets may give rise to dermatitis in nickel-sensitive persons (Christensen and Mollar, 1975; Cronin et al, 1980; Jordan and King, 1979).

In rats, after gavage administration of 0.014 - 64 mg/kg ^{63}Ni (as $NiCl_2$), 3 - 6% of the label was absorbed and recovered in the urine while most of the radioactivity appeared in the faeces (Ho and Furst, 1973). In situ experiments with a perfused intestinal loop preparation demonstrated that the nickel absorption from the jejunum is a saturable process at > 20 µM concentration (Foulkes and McMullen, 1986).

In mice approximately 2% of 0.58 mg/kg ^{63}Ni (as nickel chloride in the diet) was excreted in the urine, similarly indicating a limited intestinal absorption of soluble Ni compounds. Thiuram disulphides increased the intestinal absorption (and renal excretion) up to approximately 20% (Jasim and Tjalve, 1984).

Forms of nickel which are insoluble and not solubilised by intestinal fluids are likely to remain unabsorbed and excreted via the faeces.

2.3 Inhalation

About 0.1 - 0.7 g Ni/day with median particle size diameters of about 1 m enters the human respiratory tract from non-occupational environmental sources (WHO, 1988). Higher amounts may be inhaled under certain occupational conditions or in areas of environmental pollution (Schröder, 1970).

In rats and mice soluble $NiCl_2$ is absorbed from the lung rapidly and excreted via the kidney with a half-life of 1 - 4 days; there is transient translocation to lung, adrenals, pancreas, spleen, heart and testes in decreasing order (Graham et al, 1978; English et al, 1981; Williams et al, 1980; Clary, 1975). After

intratracheal instillation of microgram amounts of $^{63}NiCl_2$ to rats > 70% of the radioactivity was recovered in the urine within 1 day. The lungs retained < 30% of their initial burden, decreasing to < 1% on day 21 (Machado-Carvalho and Ziemer, 1982).

Following intratracheal instillation of approximately 12 µg $^{63}Ni_3S_2$ (1.7 µm median diameter) to mice, lung clearance over a 35-day observation period occurred in two phases with half-lives of 1.2 days (rapid phase) and 12.4 days (slower phase); about 60% was found in the urine and about 40% in the faeces after 35 days (Valentine and Fisher, 1984). This is consistent with a relatively rapid solubilisation, translocation and elimination of Ni_3S_2.

After intratracheal instillation insoluble ^{63}Ni (as NiO) was partially translocated to other organs. Within 3 days approximately 1/3 of the dose was translocated, presumably after conversion to soluble forms, although even 15 and 90 days later increased tissue levels of Ni were still found in lung and mediastinal lymph nodes, showing considerable retention close to the site of exposure (English et al, 1981).

In rats NiO (green) aerosol exposures (0.6 to 70 mg NiO/m^3; 1.2 or 4 µm particles, 7 hours/day, 5 days/week) for 1 month resulted in dose-dependent deposition and clearance rates. A biological half-life was found of 11.5 months for the smaller particles (1.2 µm) and 21 months for the larger particles (4 µm). In the high exposure groups nickel concentrations in liver, spleen and blood were slightly increased with increasing time of clearance (Tanaka et al, 1985). An increase of deposition was also seen upon longer exposure (up to 12 months) to green NiO dusts in male rats (0.3 or 1.2 mg NiO/m^3; 0.6 µm). Lung weights were also increased, while in liver, kidney, spleen and blood Ni concentrations only rose slightly (Tanaka et al, 1986). Again, the authors found increasing clearance rates with decrease of particle size.

In Syrian hamsters, 3 week and 3 month inhalation exposures to black NiO (approximately 40 and 50 mg Ni/m^3; particle size 1.0 -

2.5 μm) resulted in deposition of up to 20% of the inhaled amount in the lungs. Similar values were found after successive 7-hour inhalations. By the sixth post-exposure day > 70% of this was still present in the lungs and by day 155 some 20%; no excess levels were detected in liver and kidney (Wehner and Craig, 1972). This study indicates limited absorption of this insoluble material with retention in the respiratory tract. Similar clearance rates from the site of deposition were reported by others (Mushak, 1980; Leslie et al, 1976).

Thus, clearance rates and biological half-life times are largely dependent on the dose, solubility and the size of the particles inhaled. Smaller particles are deposited deeper in the lung and also have a higher surface-weight ratio, allowing more nickel to be absorbed (EPA, 1986). Soluble particles are absorbed quickly and less is available for mucociliary (short-term) clearance. Insoluble nickel materials are at least partially engulfed by the lung macrophages (Sanders et al, 1971). Upon prolonged exposure this leads to detrimental effects on the long-term clearance capacity of the lung and may cause an increasing tissue burden. For instance in rats, dust inhalation of NiO (50 $\mu g/m^3$; up to 15 weeks) gradually decreased the long-term clearance rates for this and other materials (such as Fe_2O_3). This essential defence mechanism relies mainly on the integrity of macrophages. Short-term clearance rates, which are mediated by the mucociliary apparatus, remain unaffected (Oberdoester and Hochrainer, 1980). Similar observations were also made with metallic nickel dust (0.1 - 1 mg/m^3) and with 0.2 mg/m^3 of $NiCl_2$ (Camner et al, 1983).

Quantitative metabolic data in man after nickel inhalation is not available. In some studies increased serum and urinary levels were observed after occupational exposure; these returned to normal within several weeks upon termination of the exposure. This does not mean that all nickel was cleared from tissues where exposure was to an insoluble nickel compound. For instance, Kalliomaki et al (1981) found no increase of urinary levels after exposure to fumes containing up to 30 μg Ni/m^3 (0.01 ppm); the nickel may have been retained in the respiratory tissues.

Torjussen and Andersen (1979) found that the Ni content of nasal mucosa was increased in workers exposed to insoluble materials like Ni_3S_2 and NiO, but unchanged when exposed to soluble $NiCl_2$ or $NiSO_4$. Sunderman et al (1986) and Morgan and Rouge (1984) have demonstrated that the analysis of urine and blood for nickel concentrations is in certain circumstances a useful biomonitoring tool. Such concentrations are an indication of current exposure and are not necessarily associated with any adverse health effects. Lower concentrations of nickel are found in blood and urine following exposure to insoluble as opposed to soluble nickel compounds.

Since Ni_3S_2 is slightly soluble in body fluids and may be translocated from its sites of deposition, it seems reasonable to expect that Ni_3S_2 exposure will give higher plasma and urinary nickel levels than NiO exposure.

In summary, fundamental differences appear between soluble and insoluble materials with regard to absorption and tissue bioavailability after inhalation exposure: soluble compounds are quickly absorbed, translocated and excreted, whereas insoluble materials are retained longer in or close to the respiratory tract.

2.4 Dermal Exposure

Nickel in aqueous solutions of $NiSO_4$ can penetrate the skin of man and laboratory animals (Norgaard, 1955, 1957; Mathur et al, 1977). Fullerton et al (1986) found in in vitro experiments with excised human skin that 'occlusive' conditions enhance percutaneous penetration and that $NiCl_2$ is absorbed approximately 50 times faster than $NiSO_4$.

2.5 Parenteral Exposure

Soluble nickel compounds are removed from the site of injection and rapidly excreted as shown by experiments in rats and rabbits where after i.p. or i.v. administration of $^{63}NiCl_2$ more than 80%

of the radioactivity appeared in the urine, the majority within 24 hours (Ho and Furst, 1973; Sayoto et al, 1981; Tandon, 1982; Smith and Hackley, 1968; Onkelinx et al, 1973; van Soestbergen and Sunderman, 1972; Oskarsson and Tjalve, 1979).

Shortly after i.v. injection of $^{63}NiCl_2$ (40 - 200 µg Ni/kg) radioactivity was found in the kidneys, lungs, CNS, skin, cartilage and connective tissue of mice (Oskarsson and Tjalve, 1979). After 3 weeks, radioactivity still occurred in kidney and even in lung (see Section G 5).

With rats the highest Ni concentrations appear in kidney and urine after i.p. injection of $NiCl_2$ (Sarkar, 1984). In contrast, in the mouse after i.p. injection of 6 mg ^{63}Ni/kg (as $^{63}NiCl_2$) most was excreted via the faeces within a 12 hour period (Wase et al, 1954). The authors also found a relatively high retention of Ni in the lung after 72 hours.

Insoluble nickel compounds are very slowly translocated from the injection site. The loss of radioactivity from radiolabelled Ni_3S_2 injected i.m. occurred gradually within months from the injection site with increasing biological half-lives for the less soluble residues (Kasprzak, 1974). The particles were demonstrated to persist mostly extracellularly at the injection site and became surrounded by neoplastic tissues (rhabdomyosarcomas). Under similar experimental conditions small quantities of radioactivity could also be detected in liver, spleen and lymph nodes (Sunderman et al, 1976; Oskarsson and Tjalve, 1979).

3. Excretion

The main excretion route of absorbed nickel is via the kidneys (Smith and Hackley, 1968; Onkelinx et al, 1973; Clary, 1975; Parker and Sunderman, 1974). Urine levels closely reflect serum levels. Unabsorbed ingested nickel is excreted in the faeces; under normal environmental conditions this amounts to approximately 250 µg/day in man (Horak and Sunderman, 1973).

In several non-occupationally exposed human populations the mean urinary nickel excretion was 4 µg with a range of < 2.5 - 30 µg/person/day (Nomoto and Sunderman, 1970; McNeely et al, 1972; Zober et al, 1984).

Other routes of excretion are sweat, with mean concentrations ranging from 50 - 130 µg/l and single values from 7 - 270 µg/l (Hohnadel et al, 1973), and hair with a mean of 0.22 µg/g (Nechay and Sunderman, 1973). The physiological relevance of these excretion routes in the regulation of nickel homeostasis is unknown but may be considerable with sweat; they may represent confounding factors in certain investigations.

Biliary excretion was small in rats (< 0.5% after s.c. injection of 1.7 - 250 µM $NiCl_2$/kg), and the concentrations in bile were only about 10% of the corresponding Ni levels in plasma. Thus in rats bile excretion is quantitatively unimportant for elimination of exogenous nickel (Marzouk and Sunderman, 1985). In rabbits higher nickel levels were observed in bile (van Soestbergen and Sunderman, 1972); the high (about 70%) faecal excretion in mice after i.p. injection (Wase et al, 1954) also indicates the significance of biliary transportation in this species at the high dose employed (102 µg ^{63}Ni per mouse).

After a single i.v. injection in rats (17 µg $^{63}NiCl_2$ per animal) and rabbits (8 - 16 µg/animal) urinary excretion followed a 2-compartment model with a rapid first order clearance phase from plasma during day 1 - 2 accounting for about 70% of the label and a much slower rate from day 3 - day 7 (Onkelinx et al, 1973). This may reflect some retention in several tissues with a less mobile pool (see Section G.5).

Nickel excretion in urine was increased with raised dietary levels (Menne and Thorboe, 1976) and decreased in patients placed on low nickel diet for treatment of their chronic dermatitis and history of nickel allergy (Kaaber et al, 1978; Veien et al, 1985). Urinary nickel excretion was also increased following oral administration of tetraethylthiuram disulphide to patients with dermatitis (Menne et al, 1980) and human volunteers (Menne et al, 1978; Christensen and

Lagesson, 1981). In all these experiments the excretion rate closely reflected the intestinal absorption (Section G.2.2).

4. Transplacental Transfer

In animals nickel normally occurs in foetal tissues and body fluids in similar concentrations as in maternal tissues and fluids (Schroeder et al, 1962; McNeely et al, 1971), but apparently does not enter the rodent embryo before day 5. In later stages of pregnancy the concentration may reach even higher levels than in the dam (Olsen and Sonsen, 1979; Jacobsen et al, 1978; Leonard and Jacquet, 1983). Single intraperitoneal injections into pregnant mice of 3.5 mg $NiCl_2$/kg produced the maximal foetal concentration after 8 and 24 hours (about 1.5 µg/g) and a rapid decrease between 24 and 48 hours. The maximum levels in placenta were 4 µg/g after 2 hours (Lu et al, 1981).

Nickel also has been found in human foetal tissues at levels similar to those in maternal blood (Schroeder et al, 1962).

5. Sites of Retention/Potential of Accumulation

After inhalation or parenteral exposure insoluble nickel compounds and metallic nickel are retained at their site of deposition and only gradually release nickel ions into surrounding tissue and the blood, depending on solubility and particle size. Respired particles are phagocytosed by the respiratory epithelium or engulfed by macrophages and may stay there for a long time unless they are cleared by the mucociliary apparatus (Section G.2.3). If total surface and solubility allow, the rate of nickel leached from a deposit may also cause increases in plasma and urinary levels and some tissues. The half-life of nickel in serum after a single oral administration is around 11 h (Christensen and Lagesson, 1981). If the nickel levels in the circulation are considerably increased - by whatever exposure route - kidney and lungs may concentrate the material and also other organs may exhibit increased nickel levels. Mathur et al (1978) found that repeated oral exposures could have cumulative effects, particularly on kidneys and heart (see below).

Sites for potential nickel deposition after oral or parenteral administration of soluble nickel salts are mainly kidney, lung, liver, adrenals and cartilage (Oskarsson and Tjalve, 1979; Nation et al, 1985). After multiple intraperitoneal injections of soluble nickel salts Kasprzak et al (1983) observed considerable accumulation in pancreas but not in kidney and heart. This finding may indicate a link between nickel and zinc/insulin metabolism and relate to nickel-induced serum glucose increases (Clary, 1975; Sunderman, 1976). An increase of nickel content was also seen in guinea pig pituitary after 5 daily s.c. injections of 1 mg/kg (Clary, 1975) and also after single and repeated injections of $^{63}NiCl_2$ into rabbits (Parker and Sunderman, 1974).

Little nickel is deposited in the nervous system. The neural toxicity of divalent nickel compounds is low; $Ni(CO)_4$, however, which easily enters the CNS, is neurotoxic.

1000 ppm Ni (as sulphate) in the diet of rats for 15 days led to increased nickel concentrations in kidney, testis, liver, spleen and myocardium (Mathur et al, 1977 and 1978). A similar effect in the rat kidney was found after dietary administration of 10 and 20 mg Ni/kg (as $NiCl_2$) for 14 days; liver and testis showed no increase of nickel content (Nation et al, 1985). In other studies with weanling rats (Whanger et al, 1973) and lambs (Spears et al, 1978) at varying diet levels up to 1000 ppm, Ni accumulation was found in kidney and at the higher levels also in lung, liver, heart and testis. 5 ppm Ni in the drinking water of mice for life-time did not increase the Ni levels in kidney, liver, lung, spleen and heart and no measurable uptake of Ni was found (Schroeder et al, 1974). Similarly, 2.5 ppm Ni in the drinking water of guinea pigs did not result in elevated organ concentrations (Schreiner, 1976).

Studies in calves receiving 0, 62.5, 250 and 1000 ppm Ni as nickel carbonate in the diet for 8 weeks showed a dose-dependent increase of urinary nickel levels; total nickel excretion in urine was 0.47 mg in the control and 7.16, 24.75 and 45.31 in the other groups. At 1000 ppm reduced feed intake and weight gain and an increase of total nickel in serum, various organs and tissues was observed; the highest values

were found in serum and kidney (approximately 38 and 23 µg/g dry matter) and the lowest in liver, heart and brain (0.5 - 1.3 µg/g). Significant increases were also found in pancreas, testis and bone. At 62.5 and 250 ppm these effects were smaller and statistically not significant (O'Dell et al, 1971).

It is concluded that soluble nickel compounds when administered orally or parenterally in dose levels at which urinary excretion is overloaded, deposit nickel in extrarenal tissues. Upon termination of exposure the excess nickel is rapidly removed from the tissues and excreted. Thus, soluble nickel compounds do not accumulate at lower dose levels or with short exposures.

In contrast, insoluble nickel compounds are retained at their site of deposition for long periods of time.

Chelating agents like diethyldithiocarbamate and penicillamine may be used to remove nickel from binding sites in tissues. It is doubtful whether such medication would be effective for the removal of solid particles.

6. Bioavailability at the Cellular Level

The main factors determining the genotoxicity, cytotoxicity and cellular transforming activity of all nickel compounds are the mechanism of entrance into the cells and the bioavailability at the cellular level (Hansen and Stern, 1983; Costa and Mollenhauer, 1980), which is generally *inversely* correlated with the solubility of the materials in body fluids (Hansen and Stern, 1983).

Soluble Ni compounds (in aqueous media and body fluids) enter the cells only to a limited extent. Under in vivo conditions the contact time of soluble nickel with cells is short (Costa and Heck, 1984). Nickel is rapidly cleared from the cells and the body and hence is unlikely to cause genotoxic and transforming effects. In in vitro experiments, however, the extracellular concentrations can be controlled and soluble nickel compounds may achieve significant intracellular concentrations and thus may cause strand breaks in

mammalian cell cultures under certain conditions (Robinson and Costa, 1982). Serum factors such as the presence of metal binding amino acids (cysteine, histidine) in the culture media may account for diverging results from various reports of *in vitro* assays (Abbracchio *et al*, 1982a; Cantoni *et al*, 1984): It has been shown that L-histidine and human serum albumin may inhibit the cellular uptake of Ni^{2+} at physiological concentrations or sequester Ni^{2+} from cells preloaded with this ion, while diethyldithiocarbamate attracts Ni^{2+} into the cells (Nieboer *et al*, 1983). This is opposite to the *in vivo* effects of diethyldithiocarbamate which removes nickel from the body.

Insoluble Ni compounds, however, may enter cells by an active phagocytic mechanism (Costa and Mollenhauer, 1980a-c). Having entered the cell, the particles form an intracellular depot, from which nickel ions may be gradually and continuously released and achieve considerable intracellular bioavailability. The Ni^{2+} ions may be distributed throughout various cellular compartments (Abbracchio *et al*, 1982b) and potentially cause cytotoxic, genotoxic and carcinogenic effects. Lysosomes may be activated by the cell in efforts to degrade the particles (Abbracchio *et al*, 1982b); in this process endonucleases may be released from the lysosomes and affect the DNA (Allison, 1969; Zajak and Ts'O, 1980).

The active phagocytic uptake of nickel compounds appears to be related to the surface charge of the material (Costa, 1983). Thus surface charge would indirectly determine intracellular bioavailability and, finally transforming potency (Costa and Mollenhauer, 1980a-c; Costa and Heck, 1982; Costa, 1982).

Some examples may illustrate these correlations and underline the importance of phagocytosis :

- Crystalline nickel sulphide (alpha-NiS), which is phagocytosed and may transform cells has a negatively charged surface. In contrast, amorphous NiS, which is more soluble and not phagocytosed by cells (Costa and Mollenhauer, 1980c) and is non-transforming, carries a slightly positive charge at physiological pH (Abbracchio *et al*, 1982c). Under strongly

reducing conditions amorphous NiS particles may apparently be altered in charge which facilitates entry and transformation of Syrian hamster embryo cells (Heck and Costa, 1982; Abbracchio et al, 1982c). Thus, charge seems to be an important factor.

- Costa et al (1981) demonstrated with a series of nickel materials, that transforming potency correlated with phagocytic activity. In their experiments the most potent inducers of in vitro transformation were alpha-Ni_3S_2, alpha-Ni_3Se_2 and crystalline NiS.

- Nickel oxide (NiO) exists in several forms, from green to black depending on the temperature of formation (Kuehn et al, 1982): "one material is actively phagocytosed and a carcinogen" (Costa and Heck, 1984), while another form is not phagocytosed and exhibits little transforming activity (Hansen and Stern, 1983). Sunderman (1987a) has reported that the ability of these oxides to induce increased erythrocytosis after intrarenal injection varies greatly, and he believes this to be a good indicator of carcinogenicity.

- BHK (baby hamster kidney) cells, which are only able to phagocytose particles smaller than 5 µm (Costa et al, 1981) were neither transformed by nickel powder nor affected by cellular toxicity, when < 50% of the particles were larger than 5 µm (Hansen and Stern, 1983).

In addition to the higher absolute amount of nickel uptake via phagocytosis of particles, more recent studies (Costa and Mollenhauer, 1980; Evans et al, 1982; Sen and Costa, 1986) provided increasing evidence that the rate and pathway of nickel uptake into the cell influences its intracellular distribution pattern to such an extent that interaction with certain nuclear sites (the heterochromatic long arm of the X-chromosome) has been observed whereas interaction with cytoplasmic ligands was limited. $NiCl_2$ did not exert this effect unless it was offered to the cells as a $NiCl_2$-albumin complex encapsulated into liposomes (Sen and Costa, 1986), under which

circumstances it now could enter the cell via endocytosis (modelling the delivery of particles via phagocytosis).

7. Intracellular Sites of Nickel Binding

Many nickel compounds are markedly more soluble in cellular cytosol than in serum (Costa and Heck, 1984). The intracellular binding sites attract nickel ions released from intracellular deposits of insoluble material : in Chinese hamster ovary (CHO) cells, for instance, intracellular particles became smaller and smaller, although the radioactivity within the cell was not lost at the same rate (Abbracchio et al, 1982b). It has also been suggested that intracellular Ni_3S_2 particles may pick up sulphur from the host cell and be converted to NiS (Dewally and Hildebrand, 1980)

One of the binding sites of Ni^{2+} which is probably most closely associated with the issue of carcinogenicity is DNA (see Section I).

8. Interaction With Other Metals

An interesting aspect of nickel toxicology is the interaction of nickel with other metals (e.g. iron or magnesium) in the competition for intracellular and extracellular binding sites. The antagonistic effect of magnesium upon the nickel-produced inhibition of intracellular communication has been observed (Miki et al, 1987), and recently it has been shown that iron (ferric sulphate) may inhibit the formation of local sarcomas following intramuscular injection of nickel subsulphide in Fisher rats (Kasprzak, 1988). CuO, however, seems to increase NiO toxicity in the i.m. injection studies (Sunderman, 1987).

Addition of manganese dust to parenterally administered Ni_3S_2 dust, which also decreased carcinogenicity at the injection site, resulted in a diminished ^{63}Ni content in ultrafiltered homogenates from muscle tissue. The gross excretion of ^{63}Ni, however, was not affected (Sunderman et al, 1976). These facts may indicate a competition of particles for cellular uptake or a shift in distribution within the cell.

Furthermore, the transforming activity of nickel ions may also be related to substitution of magnesium ions in DNA. Magnesium ions were found to be important for the chromatin condensation/decondensation cycle (Aaronson and Woo, 1981).

The intestinal absorption of nickel may be enhanced by iron deficiency (Forth and Rummel, 1971; Becker et al, 1980).

9. Summary

1. A fundamental difference exists between soluble and insoluble nickel compounds in their kinetic pattern and extracellular and intracellular bioavailability.

2. Soluble nickel materials are rapidly cleared from the body and enter cells only to a limited degree. They become bioavailable only at higher dose levels and with continuous exposure.

3. Insoluble particles have a much higher tendency to be retained at their site of deposition. They enter cells via active phagocytosis and achieve higher and long-lasting bioavailability. Particle size and surface charge are important factors for the induction of phagocytosis.

4. Having entered a cell, insoluble nickel particles form a depot within the cell, from which they may gradually and continuously release Ni^{2+} ions to extra- and intracellular binding sites. Additionally, the deposited particles may derange the cytoskeleton and activate lysosomes, thereby contributing to the transforming potential.

H. CARCINOGENICITY STUDIES IN ANIMALS

Although a prodigious number of experimental animal studies have been conducted on the carcinogenicity of nickel and nickel compounds, a majority of these have involved parenteral administration by the intra-muscular and other routes (Sunderman, 1981; IARC, 1976). Frequently tumours, mainly rhabdomyosarcomas, have been induced at the injection site with insoluble nickel compounds but not with soluble nickel salts. While these studies are of academic interest, are relatively cheap to perform and allow comparisons to be drawn between different nickel compounds, they have little relevance in assessment of carcinogenic risk to man. For the latter adequately designed and conducted experiments employing a route of exposure which is relevant to exposure in man are required (ECETOC, 1986). In the case of nickel and nickel compounds inhalation studies are considered to be particularly useful in this respect. Animal carcinogenicity studies with nickel compounds are briefly summarised in Table 4.

Those studies which are considered to be most relevant to assessment of carcinogenic hazard in man are also reviewed in more detail by compound below.

1. Nickel Metal

Heuper (1958) exposed guinea pigs, rats and mice by inhalation to powdered metallic nickel, >99% purity, at an average concentration of 15mg/m^3 for 6 hours per day for 4 to 5 days per week for up to 21 months. A majority of the nickel particles had a diameter of 4 μm or less. In total 42 guinea pigs, 160 rats and 20 mice were used and all died during exposure. There were no concurrent controls. Most of the guinea pigs had died by 15 months with severe pulmonary lesions, including proliferative epithelial changes resembling carcinoma. A frank anaplastic carcinoma was seen in one animal and a metastatic deposit considered to have arisen from an occult primary lung tumour in a second. The rats frequently showed pneumonia, pleurisy and bronchiectasis and chronic inflammation of the para-nasal sinuses. In 15 cases there were adenomatoid changes in the alveoli and terminal bronchioles similar to those seen in the guinea pigs. The author attributed these hyperplastic changes to the nickel dust. The only

changes seen in the lungs of mice were hyperaemia and haemorrhage. Heuper and Payne (1962) exposed rats (60 males and 60 females) and hamsters (100 males) by inhalation to powdered nickel and limestone together with sulphur dioxide. The majority of the nickel particles were 1 to 3 μm in diameter. The experiment ran for two years. Chronic inflammatory changes were produced in the lungs of the rats but not in the hamsters. No lung tumours were found in either species. Precise exposures were not given but between 50 and 65 g of the nickel:limestone mixture (1:1 for rats and 3:1 for hamsters) was discharged into the exposure chamber daily with compressed air containing up to 35 ppm sulphur dioxide.

Kim (1969) exposed a group of male Wistar rats, 77 in total, to metallic nickel dust, equivalent to 3.1 mg/m^3 for 6 h/d, 5 d/w, followed by exposure to air alone. The experiment ran for 21 months. Ninety-eight per cent of the dust particles were less than 2 μm in diameter. Sub-groups were exposed to the dust for varying periods followed by periods of recovery. One rat exposed to 7 months dust - 2 months fresh air - 6 months dust had a tumour of carcinoid pattern in the lung. Three other rats exposed to the same regime had severe bronchiectasis and pneumonia. In another sub-group given 7 months dust - 2 months fresh air - 6 months dust - 3 months fresh air, two rats had tumours in the lung. One of these was a lymphosarcoma and was apparently part of a more generalised condition as similar lesions were present in the mesenteric lymph node. The other was said to have a carcinoid pattern. A similar tumour to the latter was found in the lung of one rat in the unexposed control group.

None of the above studies mention nasal tumours but in some cases it is not clear how thoroughly the nasal cavity was examined, if at all. Pott et al (1987) gave nickel powder by repeated weekly intra-tracheal instillation to two groups of female Wistar rats. One group received a total of 6 mg Ni (from 20 installations) and the other 9 mg Ni (from 10 instillations). The rats were then maintained for approximately two and a half years. Approximately 25% of both groups developed lung tumours, mainly squamous cell carcinomas. The earliest tumour was detected 98 weeks after the first intra-tracheal instillation while the average time to tumour detection was 120 weeks.

2. Nickel Oxide (NiO)

Wehner and his co-workers have investigated the effect of life-time exposure of 102 male Syrian golden hamsters, seven h/d for five d/w, to a respirable aerosol of black nickel oxide. The mean respirable aerosol concentration was 53.2 mg/m^3 and the median diameter 0.3 μm. Half the animals were also exposed to cigarette smoke, and there were two control groups each of 51 animals, one exposed to smoke alone and the other to 'sham' smoke and dust exposure. The nickel oxide exposed animals eventually developed massive pneumoconiosis although this did not affect survival and did not lead to an increase in tumours of the respiratory tract. In contrast in contemporary experiments in the same laboratory with crysotile asbestos hamsters developed pulmonary tumours (Wehner et al, 1975; Wehner et al, 1979; Wehner et al, 1984).

Horie et al (1985) exposed male Wistar rats by inhalation to NiO, median aerodynamic diameter 1.2 μm, for one month and examined them at intervals up to 20 months later. One rat sacrificed after 20 months had a papillary adenocarcinoma in the lung, however the design of this experiment was inadequate to assess carcinogenicity.

A long term inhalation study with nickel oxide in rats produced toxic lung effects with "severe proteinosis observed in every animal". Survival times were too short to evaluate carcinogenicity (Glaser et al, 1986). Pott et al (1987) gave green nickel oxide by repeated weekly intra-tracheal installation to two groups of female Wistar rats. One group received a total of 50 mg and the other 150 mg Ni over 10 installations. The rats were then maintained for approximately two and a half years. Lung tumours, predominantly squamous cell carcinomas, were reported in 10 of 37 rats in the low dose group and 12 of 38 rats in the high dose group. The earliest tumour was detected after 80 weeks in the low dose and 102 weeks in the high dose group. The average time to tumour detection was 115-116 weeks. No tumours were reported in a control group given saline.

3. Nickel Hydroxycarbonates ($Ni(OH)_2/NiCO_3$)

There are no specific animal studies on these compounds suitable for assessment of carcinogenic hazard.

4. Nickel Sulphate ($NiSO_4$)

In a poorly reported study groups of 24 rats were exposed to nickel sulphate dust at levels of 5 or 10mg/m^3 for four h/d for nine months. At the high dose degenerative changes occurred in bronchial and alveolar epithelium and there was intra-alveolar septal thickening and renal tubular necrosis. The only effects at the low dose were minor bronchial changes (Kosova, 1979).

Groups of 25 Wistar rats per sex were given nickel sulphate in the diet at levels of 0, 100, 1000 and 2500 ppm Ni for up to 24 months. The high dose apparently exceeded a maximum tolerated dose. No significant lesions were reported but survival was poor and pathological data was not given for animals dying during the study (Ambrose et al, 1976).

Both the above studies are judged to be inadequate to assess carcinogenicity.

5. Nickel Chloride ($NiCl_2$)

There are no specific animal studies on these compounds suitable for assessment of carcinogenic hazard.

6. Nickel Subsulphide (Ni_3S_2)

Ottolenghi et al (1974) exposed 226 male and female Fisher 344 rats to Ni_3S_2 dust for 6 h/d, five d/w for 78 weeks. Survivors were observed for an additional 30 weeks without exposure.

The concentration of Ni_3S_2 in the exposure chamber averaged 0.97 mg/m^3. Seventy per cent of the particles were less than 1 µm in diameter and 25% were between 1 and 1.5 µm. A group of 241 rats were exposed to filtered room air and served as controls. Less than 5% of the treated rats survived to the end of the study compared with 31% of the controls. The Ni_3S_2 exposed rats showed an increased incidence of inflammatory and hyperplastic lesions in the lung and an increased incidence of benign and malignant lung tumours, including squamous cell and adenocarcinomas. No effects were described in the nasal cavity but this organ was not included in the list of tissues examined histologically.

Pott et al (1987) gave nickel subsulphide via 15 weekly intra-tracheal instillations to three groups of female Wistar rats so that they received total doses 0.94, 1.88 and 3.75 mg Ni respectively. The rats were then maintained for approximately two and a half years. The incidence of lung tumours, including adenocarcinomas, squamous cell carcinomas and mixed types, was 15%, 29% and 30%, respectively in the three groups. The earliest tumour was detected after 88 weeks and the average time to tumour was 129, 126 and 125 weeks for the three groups respectively.

7. Nickel Sulphide (NiS), Nickel (III) Oxide (Ni_2O_3), Nickel Oxide (NiO_2)

There are no specific animal studies on these compounds suitable for assessment of carcinogenic hazard.

8. Nickel Carbonyl ($Ni(CO)_4$)

Sunderman et al (1957, 1959) exposed groups of 64 and 32 male Wistar rats for 30 minutes three times weekly for one year to nickel carbonyl (30 and 60 mg/m^3). A carcinoma was detected in the lungs of one rat from each exposure group which survived for two years. Sunderman and Donnelly (1965) exposed 64 male Wistar rats to 4 ppm (30 mg/m^3) for 30 minutes 3 times weekly for their lifetime. One rat sacrificed after 26 months had an adenocarcinoma of the lung which had metastasised. Two further lung tumours were reported, one each in similar sized groups of rats, exposed to the same dose of nickel carbonyl on a single

occasion. The affected rats died at 24 and 26 months after this single exposure.

The above authors claimed to have induced lung cancer by this means however, the numbers are too few to reach a definitive conclusion.

9. Summary

1. Sarcomas have been produced at the injection site following parenteral administration of *metallic nickel* in several experiments in rats. Carcinomas of the lung occurred after repeated intra-tracheal instillation of *metallic nickel powder* in one rat experiment. Long-term inhalation experiments with *metallic nickel dust* in rats, mice, hamsters and guinea pigs did not demonstrate a significant increase in respiratory tract tumours.

2. Sarcomas have been produced at the site of injection following intra-muscular and intra-peritoneal administration and carcinomas of the lung followed repeated intra-tracheal instillation of *green nickel oxide*. Inhalation experiments with *black nickel oxide* in rats and hamsters did not demonstrate an increase in respiratory tract tumours. Similar experiments in rats were inadequate to assess carcinogenicity.

3. *Nickel hydroxide* produced rhabdomyosarcomas at the injection site following intra-muscular administration.

4. No tumours have been induced with *nickel sulphate* in rats when given by intra-muscular, dietary or inhalation routes.

5. *Nickel subsulphide* has been repeatedly shown to induce sarcomas at the site of injection when given parenterally by a variety of routes in several species. It has also been shown to be carcinogenic in rats following long-term inhalation producing a combination of benign and malignant lung tumours.

6. *Nickel carbonyl* produced sarcomas at various sites following intra-venous injection. There is inadequate evidence that it may induce lung cancers after inhalation.

I. MUTAGENICITY STUDIES

1. Relevance

Many carcinogens are also mutagens and the somatic cell mutation theory of cancer hypothesises that the initiating event in the formation of cancer is mutation in somatic (non germinal) cell or cells. It is therefore important that the available genotoxicity data of nickel and nickel salts be critically reviewed. Regrettably the data set is incomplete and for many nickel salts no genotoxicity data are available. Where data are available the test result is sometimes inconclusive.

Because there appears to be a relationship between DNA adducts and carcinogenesis, DNA adducts may be useful in measuring the impact of exposure to environmental carcinogens. It is generally agreed that DNA is the target molecule in carcinogenesis and that for initiators the persistence of adducts resulting from the covalent binding of chemical compounds or their metabolites correlates better with carcinogenesis than the transient formation of adducts. The evidence for DNA adduct formation by nickel salts will be addressed.

Data on the examination of human lymphocytes from exposed workers for chromosome aberrations and other effects will be reviewed; such parameters can be used as a measure of exposure (Evans, 1985). A positive response does not necessarily mean that an exposed individual will contract cancer or that the chemical in question is a human germ cell mutagen.

1.1. Nickel Metal.

No relevant genotoxicity data are available save for an old reference (Paton and Allison, 1972) indicating chromosome aberrations induced in human lymphocytes.

1.2. Nickel Oxides (NiO)

No data were available for evaluation of gene mutation. Negative responses were obtained in bacterial tests for DNA damage (Kanematsu et al, 1980) and in mammalian cells measuring chromosome aberrations or sister chromatid exchange (SCE), (Paton and Alison, 1972). In tests for cell transformation negative or marginally weak positive responses were obtained (Costa et al, 1981; Hansen and Stern, 1983). This latter assay is indicative of possible carcinogenic potential and not necessarily mutagenic potential.

1.2.1. Human studies

Waksvig and Boysen (1982) analysed blood from exposed workers for increases in chromosome aberrations and found increases in gap damage, but the increases did not appear to be related to exposure levels. The precise nature of the form of nickel oxide to which they were exposed is uncertain. The mean age of the workers was 44 years so the possibility of this observation being age related cannot be ruled out. As stated above the value of human studies on lymphocytes from exposed workers is that they can provide an indication of exposure to chromosome damaging agents. It is concluded there are insufficient data to enable the genotoxicity of nickel oxide to be fully evaluated.

1.3. Nickel Hydroxide

No genotoxicity data are available.

1.4. Nickel Carbonate

No relevant genotoxicity data are available. There is some indication of interaction with DNA or DNA:protein following intraperitoneal injection into rats (Ciccarelli and Wetterhahn, 1982).

1.5. Nickel Subsulphide

There is some evidence of limited repair replication and of a very weak response in SCE in human lymphocytes (Saxholm et al, 1981; Robison et al, 1983). Cell transforming ability has been demonstrated by the same authors and by Costa et al (1981) when subsulphide was tested. These and other data indicate that the crystalline subsulphide form is actively phagocytosed (Abbracchio et al, 1982).

1.5.1. Human studies

No data available for evaluation. (See Section I.1.2.1. for relevant comment on the results of Waksvig and Boysen [1982]).

There are insufficient data to make an evaluation as to the mutagenic potential of Nickel subsulphide.

1.6. Nickel Sulphide

No gene mutation data are available. Chromosome damage has been demonstrated but the response varies with the form of nickel sulphide which was tested. The crystalline form was actively phagocytosed and caused chromosome aberrations in vitro in two mammalian cell lines, the damage being associated with heterochromatin (Sen et al, 1987). Some indication of interaction with DNA has been shown in SCE assays using Chinese Hamster Ovary (CHO) cells (Costa et al, 1982). Crystalline NiS also caused DNA strand breakage. Positive responses were also obtained in cell transformation and DNA repair assays when crystalline NiS was used (Sen and Costa, 1986). When the amorphous form was tested negative results were obtained for DNA single strand breaks, DNA repair synthesis and cell transformation (Costa et al, 1982).

1.6.1. Human Studies

No data available for evaluation. (See Section I.1.2.1. for relevant comment on the results of Waksvig and Boysen [1982]).

It is concluded that some evidence of mutagenic potential has been demonstrated in vitro but no convincing evidence was seen in vivo, and the human data are not sound.

1.7. Nickel Sulphate

No gene mutation data are available except for a negative response in Syrian Hamster Embryo cells (Rivedal and Sanner, 1980) and an equivocal response in Yeast cells for gene conversion (Singh, 1984).

Nickel sulphate appears to be weakly clastogenic causing chromosome aberrations and SCE in in vitro studies (Larramendy et al, 1981). In vivo, no unequivocal data are available for mammalian assays but negative responses have been claimed by Mathur et al (1978) although their data were not presented. In Drosophila a positive response was obtained in the Sex Linked Recessive Lethal assay (Rodriguez-Arnaiz and Ramos, 1986). This assay measures predominantly chromosome damage.

Positive responses have been obtained in cell transformation assays (Rivedal and Sanner, 1981; DiPaola and Casto, 1979).

1.7.1. Human studies

No data available for evaluation. (See Section I.1.2.1. for relevant comment on the results of Waksvig and Boysen [1982]).

It is concluded that nickel sulphate may be a somatic cell clastogen but data from rodent studies such as the micronucleus

assay or metaphase analysis in bone marrow or DNA repair in the liver should be available before definite conclusions can be reached.

1.8. Nickel chloride

$NiCl_2$ is not mutagenic in bacterial assays measuring gene mutation and DNA damage (Nishioka, 1975; Green et al, 1976; Kanematsu et al, 1980; Biggart and Costa, 1986), neither is it a mammalian cell gene mutagen in an assay using Chinese hamster cells (Miyaki et al, 1979). Using mouse lymphoma cells evidence for a positive response in a gene mutation assay was claimed but the possibility that the observed response was in fact due to chromosome damage, which has been frequently associated with this cell line, cannot be excluded (Amacher and Paillet, 1980).

$NiCl_2$ is clastogenic in vitro in a variety of cell lines causing both structural aberrations and also sister chromatid exchange (Newman et al, 1982; Sen et al, 1987). It appears that damage is frequently in the heterochromatic regions of the chromosome. Not all investigators have found $NiCl_2$ to be clastogenic to mammalian cells (Umeda and Nishimura, 1979; Sen and Costa 1986).

In in vivo studies, negative responses have been obtained in bone marrow (Micronucleus assay) and in germinal cell studies, even when toxic concentrations have been administered using the intra peritoneal route to provide optimum distribution of compound (Deknudt and Leonard, 1982).

No evidence for interaction with DNA has been demonstrated in bacterial cells although indirect evidence of this has been claimed by Sirover and Loeb (1976). With mammalian cells some evidence of interaction has been obtained, mainly demonstrated as DNA strand breakage but there is also weak evidence of repair replication (Robison et al, 1983). Lack of evidence of cell transforming ability has been claimed by McGregor et al (1983), but their data have not been available for review.

1.8.1 Human Studies

No data available for evaluation.

Data support the contention that $NiCl_2$ possesses clastogenic potential which is not expressed *in vivo*. The evidence suggests that, *in vitro*, $NiCl_2$ interacts with histones or other proteins on the chromosome, such proteins being more prevalent in heterochromatin.

1.9. Nickel Nitrate

No mutagenic response was detected using embryo cultures obtained from pregnant mice mated to male animals exposed i.p. to 40 and 56 mg/kg $NiNO_3$ as measured by the ability of the chemical to interfere with cell division (Jacquet and Mayence, 1982). Conventional Dominant Lethal or Micronucleus assays were negative (Deknudt and Leonard, 1982).

1.10. Nickel Carbonyl

1.10.1 Human Studies

No relevant experimental data were available for evaluation. No increase in chromosome damage was seen when lymphocytes from exposed workers were examined (Decheng *et al*, 1987).

2. DNA adducts

Very sensitive methods are necessary to detect DNA adducts. In addition to indirect methods, the following direct methods can be used: radiochromatographic, ^{32}P-post labelling, fluorescent spectrophotometry, and immunological techniques. Of these ^{32}P-post labelling is probably the most sensitive.

It has not been conclusively demonstrated that covalent binding occurs between nickel and DNA. The evidence to date appears to suggest that binding of nickel to DNA is indirect, probably occurring via DNA:

protein cross links to form stable protein:nickel:DNA complexes. For example, an in vivo study showed the DNA damage observed in rat kidney treated with nickel carbonate may be directly related to the observed formation of protein:nickel:DNA complexes and single strand damage (Ciccarelli and Wetterhahn, 1982). There are no published data reporting the presence of DNA adducts using the ^{32}P-post labelling technique.

The available in vivo and in vitro data support the contention that nickel-DNA adducts are not the initiating events in nickel carcinogenesis as they have not been detected.

3. Summary

Many nickel compounds are insoluble and therefore not readily bioavailable to man but when available there is a suggestion that nickel per se is responsible for any toxicity rather than the form of salt in which it is administered. Phagocytosis of nickel into cells is the most likely way in which insoluble forms of nickel are ingested. Their dissolution and clearance will vary with the form of nickel under consideration. Whilst interaction with DNA can occur, the most likely mechanism of interaction of nickel with cellular macromolecules is by forming a complex with chromosomal protein. Both the human studies relate to chromosome damage of workers exposed to insoluble compounds. Experimentally, no convincing evidence of mutagenic potential of insoluble nickel compounds has been forthcoming. Evidence of mutagenic potential of soluble nickel compounds has been demonstrated largely from in vitro studies and in vivo data, where available, were negative.

J. EPIDEMIOLOGICAL STUDIES

This section reviews the major epidemiological studies that have been carried out in the nickel-producing and using industries in recent years. The majority of the early studies reported on health effects in nickel refinery workers. In the last decade studies of other occupational groups that are exposed to nickel have been conducted. These groups include miners, smelter workers, foundry workers, stainless steel producers, high nickel alloy workers, metal platers, aero engine factory workers, welders and nickel cadmium battery manufacture employees.

Extensive reviews of these investigations have been published, and the reader who requires more detail than that given here is referred to the original studies, or to Sunderman (1983), the NIPERA Monograph 2/7/83 (1983) or Rigaut (1983). Later material not included in these reviews is published in the reports of the International Symposium on Nickel in the Human Environment at Lyon in 1983 (IARC, 1984) and the IUPAC Conference on Nickel Toxicology held in Paris in 1985 (Brown & Sunderman, 1985).

The available studies vary in design, sample size, nature and duration of actual exposure, availability and specificity of exposure information (occupational and environmental), completeness and length of follow-up of cohorts, length of latency and statistical methodology. Unfortunately, they suffer from lack of good information on the forms of nickel and their concentrations in workroom air. The studies are briefly summarised in Table 5 and are discussed in more detail below.

1. Nickel Production Workers

1.1. Sulphide Ores.

Mortality experience of workers at the Clydach, Wales Nickel Refinery has been studied on numerous occasions (Hill,1939; Morgan, 1958; Doll, 1958; Doll et al, 1970, 1977; Cuckle et al, 1980; Peto et al, 1984). This plant has until recently refined material derived solely from sulphide ores. From 1902-1949 this was a sulphide matte (see Appendix 3) comprising 20-35% of nickel subsulphide but in 1944 the feed started to change to nickel oxide sinter.

The copper content of the matte was originally about 35-45% but a change of feed material occurred in 1935 resulting in receipt of a concentrate containing 75% nickel and only 2% copper. Nickel subsulphide is found in the refinery as a process intermediate to the present day.

All the studies of this occupational group indicate a large excess mortality due to lung cancer in men employed prior to 1925. In the Peto (1984) study the Standardised Mortality Ratio (SMR) (see Appendix 3) in this group was 507 (Observed=137, Expected=27) but lower rates occured in men who began employment between 1925-1929 (SMR=200; O=11, E=5.5), and 1930-1945 (SMR=121; O=11, E=9.1). The 1930-45 rate was not statistically significant being based on only 192 men at risk and local rates were not used.

The reduction in mortality due to sinonasal cancer was even more pronounced. The employees hired prior to 1925 showed an SMR of 28,000 (O=56 E=0.2), but there have only been two cases in men employed after 1925. Morgan (1958) narrowed the investigation by showing that the men most at risk were those in very dusty operations. No specific measurements of atmospheric concentrations are available but nickel bearing dust was estimated to have been in the order of 10-100 mg/m^3 in the relevant areas and was associated with high concentrations of copper, arsenic and sulphur dioxide. The high mortality in this area was confirmed by Peto et al (1984), who described the group being principally at risk as men involved in matte roasting including calcining and furnace work, and also in copper sulphate manufacture and crushing. Further analysis of an enlarged cohort is now underway in order to determine what happened to the risk of lung cancer after 1930. (See Appendix 4)

A study of Clydach workers accidentally exposed to high concentrations of nickel carbonyl gas (Morgan, 1979) did not show any significant excess respiratory cancer mortality. Furthermore, the carbonyl section of the Clydach refinery operated essentially

unchanged until 1957, long after the dramatic decline in the respiratory cancer hazard. It is, therefore, unlikely that nickel carbonyl was responsible for the increased incidence noted in the early years.

Increased rates of sinonasal and pulmonary cancer in Canadian nickel workers were first reported by Sunderman (1959, 1969). The mortality experience has been reported in separate studies by Roberts et al (1984) and Shannon et al (1984).

The Roberts study included employees in INCO's Ontario Division who had worked there for six months or more during the period 1950-1976. This retrospective cohort study is one of the largest of its kind. It included 54,724 men. Vital status was determined by a method of record-linkage; 95% of the cohort were either traced or assumed to be alive at the time of the study. A wide variety of causes of death were studied with special attention being paid to lung, sinonasal, laryngeal and kidney cancers. The known high risk occupational subgroup, i.e. "sinter plant" workers, who were involved in high temperature roasting of sulphide matte to oxide in very dirty conditions, was investigated in detail. Warner (1984) reported a single total dust figure of 46.4 mg/m^3 on the operating floor and nickel concentrations in the dusty air leaving the building as high as 370 mg/m^3 with a mean in 1951 of 230 mg/m^3. Lung and sinonasal cancer were significantly increased at two production plants.

In the Copper Cliff Sinter plant, the lung and sinonasal cancer SMRs were 462 (O=42, E=9.1) and 2174 (O=2, E=0.09) respectively, whereas in the Port Colborne Leaching, Calcining and Sintering plants the SMRs were 298 (O=49, E=16.4) for lung and 9,412 (O=16, E=0.17) for sinonasal cancers. An increasing SMR with increasing exposure was also demonstrated, which suggested a causal relationship. No increase of either cancer appeared in the electrolytic tank house workers nor, when all other occupations were reviewed, was any statistically significant cancer increase apparent. A recent update (Roberts, 1988) while not materially altering the findings of the earlier paper has shown a

statisticaly significant elevation of lung cancer in miners (SMR=112). Similarly, a significant increase in prostatic cancer was observed but the authors considered it to be unlikely that this was related to nickel exposure. This large study reinforces the hypothesis that the majority of the respiratory cancer risk was limited to very specific refining processes, in this case sintering and calcining of Ni_3S_2 to NiO. It has not been yet possible to determine whether the risk in the "Leaching, Calcining and Sintering" Department at Port Colborne was confined to the sintering operation or extended to the other operations as well (See Appendix 2).

Shannon (1984) reported results of a study using a methodologically similar protocol but involving 11,594 Falconbridge mine/mill/smelter workers in Sudbury. The major excess in mortality was due to accidental and violent deaths. A statistically significant increase in cancer mortality from laryngeal cancer (SMR=261; O=5, E=1.9) was noted, but was confined to miners. Non significant excesses of cancer of the lung (SMR=123; O=46, E=38) and prostate (SMR=140; O=8, E=5.7) were also noted but not in high nickel exposure groups. The significant causes of death are not consistent between similar occupations in INCO and Falconbridge. The data is currently being updated (see Appendix 2).

The earlier mortality studies of this group by Sunderland (1959, 1969, 1971) and Chovil et al (1981) all indicated the high risk in the Sinter group.

Norway has received Canadian matte at Kristiansand since 1930. Until 1974 the matte was calcined by a process comparable to that used at Clydach and Port Colborne and then refined electrolytically. Early studies of Falconbridge Norwegian workers by Pedersen et al (1973, 1981) were updated by Magnus in 1982. The results showed significant excesses of sinonasal cancer in men involved in roasting and smelting (SMR=4,000; O=8, E=0.2), electrolysis (SMR=2,670; O=8, E=0.3) but also in other unspecified processes (SMR=2,000; O=2, E=0.1) and administration

(SMR=1,500; O=3, E=0.2) and smaller but still significant excesses of lung cancer in roasting and smelting workers (SMR=360; O=19, E=5.3) and electrolysis (SMR=550; O=40, E=7.3) with again excesses apparent in "other unspecified processes" (SMR=390; O=12, E=3.1) and administration (SMR=170; O=11, E=6.3). The results of these studies, therefore, differ materially from the Canadian studies in that an elevated mortality was noted for respiratory cancer in electrolysis, roasting and smelting workers in Norway but not in Canada.

Interestingly, the sinonasal cancer risk in Norway appears to have lessened for men entering the refinery after 1945, while the lung cancer rate continues to be elevated. Smoking histories were available for Norwegian workers. Kreyberg (1978) suggested that smoking was an important factor in lung cancer causation in Kristiansand refinery workers.

Tatarskaya (1967) from the USSR reported six cases of sinonasal cancer and three cases of pulmonary cancer at an electrolytic refinery processing sulphide ores. The SMR was not calculated.

Mortality at a hydrometallurgical nickel refinery located in Saskatchewan Canada was investigated by Egedahl et al (1984), where exposure was to partially oxidised sulphur compounds of nickel (including Ni_3S_2 and amorphous NiS), as well as nickel sulphate and metallic nickel powder. Exposure levels ranged from 19.7 $mgNi/m^3$ in the concentrating plant and 8.56 $mgNi/m^3$ in the metals fabrication building. Nevertheless, there were no cases of sinonasal or pulmonary cancer in the nickel exposed group and the SMR for the whole study population was 83.

1.2. Laterite Ores.

In the U.S.A. a study of the Hanna Nickel Smelting Company's employees in Oregon by Cooper and Wong (1981) involved 1,307 employees and 129 deaths and showed no increase in any occupational group that included exposure to nickel. This study was concerned with nickel silicate ore rather than sulphide and

exposure was to a complex of nickel and iron oxides. However, exposures were all less than 1.0 mg Ni/m^3 and this low exposure coupled with the small size of the study population limits the usefulness of the study.

There are no epidemiological studies of nickel refiners in mainland France but since the middle of the 19th century, nickel has been recovered from silicate oxide ores of New Caledonia. Lessard (1978) suggested the possibility of an increased risk of pulmonary cancer among nickel workers on the island. His paper contained many methodological faults and the population has been restudied using a different approach. Goldberg (1984, 1988) concluded that in a 10 year period there was no excess of either lung or sinonasal cancer in the nickel workers when compared with the island population on an age matched basis.

Saknyn et al (1973) reported an excess of pulmonary cancer at a cobalt/nickel refinery in Russia of 2.8- to 3.8-fold over local rates. Exposure was to nickel silicate ores and nickel matte as well as cobalt and arsenic. Neither the number of men at risk nor the number of cases was stated.

1.3. Other Production Processes

Norwegian studies by Pedersen et al (1973) also indicate an excess of pulmonary and sino-nasal but not laryngeal cancer in electrolysis workers, who had mixed exposures to soluble and insoluble nickel, copper and arsenic compounds (the Hybinette process). These findings are at variance with the INCO Canada experience. (See Appendix 2 and Section 1.1 above.) The reasons for this are still not clear but are probably related to the higher exposures to a variety of soluble and insoluble nickel/copper compounds that are associated with the Hybinette process.

New data (Easton, 1988) also suggests that there was an increased risk in the hydrometalurgy area at Clydach in the period prior to 1935. In this area Bessemer matte and other process residues were

used to produce nickel sulphate for market and a concentrate containing a variety of nickel, copper and cobalt compounds which were sent elsewhere for further processing.

Fifteen cases of lung cancer and two of sinonasal cancer were reported from a group of 229 men manufacturing nickel powder in Germany (Raithel et al, 1984). They also reported 5 cases of respiratory cancer in a group of 11 men employed in an electrolysis plant where nickel sulphate and nickel metal were manufactured but the paper does not make clear to what other materials the men may have been exposed in this work or any other.

Cuckle et al (1980) showed a small excess of lung cancer (O=13 E=10) in a group of 297 Clydach workers exposed to soluble nickel and cobalt salts.

2. Nickel-Using Industries.

Enterline (1982) studied a group of 1,855 nickel alloy production workers at a West Virginia plant; there was also a small refinery which involved the calcining of nickel subsulphide. A statistically significant increase in sinonasal cancer was found in the 266 refinery workers at risk (SMR =2443; O=2, E=0.08), but no significant increase in lung cancer. All of these men had been hired prior to 1947 when the calcining operation ceased. There was no elevated risk of disease in non-refinery workers or in workers hired after 1946. The refinery workers were defined as possibly having been exposed to the dust and fumes arising from the oxidation of nickel subsulphide in calciners. There was no excess pulmonary cancer and no sinonasal cancer in the nickel alloy workers.

Redmond (1984) made a follow-up of 28,261 workers at 12 plants in the US involved in the production of high nickel alloys during the late 1950's and 1960's, until December 31, 1977. Of the 4,109 deaths, there was a significant increase in lung cancer only in maintenance workers (SMR=120; O=242, E=201.74). This occupational category was a large heterogenous group with unclear exposure to nickel, so the

possibility of a causal relationship between nickel and this increase in lung cancer is dubious.

Cox and Doll (1981) studied the mortality of men employed at an alloy manufacturing plant at Hereford, England. The cohort consisted of 1,925 men traced to April 1, 1978, with a follow-up of 98.9%. Exposure measurements that were available indicated that since 1975 most of the men were likely to have been exposed to average concentrations of nickel between 0.5 and 0.9 mg Ni/m^3. No significant excesses were found when compared with national or local mortality rates. An unpublished up-date of this study extends the follow-up by 5 years and almost doubles the number of observed deaths. The preliminary results are similar to those of the original paper with a non-significant deficit of lung cancer cases (SMR=87).

Bernacki et al (1978) carried out a case control study of U.S. aircraft engine factory workers dying of lung cancer. Exposures were to nickel oxide, nickel alloys and mists of $NiCl_2$ and $NiSO_4$ all in the order of <0.3 mg Ni/m^3. No increased risk of lung cancer was observed in these nickel exposed workers but the results could be criticised because only active workers (not leavers and pensionists) were studied and the exposures were low, even by modern standards.

Cornell (1984) studied seven plants engaged in the production of stainless steel in the U.S., by a proportional mortality analysis. The study included 4,487 deaths and showed no increase in cancer mortality. Cornell and Landis (1984) also studied foundry workers exposed to oxides of iron, nickel and chromium. They reviewed all deaths occurring between 1968-76 in 26 foundries and compared 851 exposed men with 141 unexposed. They concluded that there was no excess of lung cancer deaths; the SMR was 105 (O=60 E=57).

Godbold and Tompkins (1979) and Cragle et al (1984) studied employees of the Oak Ridge Gaseous Diffusion Plant (ORGDP). The ORGDP employed 814 workers, between January 1, 1948 and December 31 1953 in the manufacture of "barrier" material from pure nickel powder. This group was compared to 7,552 other workers at ORGDP who had no known nickel exposure. Air monitoring data indicated exposure levels of nickel

powder from 0.1-1.0 mg Ni/m^3. There was no evidence of any increase in lung cancer in the exposed group (SMR=59; O=6, E=10.2), nor were there any cases of sinonasal cancer. Again, the problem with this study is small sample size. Follow-up is continuing and future updates may yield further insight (Appendix 1).

Kjellstrom et al (1979) and Andersson et al (1983) studied the mortality of men working at a nickel cadmium battery manufacturing plant with mixed exposure to both metals and nickel hydroxide. Increased respiratory, renal and prostatic cancer mortality were noted. Although there was no increase in general cancer mortality, there were two cases of nasopharyngeal cancer. One started employment before 1948, the other between 1948-61. Exposure to nickel powder was very high indeed, exceeding 100 mg Ni/m^3 in the work area. The authors stated that the low risk ratio for lung cancer rendered the study inconclusive as to the effect of nickel compounds.

Sorahan & Waterhouse (1983) studied a cohort of 3025 nickel cadmium battery workers in the U.K. The authors stated that the study could not distinguish between exposure to cadmium oxide or nickel hydroxide. There was a slight excess of respiratory cancer (SMR=127; O=89, E=70) but there were no cases of sinonasal cancer.

Stainless steel welders were studied by Sjogren (1980). He reported a lung cancer SMR of 444 (O=4, E=0) but no sinonasal cancer. Becker et al (1985) in the Federal Republic of Germany carried out a retrospective follow-up study of 1,224 chromium and nickel exposed welders. They found the SMR for welders was 95.4 (O=6, E=6.3) and for the control group of turners 69.2 (O=10, E=14.5). Both studies were confounded by exposure to smoking, chrome and possibly asbestos and should be interpreted with caution. Polednak (1981) in the USA compared the mortality experience of 536 welders, working on nickel alloy pipes, with US white males and found an SMR of 126 (O=6, E=4.76), but again no sinonasal cancer. It is unclear at the present time whether there is any risk associated with welding of nickel-containing materials, however IARC has commissioned a large study which will be reported early in 1989 and which it is hoped will help to clarify this point.

Jones and Warner (1972) reported upon Welsh stainless steel workers exposed to iron, chromium and nickel oxides. Four out of sixteen men had evidence of pneumoconiosis which was attributed to the mixed exposure. No cases showed evidence of pulmonary or sinonasal cancer after 19 years of exposure.

Sorahan et al (1987) have recently completed a mortality study of a group of UK nickel and chromium platers. While significant excesses were found of cancer of the liver, lung and and nasal cavities, the only excess that correlated with occupational exposure was that of lung cancer and the duration of chrome bath work. The authors specifically state that nickel exposure was not shown to be a confounding factor. The study did not confirm an earlier observation of an increased incidence of cancer of the stomach in workers from the same factory (Burgess, 1980).

Silverstein et al (1981) using a proportional mortality technique and case reference analysis of 238 deaths amongst employees at a Swedish die casting and electroplating plant noted an increased Proportional Mortality Rate (P.M.R.) of 2.09 (O=28 E=14.68) for lung cancer which was believed to be work related but the study was not able to distinguish between a number of possible agents including polycyclic aromatic hydrocarbons, nickel salts and chrome salts.

3. Other Studies

Studies of sinonasal cancer have been carried out in Scandinavia, the UK and the USA, and laryngeal cancer in Denmark.

In the Scandinavian study (Hernberg et al, 1983), which did not include Norway, there was one case of sinonasal cancer in a ball mill in a nickel refinery but association of sinonasal cancer with nickel compounds was not considered significant. There was a significant excess of sinonasal cancer in welders, but the author did not feel the data allowed him to incriminate any specific compounds.

In England and Wales, Acheson et al (1981) conducted a national survey of the incidence of sinonasal cancer during the period 1963-7 with

special reference to occupation. The known excess of sinonasal cancer related to the Clydach Refinery in South Wales was noted and suggests that the technique used was reasonably sensitive. A further 22 cases were known to have occurred in furnace and foundry workers but exposure to nickel was not considered relevant to any of the occupational histories.

The US study (Roush, 1980) relates to a case control study of the occurence of sinonasal cancer occurring in Connecticut between 1935-1975. The authors state that the results do not support an association of cancer of this site with nickel in the population studied. None of these studies was designed specifically to investigate a relationship between nickel and sinonasal cancer. Nevertheless they involve 1985 cases of sinonasal cancer but except for the Clydach cases nickel does not appear to be a significant factor in their causation.

Olsen and Sabroe (1984) have performed a case control study of all new cases of laryngeal cancer occurring in Denmark from 1980-1982 and investigated their social habits and occupations. Asbestos workers were found to have high risk ratios, (1.8) but so was a group of workers with alloys, battery chemicals and chemicals used in the production of plastics (1.7). This latter group was deemed to have the potential for high nickel exposure from catalyst handling. In a similar study into the occupational risks of sinonasal cancer in Denmark, Olsen (1988) found the principal excess to be in woodworkers. A small excess was noted in men involved in the metal industries but nickel was not specifically mentioned.

4. Summary

There can be no doubt that certain stages in the refining of nickel by roasting nickel/copper sulphide ores using technological methods, which are now obsolete, were associated with a very high risk of developing cancer of the ethmoid sinuses and lungs. There does also appear to have been a risk at one refinery using these ores and operations of developing laryngeal cancer. The increased risk of

respiratory tract cancer at this particular refinery was associated with working in the electrolysis as well as the roasting areas.

There is also evidence of increased risk at one other location where nickel copper Bessemer matte and residues from nickel carbonyl extraction processes were used as feedstock for manufacture of nickel sulphate and preparation of concentrate for further refining. Recent epidemiological evidence suggests that the risks are now controlled and the reduction in risk appears to have been associated with improved environmental conditions (Mastromatteo, 1986; Peto, 1988). Neither the epidemiological data nor the process chemistry allow a clear evaluation of which form or forms of nickel or environmental conditions were responsible for the high incidence of respiratory cancer but the following were present :

> Nickel sulphides (including the subsulphide and the crystalline sulphide which have proved particularly active in experimental models), nickel oxides in a variety of forms, nickel-copper oxides and nickel-copper arsenides. It is also important to note that there were high concentrations of sulphur dioxide present in the old refineries (see also p.49). Laryngeal cancer has been associated with exposures to acid mist containing primarily sulphuric acid (Steenland et al, 1988).

While there is clear epidemiological evidence of a serious cancer risk in certain refinery operations, there is no such evidence of a risk in other refineries or in the user industries.

There is no evidence to indicate any individual nickel compound is a proven human carcinogen but the process of nickel matte roasting, refining by the Hybinette process and preparation of nickel sulphate from Bessemer matte and carbonylation residues should be so classified if this was possible.

K. EVALUATION

The previous chapters in this review indicate that there have been many epidemiological studies of nickel exposed workers and numerous experimental investigations of nickel compounds both in vivo and in vitro. The subject of nickel toxicology and carcinogenicity has also been reviewed previously (see Page 4).

There is no doubt that certain stages of the refining of nickel in the first half of this century carried a high risk of developing cancer of the respiratory tract for the exposed work force. In more recent times as technological methods of refining have been developed with the result that exposures have been controlled and general hygiene standards in the industry have improved, this risk has been considerably reduced and possibly eliminated. For the last 20 years the refining industry has aimed at exposure levels of insoluble nickel of 1 mg/m^3 with the form of nickel unspecified (see Appendix 4).

Although it has never been possible to identify accurately the form of nickel responsible for the respiratory tract cancers, the greatest suspicion falls on nickel subsulphide and this is the nickel compound which has been most intensively studied in animal carcinogenicity experiments. Nickel subsulphide consistently produces local sarcomas at the site of administration when given parenterally (see Table 4) and, of more importance in terms of extrapolation to man, it has also been shown to be carcinogenic in the rat by inhalation (Ottolenghi et al, 1974) and to be readily bioavailable (Kuehn and Sunderman, 1982). There are insufficient data to evaluate the mutagenic potential of nickel subsulphide.

The data for other forms of nickel are less clear cut. In general, insoluble nickel compounds but not soluble ones will produce local tumours when given parenterally. Several of the older inhalation studies are deficient in terms of one or more of the following : definition of exposure, small group sizes, lack of proper controls and inadequate pathological examination. None of the inhalation experiments with metallic nickel dust or nickel oxide have demonstrated an increase in tumours of the lung or upper respiratory tract (Heuper, 1958; Heuper and Payne, 1962; Kim, 1969; Wehner et al, 1975; 1979; 1984).

Recent work has indicated that nickel oxide, which can occur in a number of forms, can vary in its toxicity depending upon the temperature of formation (Sunderman, 1987). Pott et al (1987) reported the production of carcinomas of the lung in rats after a long latent period following the repeated intra-tracheal instillation of nickel powder and green nickel oxide. This result is interesting in that it demonstrated an apparent carcinogenic response in the lung towards the end of the animal's life-span. Nevertheless as the method of exposure does not accurately reflect the situation which pertains in man, less weight should be placed on it for risk assessment purposes than the more appropriate inhalation studies.

The task force is aware that long-term inhalation studies in two rodent species with green nickel oxide, nickel subsulphide and nickel sulphate are planned by the National Toxicology Programme in the USA and awaits their outcome with interest.

No relevant genotoxicity data are available for nickel metal and there are insufficient data to evaluate fully the genotoxicity of nickel oxide.

The factor which is most likely to affect the labelling of nickel compounds, other than acute toxic effects or sensitisation, is carcinogenicity. The classification of chemical compounds on grounds of carcinogenicity by the various agencies around the world vary in the criteria used. For labelling purposes in the EEC, three categories (1, 2 and 3) are used and the criteria for inclusion of a substance in these categories are given in Appendix 1.

Classifications have to be derived by an expert interpretation of all the relevant information available and guidance in this process has been provided by ECETOC (1986) and by Broecker et al (1987). Recently a meeting of the Specialised Experts of the EEC has provided a proposal for a new definition of category 3 together with comments regarding the categorisation of carcinogenic substances. These comments have been included in full in Appendix 1.

In summary, sufficient epidemiological evidence linking chemical exposure and human cancer is required to place a substance in category 1. Placement in categories 2 and 3 is based primarily on animal experiments with

supporting evidence such as genotoxicity data, metabolism studies or epidemiological studies suggesting an association.

Substances in category 2 should be regarded as if they are carcinogenic to man, whereas those placed in category 3 cause concern for man owing to possible carcinogenic effects. In practice, category 3 comprises two sub-categories :

3 (a) substances which are well investigated but for which evidence of a tumour-inducing effect is insufficient for classification in category 2;

3 (b) substances which are insufficiently investigated but raise concern for man and for which more information is required.

This last classification [3(b)] is provisional and presumably could be revised to a higher category or to non-classification when further information is available. No classification is given where the evidence is insufficient for category 3.

In the case of nickel, based on the above criteria, the epidemiological evidence clearly shows that certain processes, for example nickel matte roasting, were formerly associated with human cancer and would warrant a category 1 classification (see Table 6). However, the classification is applied to substances and not to processes.

The available data does not allow the classification of any specific nickel compound in category 1. The weight of evidence suggests that nickel subsulphide should be placed in category 2.

The data for other nickel compounds is more limited. Many of the animal experiments are not relevant for hazard assessment in man in that inappropriate routes of exposure were used and the mutagenicity data are somewhat equivocal. Taking all the available data into account we have applied the EEC classification criteria to the different nickel compounds and the outcome is shown in Table 7, together with remarks on the task force's reasoning in arriving at each classification.

L. BIBLIOGRAPHY

- AARONSON, R.W., WOO, E. (1981). Organisation in the cell nucleus : divalent cations modulate the distribution of condensed and diffused chromatin. J. Cell. Biol., 90, 181-186.
- ABBRACCHIO, M.P., EVANS, R.M., HECK, J.D., CANTONI, O., COSTA, M (1982a). The regulation of ionic nickel uptake and cytotoxicity by specific amino acids and serum components. Biol. Trace. Elem. Res., 4, 289-301.
- ABBRACCHIO, M.P., HANSEN, J.S., COSTA, M. (1982b). Toxicol. Environ. Health, 9, 663.
- ABBRACCHIO, M.P., HECK, D., COSTA, M. (1982c). The phagocytosis and transforming activity of crystalline metal sulphide particles are related to their negative surface charge. Carcinogen. 3, 175-180.
- ACHESON, E.D., COWDELL, R.H., RANG, E.H. (1981). Nasal cancer in England and Wales : An occupational survey. Brit. J. Ind. Med., 38, 218-224.
- ALLISON, A.P. (1969). Lyosomes and cancer : Dingle and Fell (eds.) Lyosomes in biol. and path., North Holland, Amsterdam, 148, 178-204.
- AMACHER, D.E., PAILLET, S.C. (1980). Induction of trifluorothymidine-resistant mutants by metal ions in L5178Y/TK+/-cells. Mutat. Res., 78, 279-288.
- AMBROSE, A.M., LARSON, P.S., BORZELLECA, J.R., HENNIGA, G.R.Jr. (1976). Long-term toxicological assessment of nickel of rats and dogs. J. Food Sci. Technol., 13, 181-187.
- ANDERSEN, J., HOGETVEIT, A.C., BARTON, R.T., GLAD, W.R. (1980). Rates of solubilisation of nickel compounds in aqueous solutions and biological fluids, in : Brown and Sunderman (1980)
- ANDERSSON, K., ELINDER, C.G., HOGSTEDT, C., KJELLSTROEM, I., SPANG, G. (1983). Mortality among cadmium workers in a Swedish cadmium factory. Ed. Cadmium Assoc.: Proc. 4th Intl. Cadmium Conf., London, 152-154.
- ANKE, M., GRUEN, M., KRONEMANN, H. (1980). Distribution of nickel in nickel-deficient goats and their offspring, in : Brown and Sunderman (1980)
- ANKE, M., GRUEN, M., GROPPEL, B., KRONEMANN, H. (1983). Nutritional requirements of nickel. Sarkar, B. ed., Biological Aspects of Metals and Metal-Related Diseases, NY, Raven Press, 89-105.
- BASRUR, P.K., et al (1970). Changes in mitochondrial ultrastructure in nickel sulphide-induced rhabdomyosarcoma. Cancer 25, 1142-1152.
- BECKER, P., DOERSTELMANN, K., FROMBERGER, W., FORTH, W. (1980). On the absorption of cobalt (III) and nickel (II) ions by isolated intestinal segments in vitro of rats. Anke, M., Schneider, H.-J., Bruckner, Chr., ed. 3.: Spurenelement-Symposium Nickel, Jena, GDR, 7-11, July 1980, Jena, Friedrich-Schiller-Universitat, 79-85.
- BECKER, N., CLAUDE, J., FRENTZEL-BEYME, R. (1985). Cancer risk of arc welders exposed to fumes containing chromium and nickel. Scand. J. Work Environ. Health 11, 75-82.
- BENNET, B.G. (1984). Environmental nickel pathways to man. IARC (1984), 487-495.
- BENSON, J.M., BURT, D.G., CARPENTER, R.L., EIDSON, A.F., HAHN, F.F., HALEY, P.J., HANSON, R.L., HOBBS, C.H., PICKRELL, J.A., DUNNICK, J.K. (1988a). Comparative inhalation toxicity of nickel sulfate to F344/N rats and B6C3F1 mice exposed for 12 days. Fund. Appl. Toxicol., 10, 164-178.
- BENSON, J.M., BURT, D.G., CHENG, Y.S, DUNNICK, J.K., EDISON, A.F., HAHN, F.F., HOBBS, C.H., PICKRELL, J.A. (1988b). Subchronic inhalation toxicity of nickel sulfate to rats and mice (abstract), The Toxicologist, 8, 68.
- BERNACKI, E.J., PARSONS, G.E., SUNDERMAN Jr., F.W. (1978). Investigation of exposure to nickel and lung cancer mortality : case control study at an aircraft engine factory. Ann. Clin. Lab. Sci. 8, 190-194.
- BIANCHI, N.O., AYRES, J. Heterochromatin location on chromosomes of normal and transformed cells from African Green Monkey (cercopithecus aethiops). Exp. Cell Res., 68, 253-258.
- BIGGERT,N.W., COSTA, M. (1986). Assessment of the uptake and mutagenicity of nickel chloride in Salmonella tester strains. Mutat. Res., 175, 209-215.
- BOLDT, J.R., QUENEAU, P. (1967). The winning of nickel, its geology, mining, and extractive metallurgy. Meuthen & Co. Ltd., London.
- BRIDGE, J.C. (1932). Annual report of the chief inspector of factories and workshops for the year 1932, HMSO, London, 103-104.
- BRIGGS, G.W.D., JONES, E., WYNNE-JONES, W.F.K. (1955). The nickel oxide electrode. Trans Faraday Soc., 51, 1433-1444.

- BROECKER, B., Sowinski, E.J. (1987). Criteria for identifying and classifying carcinogens, mutagens and teratogens. Regul. Toxicol. Pharmacol. 7, 1-20.
- BROWN, S.S., SUNDERMAN Jr., F.W. (eds) (1980). Nickel Toxicology. Academic Press, London.
- BROWN, S.S., SUNDERMAN Jr., F.W. (eds) (1985). Progress in Nickel Toxicology. Proc. 3rd Int. Conf. Nickel Metabolism and Toxicology (Paris, 4-7th Sept. 84). Blackwell, Oxford, 250 pp.
- BURGES, D.C.L. (1980). Mortality study of nickel platers, in : Brown and Sunderman (1980), 15-18
- CAMNER et al (1983). Toxicology of nickel, in : IARC (1984), 267-268.
- CANTONI, O., NELWYN, T. Chr., ROBISON, S.T., COSTA, M. (1984). Characterisation of DNA lesions produced by $HgCl_2$ in cell culture systems. Chem. Biol. Interact., 49, 209.
- CARVALHO, S.M., ZIEMER, P.L. (1982). Distribution and clearance of ^{63}Ni administered as $^{63}NiCl_2$ in the rat : intratracheal study. Arch. Environ. Contam. Toxicol., 11, 245-248.
- CASTO, B.C., MEYERS, J., DIPAOLO, J.A. (1979). Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res., 39, 193-198.
- CEC Commission of the European Communities (1987). European inventory of existing commercial substances (EINECS), Advanced edition, Vol.V, 678.
- CICCARELLI, R.B., WETTERHAHN, K.E. (1982). Nickel distribution and DNA lesions induced in rat tissue by the carcinogenic nickel carbonate. Cancer Res., 42, 3544-3549.
- CHOVIL A., SUTHERLAND R.B., HALLIDAY M. (1981). Respiratory cancer in a cohort of nickel sinter plant workers. Brit. J. Ind. Med., 38, 327-333.
- CHRISTENSEN, O.B., LAGESSON, V. (1980). Concentrations of nickel in blood and urine after oral administration, in : Brown and Sunderman (1980)
- CHRISTENSEN, O.B., LAGESSON, V. (1981). Nickel concentrations of blood and urine at oral administration. Ann. Clin. Lab. Sci. 11, 119-125
- CHRISTENSEN, O.B., MOELLER, H. (1975). Nickel allergy and hand eczema. Contact Dermatitis 1, 129-135.
- CLARY, J.J. (1975). Nickel chloride-induced metabolic changes in the rat and guinea pig. Toxicol. Appl. Pharmacol. 31, 55-65.
- CLEMENTE, G.F., CIGNA-ROSSI, L., SANTORINI, G.P. (1980). Nickel in foods and dietary intake of nickel. Nickel in the Environ., ed. Nriagu, J.O., John Wiley & Sons, 493-498.
- COOPER W.C., WONG O. (1981). A study of mortality in a population of nickel miners and smelter workers. Unpublished Report for Hanna Nickel Smelting Co., Riddle. Oregon.
- COSTA, M. (1978). Alteration in morphology of Chinese hamster ovary cells by Nickel sulphide and dibutyryl cAMP. Toxicol. and Appl. Pharmacol., 44, 555-566.
- COSTA, M., ABBRACCHIO, M.P., SIMMONS-HANSEN, J. (1981). Factors influencing the phagocytosis, neoplastic transformation and cytotoxicity of particulate nickel compounds in tissue culture systems. Toxicol. Appl. Pharmacol. 60, 313-323.
- COSTA, M., HECK, D. (1984). Perspectives on the mechanism of nickel carcinogenesis. Advances in Inorg. Biochem. 6, 285-309.
- COSTA, M., HECK, J.D., ROBISON, S.H. (1982). Selective phagocytosis of crystalline nickel sulphide particles and DNA strand breaks as a mechanism for the induction of cellular transformation. Cancer Res., 42, 2757-2763.
- COSTA, M., MOLLENHAUER, H.H. (1980a). Phagocytosis of particulate nickel compounds is related to their carcinogenic activity, in : Brown and Sunderman (1980), 43-56.
- COSTA, M., MOLLENHAUER, H.H. (1980b). Carcinogenic activity of particulate nickel compounds is proportional to their cellular uptake. Science 209, 515-517.
- COSTA, M., MOLLENHAUER, H.H. (1980c). Phagocytosis of nickel subsulphide particles during the early states of neoplastic transformation in tissue culture. Cancer Res. 40, 2688-2694.
- COSTA, M., SIMMONS-HANSEN, J., BEDROSSIAN, C.W.M., BONURA, J., CAPRIOLI, R.M. (1981). Phagocytosis, cellular distribution and carcinogenic activity of particulate nickel compounds in tissue culture. Cancer Res., 41, 2868-2876.
- COX J.E., DOLL R., SCOTT W.A., SMITH S. (1981). Mortality of nickel workers. Experience with men working with metallic nickel. Brit. J. Ind. Med., 38, 235-239.
- CORNELL R.G. (1984). Mortality patterns among stainless steel workers, in : IARC (1984), 65-72.
- CORNELL R.G., LANDIS J.R. (1984). Mortality patterns among nickel/chromium alloy foundry workers, in : IARC (1984), 87-95.

- CRAGLE D.L., HOLLIS D.R., SHY C.M., NEWPORT I.H. (1984). A retrospective cohort mortality study of workers exposed to metallic nickel dust at the Oakridge Gaseous Diffusion Plant, in : IARC (1984), 57-64.
- CRONIN, E., DI MICHIEL, A.D., BROWN, S.C. (1980). Oral challenge in nickel-sensitive women with hand eczema, in : Brown and Sunderman (1980)
- CUCKLE H., DOLL R., MORGAN L.G. (1980). Mortality study of men working with soluble nickel compounds, in : Brown and Sunderman (1980), 11-14.
- DALDRUP, T., HAARHOF, K., SZATHMARY, S.C. (1983). Toedliche Nickelsulfatintoxikation, Ber. Gerichtl. Med. 41, 141-144.
- DAMJANOV, I., SUNDERMAN Jr., F.W., MITCHELL, J.M., ALLPASS, P.R. (1978). The induction of testicular sarcomas in Fischer rats by intratesticular injection of nickel subsulphide. Cancer Res. 38, 268-276.
- DANIEL, M.R. (1966). Strain differences in the response of the rats to the injection of nickel sulphide. Brit. J. Cancer, 20, 886-895.
- DECHENG, C., MING, J., LING, H., SHAN, W., ZIQING, X., XINSHUI, Z. (1987). Cytogenetic analysis in workers occupationally exposed to nickel carbonyl. Mutat. Res., 188, 149-152.
- DEKNUDT, G.H., LEONARD, A. (1982). Mutagenicity tests with nickel salts in the male mouse. Toxicol., 25, 289-292.
- DEWALLY, D., HILDEBRAND, H.F. (1980). The fate of nickel subsulphide implants during carcinogenesis, in : Brown and Sunderman (1980)
- DFG (1988). Maximale Arbeitsplatzkonzentrationen und biologische Arbeitsstofftoleranzwerte 1988, VCH, Weinheim.
- DIPAOLO, J.A., CASTO, B.C. (1979). Quantative studies of in vitro morphological transformation of Syrian golden hamster cells by inorganic metal salts. Cancer Res., 39, 1008-1013.
- DOLL R. (1958). Cancer of the lung and nose in nickel workers. Brit. J. Ind. Med., 15, 217-223.
- DOLL R., MORGAN L.G., SPEIZER F.E. (1970). Cancers of the lungs and nasal sinuses in nickel workers. Brit. J. Cancer, 24, 623-632.
- DOLL R, MATHEWS J.D., MORGAN L.G. (1977). Cancer of the lung and nasal sinuses in nickel workers : A reassessment of the period of risk. Brit. J. Ind. Med. 34, 102-105.
- DOLL R. (1984). Nickel exposure a human health hazard, in : IARC (1984), 3-22.
- DUNNICK, J.T., BENSON, J.M., HOBBS, C.H., HAHN, F.F., CHENG, Y.S., EIDSON, A.F. (1988). Comparative toxicity of nickel oxide, nickel sulphate hexahydrate, and nickel subsuphide after 12 days of inhalation exposure to F344/N rats and B6C3F1 mice. Toxicol. 50, 145-156.
- EEC (1983) 5th Adaptation to Council Directive 67/548/EEC (83/467/EEC). O.J. of the European Communities L257 1-33.
- EEC (1988) Paper XI/57/88 - Rev.2 from the 6th meeting of the Specialized Experts of the EEC, Brussels.
- ECETOC (1986). A guide to the classification of carcinogens, mutagens and teratogens under the sixth amendment. Tech. Rep. 21.
- EGEDAHL R., RICE E. (1984). Cancer incidence at a hydrometalurgical nickel refinery, in : IARC (1984), 47-55.
- ENGLISH, J.C., PARKER, R.D.R., SHARMA, R.P., OBERG, S.G. (1981). Toxicokinetics of nickel in rats after intratracheal administration of a soluble and insoluble form. Am. Ind. Hyg. Assoc. J. 42, 486-492.
- ENTERLINE P.E., MARSH G.M. (1982). Mortality among workers in a nickel refinery and alloy manufacturing plant in West Virginia. J. Nat. Cancer Inst., 68, 925-933.
- EPA (1986). Health assessment document for nickel and nickel compounds. Final report : ORD, OHEA, ECAO-RTP. EPA 600/8-83-012FF
- EVANS, H.S. (1985). Cytogenic and alied studies in populations exposed to radiation and chemical agents in assessment of risk from low level exposure to radiation and chemicals. Eds. Woonead, Shellabaiger, Pond and Hollaende. Plenum Press, NY, 429.
- EVANS, R.M., DAVIES, P.J.A., COSTA, M. (1982). Video time-lapse microscopy of phagcytosis and intracellular fate of crystalline nickel sulphide particles in cultured mammalian cells. Cancer Res., 42, 2729-2735.
- FAIRHURST, S., ILLING, H.P.A. (1987). The toxicity of nickel and its inorganic compounds, UK Health & Safety Executive, Advisory Committee on Toxic Substances.

- FISHBEIN, W.N., SMITH, M.J., NAGARAJAN, K., SOURZI, W. (1976). The first natural nickel metalloenzyme : urease. Fed. Proc. 35, 1680A.
- FISHER, G.L., CHRISP, C.E., MCNEILL, D.A. (1986). Lifetime effects of intratracheally instilled nickel subsulphide of B6C3F1 mice. Environ. Res., 40, 313-320.
- FORTH, W., RUMMEL, W. (1981). Absorption of iron and chemically-related metals in vitro and in vivo : specificity of the iron-binding system in mucosa of the jejunum. Shoryna, S.S., Waldron-Edward, D., ed. : Intestinal absorption of metal ions, trace elments and radionuclides, NY, Pergamon Press, 173-191.
- FOULKES, E.C., MCMULLEN, D.M. (1986). On the mechanism of nickel absorption in the rat jejunum. Toxicol. 38, 35-42.
- FRIBERG, L. (1950). Health hazards in the manufacture of alkaline accumulators with special reference to chronic poisoning. Acta Medica Scand., Suppl. 240 to Vol. 138.
- FULLERTON, A., ANDERSEN, J.R, HOELGARD, A., MENNE, T. (1986). Permeation of nickel salts through human skin in vitro. Contact Dermatitis 15, 173-177
- FURST, A., and CASSETTA D. (1973). Carcinogenicity of nickel by different routes. Proceed. Amer. Ass. Cancer Res., 14, 121.
- FURST, A., CASSETTA, D., and SASMORE, D.R. (1973). Rapid induction of pleural mesotheliomas in the rat. Proc. West Pharmacol. Soc., 16, 150-153
- FURST, A. and SCHLAUDER, M.C. (1971). The hamster as a model for metal carcinogenesis. Proc. West Pharmacol. Soc., 14, 68-71.
- GHIRINGHELLI, (1975) . Nickel. Medical and biological effects of environmental pollutants. Nat. Acad. Sci., Washington DC, 67.
- GILMAN, J.P.W. (1962). Metal carcinogenesis II. A study on the carcinogenic activity of cobalt, copper, iron and nickel compounds. Cancer Res., 22, 158-162.
- GILMAN, J.P.W., DANIEL, M.R., BASRUR, P.K. (1966). Observations on tissue selectivity in nickel tumourigenesis. Proc. Amer. Ass. Cancer Res., 7, 24.
- GLAISER, D. et al (1986). Long-term inhalation studies with nickel oxide and arsenic trioxide aerosols in Wistar rats. Int. Cong. Ser. Exerpta Med., 676, 325-328. Chem. Abstr. 105 (17), 147914.
- GODBOLD, Jr., J.H. TOMPKINS. E.A. (1979). A long term mortality study of workers occupationally exposed to metallic nickel at the Oak Ridge plant. J. Occup. Med. 21, 799-806.
- GOLDBERG, G. (1984). An epidemiological study of S.L.N. workers in New Caledonia, in : IARC (1984), 211-218.
- GOLDBERG, M., GOLDBERG. P., LECLERC, A., CHASTANG, J.F., FUHRER, R. (1988). Epidemiology of respiratory cancers related to nickel mining and refining in New Caledonia. Int. J. Cancer 40, 300-304.
- GMELINS HANDBUCH DER ANORGANISCHEN CHEMIE (1966). Nickel B-2, Verlag Chemie, Weinheim, 487.
- GRAHAM, J.A., MILLER, F.J., DANIELS, M.J., PAYNE, E.A., GARDNER, D.E. (1978). Influence of cadmium, chromium and nickel on primary immunity in mice. Environ. Res., 16, 77-87.
- GREEN, M.H.L., MURIEL, W.J., BRIDGES, B.A. (1976). Use of a simplified fluctuation test to detect low levels of mutagens. Mutat. Res., 38, 33-42.
- GREENWOOD, N.N., EARNSHAW, A. (1984). Chemistry of the elements, Pergamon Press, Oxford, 1333.
- HANSEN, K., STERN, R.M. (1983). In vitro toxicity and transformation potency of nickel compounds. Environ. Hlth. Persp., 51, 223-226.
- HEATH, J.C. and DANIEL, M.R. (1964). The production of malignant tumours by nickel in the rat. Brit. J. Cancer, 18 (2), 261-264.
- HECK, D., COSTA, M. (1982). Surface reduction of amorphous NiS particles potentiates their phagocytosis and subsequent induction of morphological transformation in syrian hamster embryo cells. Cancer Lett., 15, 19.
- HENDEL, R.C., SUNDERMAN Jr., F.W. (1972). Species variations in the proportions of ultrafilterable and protein-bound serum nickel. Res. Commun. Chem. Pathol. Pharmacol., 4, 141-146.
- HERCHEN, H. and GILMAN, J.P.W. (1964). Effect of duration of exposure on nickel sulphide tumourogenesis. Nature 202, 306.
- HERNBERG, S., WESTERHOLM, P., SCHULTZ-LARSEN, K., DEGERTH, R., KUOSMA, E., ENGLAND, A., ENGZELL, U., SAND, HANSEN, H., MUTANEN, P. (1983). Nasal and sinonasal cancer. Connections with occupational exposures in Denmark, Finland and Sweden. Scand. J. Work Environ Health, 9, 315-326.

- HEUPER, W.C. (1952). Experimental studies in metal carcinogenesis I. Nickel cancers in rats. Texas Reps. Biol. Med., 10, 167-186.
- HEUPER, W.C. (1955). Experimental studies in metal carcinogenesis IV. Cancer produced by parentarally induced nickel. J. Nat. Cancer Inst., 16, 55-73.
- HEUPER, W.C. (1958). Experimental studies in metal carcinogenesis IX. Pulmonary lesions in guinea pigs and rats exposed to prolonged inhalations of powdered metallic nickel. Arch. Pathol. 65, 600-607.
- HEUPER, W.C. and PAYNE, W.W. (1962). Experimental studies in metal carcinogenesis. Chromium nickel, iron and arsenic. Arch. Envir.Health 5, 445-462.
- HILDEBRAND, H.F. and BISERTE, G. (1978). Ultrastructural investigation of Ni_3S_2-induced rhabdomyosarcoma in Wistar rats. Cancer Res., 42, (2), 528-554.
- HILDEBRAND, H.F. and BISERTE, G. (1979). Nickel subsulphide-induced leiomysarcoma in rabbit white skeletal muscle : a light microscopical and ultrastructural study. Cancer Res., 43 (4), 1358-1374.
- HILL A.B. (1939). Statistical Report to Mond Nickel Company relating to the incidence of carcinoma of the respiratory system at the Clydach Works. Cited by MORGAN (1958).
- HO, W., FURST, A. (1973). Nickel excretion by rats following a single treatment. Proc. West. Pharmacol. Soc., 16, 245-248.
- HOBBS, C.H., BENSON, J.M., CHENG, Y.S, EIDSON, A.F., HAHN, F.F., PICKRELL, J.A., DUNNICK, J.K. (1987). Inhalation toxicity of nickel subsulphide to F344/N rats and B6C3F1 mice exposed for 13 weeks (abstract). The Toxicologist, 7, 197.
- HOBBS, C.H., BENSON, J.M., BURT, D.G., CHENG, Y.S., DUNNICK, J.K., EIDSON, A.F., HALEY, P.J., PICKRELL, J.A. (1988). Subchronic inhalation toxicity of nickel oxide to rats and mice (abstract). The Toxicologist, 8, 68.
- HOHNADEL, D.C., SUNDERMAN Jr., F.W., NEHCAY, M.W., MCNEELY, M.D. (1973). Atomic absorption spectrometry of nickel, copper, zinc, and lead in sweat collected from healthy subjects during sauna bathing. Clin. Chem., 19, 1288-1292.
- HORAK, E., SUNDERMAN Jr., F.W. (1973). Fecal nickel excretion by healthy adults. Clin. Chem., 19, 429-430.
- HORIE, A., TANAKA, T., HARATAKE, J., KODAMA, Y., TSUCHIYA,K. (1985). Electron microscopy of pulmonary lesions, including carcinoma induced by inhalation exposure of rats to nickel oxide aerosol, in : Brown and Sunderman (1985), 41-44.
- INTERNATIONAL AGENCY FOR RESEARCH ON CANCER. (1976). IARC Monographs on the evaluation of the carcinogenic risk of chemicals to man : cadmium and nickel, Lyon, 11.
- INTERNATIONAL AGENCY FOR RESEARCH ON CANCER. (1984). Nickel in the human environment. IARC Scientific Publications No. 53, Sunderman Jr., F.W. (ed.) IARC, Lyon
- INCO (1976). Nickel and its inorganic compounds (including nickel carbonyl). A supplementary submission to the National Institute for Occupational Safety and Health by International Nickel (U.S.) Inc.
- JACOBSEN, N., ÄLFHEIN, I., JONSEN, J. (1978). Nickel and strontium distribution in some mouse tissues and passage through placenta and mammary glands. Res. Comm. Chem. Pathol. Pharmacol., 20, 571-584.
- JACQUET, P., MAYENCE, A. (1982). Application of the *in vitro* embryo culture to the study of the mutagenic effects of nickel in the male germ cells. Toxicol. Lett., 11, 193-197.
- JASMIN, G. (1963). Effects of methandrostenolone on muscle carcinogenesis induced in rats by nickel sulphide. Brit. J. Cancer 17, 681.
- JASMIN, G., TJALVE, H. (1984). Effects of thiuram sulphides on the uptake and and distribution of nickel in pregnant and non-pregnant mice. Toxicol., 32, 279-313.
- JONES J.G., WARNER C.G. (1972). Chronic exposure to iron oxide, chromium oxide, and nickel oxide fumes of metal dressers in a steelworks. Brit. J. Ind. Med., 29, 169-177.
- JORDAN, W.P., KING, S.E. (1979). Nickel feeding in nickel-sensitive patients with hand eczema. J. Am. Acad. Dermatol., 1, 506-508.
- KAABER, K., VEIEN, N.K., TJELL, J.C. (1978). Low nickel diets in the treatment of patients with chronic nickel dermatitis. Brit. J. Dermatol., 98, 197-201.
- KALLIOMAKI, P.L., RAHKONEN, E., VAARAMEN, V., KALLIOMAK, K., AITTONIENI, K. (1981). Lung-retained contaminants, urinary chromium and nickel among stainless steel welders. Int. Arch. Occup. Environ. Health, 49, 67-75

- KANEMATSU, N., HARA, M., KADA, T. (1980). REC assay and mutagenicity studies in metal compounds. Mutat. Res., 77, 109-116.
- KASPRZAK, K.S. (1974). An autoradiography study of nickel carcinogenesis in rats following injection of $^{63}Ni_3S_2$ and $Ni_3{}^{35}S_2$. Res. Commun. Chem. Pathol. Pharmacol. 8, 141-150.
- KASPRZAK, K.S., GABRYEL, P., JARCZEWSKA, K. (1983). Carcinogenity of nickel(II)hydroxides and nickel(II)sulphate in Wistar rats and its relation to the in vitro dissolution rates. Carcinogen. 4 (3), 275-279.
- KASPRZAK, K.S., POIRIER, L.A. (1983). Effects of calcium, magnesium and sodium acetate on tissue distribution of Nickel(II) in strain A mice. Chem. Toxicol. Clin. Chem. Metals., Proc. Int. Conf., 2nd, Acad. Press, London, UK, 373-376, eds. Brown and Savory.
- KASPRZAK, K.S., QUANDER, R.V., POIRIER, L.A. (1985). Effects of calcium and magnesium salts on nickel subsulphide carcinogenicity in Fischer rats. Carcinogen. 6, 1161-1166.
- KASPRZAK, K.S. (1988). Inhibitory effect of iron on the carcinogenicity of nickel subsulphide in F344/NCr rats. The Toxicologist; SOT meeting, 767A, 193.
- KIM, M.K. (1969). Pulmonary effects of metallic dusts. - Nickel and Iron - Thesis, University of Toronto, School of Hygiene, Dept. of Physiolog. Hygiene, 1-6.
- KINCAID, J.F., STRONG,. J.S., SUNDERMAN Jr., F.W. (1953). Nickel poisoning. Arch. Ind. Hyg. Occup. Med., 8, 48-60.
- KJELLSTROM, T., FRIBERG, A., RAHNSTER, B. (1979). Mortality and cancer morbidity among cadmium exposed workers. Environ Health Perspect. 28. 199-204.
- KOSOVA, L.V. (1979). Toxicity of nickel sulphate. Gig. Tr. Prof. Zabol., 6, 48-49.
- KREYBERG L. (1978). Lung cancer in workers in a nickel refinery. Brit. J. Ind. Med. 35, 109-116
- KUEHN, K., SUNDERMAN Jr., F.W. (1982). Dissolution half-times of nickel compounds in water, rat serum, and renal cytosol. J. Inorg. Biochem. 17, 29-39.
- KUEHN, K., FRASER, C.B., SUNDERMAN Jr., F.W. (1982). Phagocytosis of particulate nickel compounds by rat peritoneal macrophages in vitro. Carcinogen. 3, 321-326.
- LANDOLT-BOERNSTEIN (1962). Eigenschaft der Materie in ihren Aggregatzustanden, 2. Teil, b : Losungsgleichgewichte I, Springer, Berlin.
- LARRAMENDY, M.L., POPESCU, N.C., DIPAOLO, J.A. (1981). Induction by inorganic metal salts of sister chromatid exchanges and chromosome aberrations in human and Syrian hamster cell strains. Environ. Mutagen., 3, 597-606.
- LAU, T.J., HACKETT, R.L., SUNDERMAN Jr., F.W. (1972). The carcinogenicity of intravenous nickel carbonyl in rats. Cancer Res., 32, 2253-2258.
- LEONARD, A., JACQUET, P. (1984). Embryotoxicity and genotoxicity of nickel, in : IARC (1984), 227-291.
- LESLIE, A.C.D., WINCHESTER, J.W., LEYSEIFFER, F.W., AHLBERG, M.S. (1976). Predition of health effects of pollution aerosols. Trace Subst. Environ. Health 10, 497-504.
- LESSARD, R., REED, D., MAHEUX, B., LAMBERT, J. (1978). Lung cancer in New Caledonia, a nickel smelting island. J. Occup. Med. 20, 815-817.
- LU, C.C., MATSUMATO, N., JIJIMA, S. (1981). Placental transfer and body distribution of nickel chloride in pregnant mice. Toxicol. Appl. Pharmacol. 59, 409-413.
- LUMB, G.D., SUNDERMAN Jr., F.W., SCHNEIDER, H.P., CHOU, R.H. (1987). Histogenesis of subcutaneous malignant tumours resulting from nickel subsulphide implantation. Ann. Clin. Lab. Sci. 17, 286-299.
- LUMB, G.D., SUNDERMAN, Sr., F.W., SCHNEIDER, H. (1985). Nickel induced malignant tumours. Ann. Clin. Lab. Sci., 15, 374-379.
- MACHADO-CARVALHO, S.M., ZIEMER, P.L. (1982). Distribution and clearance of ^{63}Ni administered as $^{63}NiCl_2$ in the rat : intratracheal study. Arch. Environ. Contam. Toxicol. 11, 245-248.
- MAENZA, R.M., PRADHAN, A.M., SUNDERMAN Jr., F.W. (1971). Rapid induction of sarcomas in rats by combination of nickel sulphide and 3,4-benzpyrene. Cancer Res., 31, 2067-2071.
- MAGNUS, K., ANDERSON, A., HOGETVEIT, A.C. (1982). Cancer of respiratory organs among workers at a nickel refinery in Norway. Int. J. Cancer 30, 681-685.
- MAK Commission (1983). Technical regulations for dangerous working materials, specific substance related criteria for the effects and action of nickel and nickel compounds, MAK Commission, FRG.
- MARZOUK, A., SUNDERMAN Jr., F.W. (1985). Biliary excretion of nickel in rats. Toxicol. Lett. 27, 65-71.
- MASON, M.M. (1972). Nickel sulphide carcinogenesis. Environ. Physiol. Biochem. 2, 137-141

- MASTROMATTEO, E. (1986). Nickel. Am. Ind. Hyg. Assoc. J. 47, 589-601.
- MATHUR, A.K., DATTA, K.K., TANDON, S.K., DIKSHITH, T.S.S. (1977). Effect of nickel sulphate on male rats. Bull Environ. Contam. Toxicol. 17, 241-247.
- MATHUR, A.K., DIKSHITH, T.S.S., LAL, M.M., TANDON, S.K. (1978). Distribution of nickel and cytogenetic changes in poisoned rats. Toxicol. 10, 105-113.
- MCGREGOR, D.B. et al (1983). Five metal compounds : induction of morphological transformation in C3H10T1/2 cells. Inveresk report, international report No.2607
- MCNEELY, M.D., SUNDERMAN Jr., F.W., NEACHAY, M.W., LEVINE, H. (1971). Abnormal concentrations of nickel in serum in cases of myocardial infarction, stroke, burns, hepatic cirrhosis and uremia. Clin. Chem. 17, 1123-1128.
- MCNEELY, M.D., NEACHY, M.W., SUNDERMAN Jr., F.W. (1972). Measurements of nickel in serum and urine as indices of environmental exposure to nickel. Clin. Chem. 18, 992-995.
- MENNE, T., THORBOE, A. (1976). Nickel dermatitis - nickel excretion. Contact Dermatitis 2, 353-354.
- MENNE, T., KAABER, K., TJELL, J.C. (1980). Treatment of nickel dermatitis. Ann. Clin. Lab. Sci. 10, 160-164.
- MENNE, T., MIKKELSEN, H.I., SOLGARD, P. (1978). Nickel excretion in urine after oral administration. Contact Dermatitis 4, 106-108.
- MIKI, H., KASPRZAK, K.S., KENNEY, S., HEINE, U.I. (1987). Inhibition of intercellular communication by nickel(II) : antagonistic effect of magnesium. Carcinogen. 8, 1757-1760.
- MITCHELL, D.F., SHANKWALKER, G.B., SHAZER, S. (1960). Determining the tumourigenicity of dental materials. J. Dent. Res. 39, 1023-1028.
- MIYAKI, M., AKAMATSU, N., ONO, T., KOYAMA, H. (1979). Mutagenicity of metal cations in cultured cells from Chinese hamsters. Mutat. Res., 68, 259-263.
- MORGAN J.G. (1958). Some observations on the incidence of respiratory cancer in nickel workers. Brit. J. Ind. Med., 15, 224-234.
- MORGAN L.G. (1979). Cancer mortality in men exposed to Nickel Carbonyl Gas. Internal report to INCO Europe Limited.
- MORGAN, L.G., ROUGE, P.J.C., (1984). Biological monitoring in nickel refinery workers, in : IARC (1984)
- MUSHAK, P. (1980). Metabolism and systemic toxicology of nickel, in : Nickel in the environment, Nriagu, J.O., John Wiley & Sons, 499-523.
- NATION, J.R., HARE, M.F., BAKER, D.M., CLARKE, D.E., BOURGEOIS, A.E. (1985). Dietary administration of nickel : effects on behaviour and metallothionein levels. Physiol. Behav. 34, 349-353.
- NATUSCH, D.F.S., WALLACE, J.R., EVANS, C.A. (1974). Toxic trace elements : preferential concentrations in respirable particles. Sci. 183, 202-204.
- NECHAY, N.W., SUNDERMAN Jr., F.W. (1973). Measurement of nickel in hair by atomic absorption spectrometry. Ann. Clin. Lab. Sci. 3, 30-35.
- NEWMAN, S.M., SUMMITT, R.L., NUNEZ, R.L. (1982). Incidence of nickel-induced sister-chromatid exchange. Mutat. Res., 101, 67-75.
- NIEBOER, E., STAFFORD, A.R., EVANS, S.L., DOLEVICH, J. (1983). Cellular binding and/or uptake of nickel(II) ions, in : IARC (1984), 321-331.
- NIELSEN, F.H., OLLERICH, D.A. (1974). Nickel : a new essential trace element. Fed. Proc. 33, 1767-1772.
- NIELSEN, G.D., FLYVHOLM, R. (1983). Risks of high nickel intake with the diet, in : IARC (1984),333-338.
- N.I.P.E.R.A. (1983). Critical evaluation of epidemiological studies of nickel-exposed workers. Final report. A report to the Nickel Producers Environmental Research Association.
- NISHIOKA, H. (1975). Mutagenic activities of metal compounds in bacteria. Mutat. Res., 31, 185-189.
- NOBLE, R.L. and CAPSTICK, V. (1963). Rhabdomyosarcomas induced by nickel sulphide in the rat. Proceed. Amer. Ass. Cancer Res., 4, 48.
- NOMOTO, S., SUNDERMAN Jr., F.W. (1970). Atomic absorption spectrometry of nickel in serum, urine and other biological materials. Clin. Chem. 16, 477-485.

- NOMOTO, S., MCNEELY, M.D., SUNDERMAN Jr., F.W. (1971). Isolation of a nickel alpha$_2$-macroglobulin from rabbit serum. Biochem. 10, 1647-1651.
- NORGAARD, O. (1955). Investigation with radioactive Ni57 into the resorption of nickel through the skin in normal and in nickel-hypersensitive persons. Acta. Derm. Venereol, 35, 111-117.
- NORGAARD, O. (1957). Investigations with radioactive nickel, cobalt and sodium on the resorption through the skin in rabbits, guinea-pigs and man. Acta. Derm. Venereol. 37, 440-445.
- OBERDOERSTER, G., HOCHRAINER, D. (1980). Effect of continuous nickel oxide exposure on lung clearance, in : Brown and Sunderman (1980)
- O'DELL, G.D., MILLER, W.J., MOORE, S.L., KING, W.A., ELLERS, S.C., JURECEK, H. (1971). Effects of dietary nickel level on excretion and nickel content of tissues in male calves. J. Animal Sci. 32, 769-773.
- OKAMOTO, M. (1987). Induction of ocular tumour by nickel subsulphide in the Japanese common newt, Cynops Pyrrhogaster. Cancer Res., 47, 5213-5217.
- OLSEN, J.H., JONSEN, J. (1979). Whole body autoradiography of ^{63}Ni in mice throughout gestation. Toxicol. 12, 165-172.
- OLSEN, J.H., SABROE, S. (1984). Occupational causes of laryngeal cancer. J. Epi. Comm. Health. 38, 117-121.
- OLSEN, J.H., SABROE, S. (1988). Occupational risks of sinonasal cancer in Denmark. Brit. J. Ind. Med., 45, 329-335.
- ONKELINX, C., BECKER, J., SUNDERMAN Jr., F.W. (1973). Compartmental analysis of the metabolism of ^{63}Ni(II) in rats and rabbits. Res. Commun. Chem. Pathol. Pharmacol. 6, 663-676.
- OSKARSSON, A., TJALVE, H. (1979). An autoradiographic study on the distribution of $^{63}NiCl_2$ in mice. Ann. Clin. Lab. Sci. 9, 47-59.
- OSKARSSON, A., ANDERSSON, Y., TJALVE, H. (1979). Fate of nickel subsulphide during carcinogenesis studied by autoradiography and x-ray powder diffraction. Cancer Res., 39, 4175-4182.
- OTTOLENGHI, A.D., HASEMAN, J.K., PAYNE, W.W., FALK, H.L., MACFARLAND, H.N. (1974). Inhalation studies of nickel sulphide in pulmonary carcinogenesis of rats. J. Nat. Canc. Inst. 54 (5), 1165-1172.
- PARKER, K., SUNDERMAN Jr., F.W. (1974). Distribution of ^{63}Ni in rabbit tissues following intravenous injection of $^{63}NiCl_2$. Res. Commun. Chem. Pathol. Pharmacol. 7, 755-762.
- PATON, G.R., ALLISON, A.C. (1972). Chromosome damage in human cell cultures induced by metal salts. Mutat. Res., 16, 332-336.
- PEDERSEN, E., HOGETVEIT, A.C., ANDERSEN, A. (1973). Cancer of respiratory organs among workers at a nickel refinery in Norway. Int. J. Cancer 12, 32-41.
- PEDERSEN, E., HOGETVEIT, A.C., ANDERSEN, A., MAGNUS, K. (1981). A follow-up study of incidence of cancer of the respiratory organs among workers at the Falconbridge Nickel Refinery in Norway. Ann. Clin. Lab. Sci. 11 (1), 75.
- PETO J, CUCKLE H, HERMON C, DOLL R, MORGAN L.G. (1984). A further update of respiratory cancer mortality of nickel workers in Clydach, Wales, in : IARC (1984), 37-46.
- POLEDNAK, A.P. (1981). Mortality among welders, including a group exposed to nickel oxides. Arch. Environ. Health, 36, 235-242.
- POTT, F., ZIEM, U., REIFFER, F.J., HUTH, F., ERNST, H., MOHR, U. (1987). Carcinogenicity studies on fibres, metal compounds and some other dusts in rats. Exp. Path. 32, 129-152.
- RAITHEL, H.J., SCHALLER K.H., VALENTIN H. (1984). Medical and toxicological aspects of occupational nickel exposure in the FDR. Clinical results (carcinogenicity, sensitization) and preventative measures (biological monitoring), in : IARC (1984), 403-415.
- REDMOND, C.K. (1984). Site specific cancer mortality among workers involved in the production of high nickel alloys, in : IARC (1984), 73-87.
- RIGAUT, J.P. (1983). Rapport preparatoire sur les criteres de sante pour le nickel. Report prepared for the Commission of European Communities. DOC CCE/LUX/V/E/24/83.
- RIVEDAL, E., SANNER, T. (1980). Synergistic effect on morphological transformation of hamster embryo cells by nickel sulphate and benzo(a)pyrene. Cancer Lett., 8, 203-208.
- RIVEDAL, E., SANNER, T. (1981). Metal salts as promoters of *in vitro* morphological transformation of hamster embryo cells initiated by benzo(a)pyrene. Cancer Res., 41, 2950-2953.
- ROBERTS R.S., JULIAN J.A., MUIR D.C.F., SHANNON H.S. (1984). Cancer mortality associated with the high temperature oxidation of nickel subsulfide, in : IARC (1984), 23-35.
- ROBERTS (1988) Press Release.

- ROBISON, S.H., CANTONI, O., COSTA, M. (1982). Strand breakage and decreased molecular weight of DNA induced by specific metal compounds. Carcinogen., 6, 657-662.
- ROBISON, S.H., CANTONI, O., HECK, J.D., COSTA, M. (1983). Soluble and insoluble nickel compounds induce DNA repair synthesis in cultered mammalian cells. Cancer Letters, 17, 273-279.
- ROBISON, S.H., COSTA, M. (1982). The induction of DNA strand breakage by nickel compounds in cultured Chinese hamster ovary cells. Cancer Letters, 15, 35-40.
- ROCKSTROH H. (1952). Zur Atiologie des Bronchialkrebses in arsenverarbeitenden Nickelhütten. Beitrag zur Syncarcinogenese des Berufkrebses. Arch. Geschwulstforsch. 14, 151-162.
- RODRIGUEZ, A.R., RAMOS, M.P. (1986). Mutagenicity of nickel sulphate in Drosphila melanogaster. Mutat. Res., 170, 115-117.
- ROUSH G.C., MEIGS J.W., KELLY J., FLANNERY J.T., BURDO H. (1980). Sinonasal cancer and occupation : A case-control study. Amer. J. Epidemiol., 111, 183-193.
- SAKNYN A.V., SHABYNINA N.K. (1973). Epidemiology of malignant neoplasms at nickel plants. Gig. Tr. Prof. Zabol., 9, 25-29.
- SANDERS, C.L., JACKSON, T.A., ADEE, R.R. (1971). Distribution of inhaled metal oxide particles in pulmonary alveoli. Arch. Int. Med. 127, 1085-1089.
- SARKAR, B. (1984). Nickel metabolism in : IARC (1984), 367-384.
- SAXHOLM, H.J.K., REITH, A., BROEGGER, A. (1981). Oncogenic transformation and cell lysis in C3H/10T1/2 cells and increased sister chromatid exchange in human lymphocytes by nickel subsulfide. Cancer Res., 41, 4136-4139.
- SAYOTO, Y., NAKAMURO, K., MATSUI, S., TANIMURA, A. (1981). Behaviour and chemical form of nickel in rats administered with ^{63}nickel chloride. J. Pharm. Dyn. 4, 5-73.
- SCHREINER, D.M., KATZ, S.A., SAMITZ, M.H. (1976). Nickel levels in hair and nickel ingestion in guinea pigs. Environ. Res. 12, 355-357.
- SCHROEDER, H.A., BALASSA, J.J., VINTON, W.H. (1964). Chromium, lead, cadmium, nickel, and titanium in mice : effects on mortality, tumours and tissue levels. J. Nutr. 83, 239-250.
- SCHROEDER, H.A., BALASSA, J.J., TIPTON, I.H. (1962). Abnormal trace elements in man - nickel. J. Chron. Dis. 15, 51-65.
- SCHROEDER, H.A. (1970). A sensible look at air pollution by metals. Arch. Environ. Health 21, 798-806.
- SCHROEDER, H.A., MITCHENER, M., NASON, A.P. (1974). Life-term effects of nickel in rats. Survival, tumours, interactions with trace elements and tissue levels. J. Nutr. 104, 239-243.
- SCOTT, B.J., BRADWELL, A.R. (1986a). Metal binding to serum proteins. Protides of the biological fluids : Proc. 31st Colloq, 1983, Oxford, England : Pergamon Press, 15-18 (cited in US, EPA).
- SEN, P., COSTA, M. (1986). Incidence and localisation of sister chromatid exchanges induced by nickel and chromium compounds. Carcinogen., 7, 1527-1533.
- SEN, P., CONWAY, C., COSTA, M. (1987). Comparison of the localisation of chromosome damage induced by calcium chromate and nickel compounds. Cancer Res., 47, 2124-2147.
- SHANNON, H.S., JULIAN, J.A., ROBERTS, R.S., MUIR, D.C.T. (1984). Mortality study of 11500 Falconbridge nickel workers, in : IARC (1984), 117-124.
- SILVERSTEIN, M., MIRER, F., KOTELCHUCK, D., SILVERSTEIN, B., BENNETT, M. (1981). Mortality among workers in a die casting and electroplating plant. Scand. J. Work Environ. Health, Supp. 4., 156-165.
- SINGH, I. (1984). Induction of gene conversion and reverse mutation by manganese sulphate and nickel sulphate in S. cerevisiae. Mutat. Res., 137, 47-49.
- SIROVER, M.A., LOEB, L.A. (1976). Infidelity of DNA synthesis in vitro : screening for potential metal mutagens or carcinogens. Science, 194
- SJOGREN B. (1980). A retrospective cohort study of mortality among stainless steel welders. Scand. J. Work Environ. Health. 6, 197-200.
- SMART, G.A., SHERLOCK, J.C. (1987). Nickel in foods and the diet. Food Addit. Contam. 4, 61-71.
- SMITH, J.C., HACKLEY, B. (1968). Distribution and excretion of nickel-63 administered intravenously to rats. J. Nutr. 95, 541-546.
- SOLOMONS, N.W., VITERI, F., SHULER, T.R., NIELSEN, F.H. (1982). Bioavailability of nickel in man : effects of food and chemically defined dietary constituents on the absorption of inorganic nickel. J. Nutr. 112, 39-50.
- SORAHAN, T, WATERHOUSE J.A.H. (1983). Mortality study of nickel-cadmium battery workers by the method of regression models in life tables. Brit. J. Ind. Med., 40, 293-300.

- SOROHAN, T., BURGES, D.C.L., WATERHOUSE, J.A.H. (1987). A mortality study of nickel/chromium platers. Brit. J. Ind. Med. 44, 250-258.
- SPEARS, J.W., HATFIELD, E.E., FORBES, R.M., KOENIG, S.E. (1978). Studies on the role of nickel in the ruminant. J. Nutr. 108, 313-320.
- SUMINO, K., HAYAKAWA, K., SHIBATA, T., KITAMURA, S. (1975). Heavy metals in normal Japanese tissues. Arch. Environ. Health 30, 487-494.
- SUNDERLAND R.B. (1959). Respiratory cancer mortality in workers employed in an Ontario nickel refinery, covering the period 1930 to 1957. Report of Div. Industr. Hygiene, Ontario. Dept. Health, Environ. Health Scies. Branch, Toronto.
- SUNDERLAND R.B. (1969). Mortality among sinter workers - The International Nickel Co. of Canada Ltd., Copper Cliff smelter. Report of Div. Industr. Hygiene, Ontario Dept. Health, Environ. Health Scies. Branch, Toronto, 22 pp.
- SUNDERLAND R.B. (1971). Morbidity and mortality in selected occupations at the International Nickel Co. Canada Ltd., Copper Cliff, Ontario, 1950 - 1060. Report of Div. Industr. Hygiene, Ontario Dept. Health, Environ. Health Scies. Branch, Toronto, 282 pp.
- SUNDERMAN Jr., F.W., DECSY, M.I., MCNEELY, M.D. (1972). Nickel metabolism in health and disease. Ann. NY Acad. Sci. 199, 300-312.
- SUNDERMAN Jr., F.W., KINCAID, J.F., DONNELLY, A.J., WEST, B. (1957). Nickel poisoning. IV. Chronic exposure of rats to nickel carbonyl : a report after one year of observation. Arch. Ind. Health 16, 480-485.
- SUNDERMAN Jr., F.W., DONNELLY, A.J., WEST, B., KINCAID, J.F. (1959). Nickel poisoning. IX. Carcinogenesis in rats exposed to nickel carbonyl. Arch. Ind. Health 20, 36-41
- SUNDERMAN Jr., F.W. - Panel Chairman (1975). Nickel : Committee on medical and biological effects of environmental pollutants. Nat. Acad. Sci. Washington DC, 82-85
- SUNDERMAN Jr., F.W., KASPRZAK, K.S., HORAK, E., GILITZ, P., ONKELINX, C. (1976). Effects of triethylenetetramine upon the metabolism and toxicity of $^{63}NiCl_2$ in rats. Toxicol. Appl. Pharmacol. 38, 177-188.
- SUNDERMAN Jr., F.W., KASPRZAK, K.S., LAU, T.S., MINGHETTI, P.P., MEANZA, R.M., BECKER, N., ONKELINX, C., GOLDBLATT, P.J. (1976). Effects of manganese on carcinogenicity and metabolism of nickel subsulphide. Cancer Res., 36, 1790-1800.
- SUNDERMAN Jr., F.W. (1977). A review of the metabolism and toxicology of nickel. Ann. Clin. Lab. Sci. 7, 377-398.
- SUNDERMAN Jr., F.W., MAENZA, R.M., ALPASS, P.R., MITCHELL J.M., DAMJANOV, I., GOLDBLATT, P.J. (1978). Carcinogenicity of nickel subsulphide in Fischer rats and Syrian hamsters after administration by various routes. Adv. Exp. Med. Biol. 91, 57-67.
- SUNDERMAN Jr., F.W., ALBERT, D.M., REID, M., DOHLMAN, H.D. (1980). Induction of amelanitoc uveal melanomas in Fischer rats by an intraocular injection of nickel subsulphide. Fed. Proc. (Fed. Amer. Soc. Exp. Biol.) 39, 330-331.
- SUNDERMAN Jr., F.W. (1981). Recent research on nickel carcinogenesis. Environ. Health Persp. 40, 131-141.
- SUNDERMAN Jr., F.W. (1983). Recent progress in nickel carcinogenesis. Toxicological and Environmental Chem. 8, 235-252.
- SUNDERMAN Jr., F.W. (1986). Recent progress in nickel carcinogenisis. Ann. Ist. Super. Sanita, 22, 669-680.
- SUNDERMAN Jr., F.W., AITO, A., MORGAN, L.G., NORSETH, T. (1986). Biological monitoring of nickel. Toxicol. Ind. Health 2, 17-78.
- SUNDERMAN Jr., F.W. (1987). Final report to the NIPERA concerning phase III of research on biological activities of nickel oxides. Farmington, Connecticut, USA.
- SUNDERMAN Jr., F.W., DINGLE, B., HOPFER, S.M., SWIFT, T. (to be publ. 1988). Acute nickel toxicity in electroplating workers who accidentally ingested a solution of nickel sulphate and nickel chloride.
- SUNDERMAN Jr., F.W., COSTA, E.R., FRASER, C., HUI, G., LEVINE, J.S., TSE, T.P.H. ^{63}Nickel-constituents in renal cytosol of rats after injection of ^{63}nickel chloride. Ann. Clin. Lab. Sci. 11, 488-496.
- TANAKA, I., ISHIMATSU, S., MATSUNO, K., KODAMA, Y., TSUCHIYA, K. (1985). Biological half-time of deposited nickel oxide aerosol in rat lungs by inhalation. Biol. Trace Elem. Res. 8, 203-210.

- TANAKA, I., ISHIMATSU, S., MATSUNO, K., KODAMA, Y., TSUCHIYA, K. (1986). Retention of nickel oxide (green) aerosol in rat lungs by long-term inhalation. Biol. Trace Elem. Res. 9, 187-195.
- TANDON, S.K. (1982). Disposition of ^{63}nickel in the rat. Toxicol. Lett. 10, 71-73.
- TATARSKAYA, A.A. (1967). Cancer of the respiratory tract in people engaged in the nickel industry. Vop. Onkol. 13, 58-60, (in Russian).
- THIESS, A.M., OETTEL, H., UHL, C. (1969). Beitrag zur Problematik berufsbedingter Lungenkrebse, Badische Anilin und Soda - Fabrik AG, Ludwigshafen, 11 Zbl. Arbeitsmed. Arbeitssi., 19, 97-113.
- UMEDA, M., NISHIMURA, M., (1979). Inducibility of chromasomal aberrations by metal compounds in cultered mammalian cells. Mutat. Res., 67, 221-229.
- US PUBLIC HEALTH SERVICES (1987). Toxicological profile for nickel : draft for public comment. Agency for Toxic Substances and Disease Registry.
- VALENTINE, R., FISHER, G.L. (1984). Pulmonary clearance of intratracheally administered $^{63}Ni_3S_2$ in strain A/J mice. Environ. Res. 34, 328-334.
- VAN SOESTBERGEN, M., SUNDERMAN Jr., F.W. (1972). ^{63}Ni complexes in rabbit serum and urine after injection of $^{63}NiCl_2$. Clin. Chem. 18, 1478-1484.
- WAKSVIK, H., BOYSEN, M. (1982). Cytogenetic analyses of lymphocytes from workers in a nickel refinery. Mutat. Res., 103, 185-190
- WARNER, J.S. (1984). Occupational exposure to airborne nickel in producing and using primary nickel products, in : IARC (1984), 419-437.
- WARNER, J.S. (1985). Estimating past exposures to airborne nickel compounds in the Copper Cliff Sinter Plant, in : Brown and Sunderman (1985), 203-206.
- WASE, A.W., GOSS, D.M., BOYD, M.J. (1954). The metabolism of nickel I; Spatial and temporal distribution of ^{63}Ni in the mouse. Arch. Biochem. Biophys. 51, 1-4.
- WEAST, R.C., ASTLE, M.J., BEYER, W.H. (1983). CRC Handbook of Chemistry and Physics, 64th ed., CRC Press, Boca Raton Fla, B115-116.
- WEBSTER, J.D., PARKER, T.F., ALFREY, A.C., SMYTHE, W.R., KUBO, H., NEAL, G., HULL, A.R. (1980). Acute nickel intoxication by dialysis. Ann. Int. Med., 92, 631-633.
- WEHNER, A.P., CRAIG, D.K. (1972). Toxicology of inhaled nickel monoxide and cobalt monoxide in Syrian golden hamsters. Amer. Ind. Hyg. Assoc. J. 33, 146-155.
- WEHNER, A.P., BUSCH, R.H., OLSON, R.J., CRAIG, D.K. (1975). Chronic inhaltion of nickel oxide and cigarette smoke by hamsters. Amer. Ind. Hyg. Ass. J. 36, 801-810.
- WEHNER, A.P., MOSS, O.R., MILLIMAN, E.M., DAGLE, G.E., SCHIRMER, R.E. (1979). Acute and subchronic inhalation exposures of hamsters to nickel-enriched fly ash. Environ. Res. 19, 335-370.
- WEHNER, A.P., STUART, B.O., SANDERS, C.L. (1979). Inhalation studies with Syrian Golden hamsters. Prog. Exp. Tumor. Res., 24, 177-198.
- WEHNER, A.P., DAGLE, G.E., MILLIMAN, E.M.(1981). Chronic inhalation exposure of hamsters to nickel-enriched fly ash. Environ. Res. 26, 195-216.
- WEHNER, A.P., DAGLE, G.E., BUSCH, R.H. (1984). Pathogenicity of inhaled nickel compounds in hamsters, in : IARC (1984), 143-151.
- WHANGER, P.D. (1973). Effects of dietary nickel on enzyme activities and mineral contents in rats. Toxicol. Appl. Pharmacol. 25, 323-331.
- WHO (1988). Nickel. Air Quality Guidlines for Europe, WHO Reg. Publ., Europ. Series, 23, 285-296.
- WILLIAMS, S.J., HOLDEN, K.M., SAMRANSKY, M., MENZEL, D.B. (1980). The distribution kinetics of Ni^{2+} in rat lung. Toxicol. Appl. Pharmacol. 55, 85-93.
- WINDHOLZ, M.W. ed. (1983). The Merck Index, 10th edit., Merck & Co., Rahway, NJ, 932-933.
- WULF, H.C. (1980). Sister chromatid exchanges in human lymphocytes exposed to nickel and lead. Danish Med. Bul., 27, 40-42 (Abstract)
- YARITA, T., NETTESHEIM, P. (1978). Carcinogenicity of nickel subsulphide for respiratory tract mucosa. Cancer Res., 38, 3140-3145.
- ZAJAK, M., TS'O, P.O.P. (1980). In vitro neoplastic transformation induced by DNAase I encapsulated in liposomes. Eur. J. Cell Biol. 22, 533.
- ZOBER, A., KICK, K., SCHALLER, K.H., SCHELLMANN, B., VALENTIN, H. (1984). Nickel and chromium content of selected human organs and body fluids. Zbl. Bakt. Hyg., I. Abt. Orig. B, 179, 80-95.

TABLE 1
PHYSICAL AND CHEMICAL PROPERTIES OF NICKEL AND NICKEL COMPOUNDS
(Weast et al, 1983, unless otherwise stated)

Name CAS Number	Synonyms and Formulae	Mol. wt.	Appearance	Density	Mp (°C)	Bp (°C)	Solubility in g/100 ml at 20 °C (d) at 37 °C		
							Water	Blood (rat)	Others
Nickel metal 7440-02-0	Ni	58.71	silver metalic	8.90	1455	2730/ 2920 (a)	<<0.1 (d) 'insoluble'	about 5 (d)	sol.in diluted acids
-hydroxycarbonates 39430-27-8 65404-96-1 (f) 12667-70-4 (f)	-carbonate basic, $2NiCO_3.3Ni(OH)_2.4H_2O$ $NiCO_3.Ni(OH)_2$ $NiCO_3.2Ni(OH)_2$	587.67 211.43 304.16	light green or brown crystals		decomp.	-	$NiCO_3$ 9.10^{-3} (c) 'insoluble'	n.a.	sol.in diluted acids
-hydroxycarbonate 39430-27-8	(Zaratite)$NiCO_3.2Ni(OH)_2.4H_2O$	376.23	green crystals	2.6		-	'insoluble'	n.a.	sol.in ammonia and diluted acids
-carbonate 3333-67-3	$NiCO_3$	118.72	light green crystals	n.a.	decomp.	-	$9.3.10^{-3}$ 'insoluble'	n.a.	sol. in acids
-chloride 7718-54-9 (Hexahydrate: 7791-20-0)	$NiCl_2$	129.62	yellow crystals (Hexahydrate: green	3.55	1001	973 (subl)	64.2	n.a.	sol.in alcohol, NH_4OH
-nitrate 13183-45-9 (Hexahydrate: 13478-00-7)	$Ni(NO_3)_2.6H_2O$	290.81	green crystals	2.05	56.7	136.7	238.5	n.a.	sol.in alcohol, NH_4OH
-oxide 1313-99-1*	(Bunsenite)NiO Nickelmonoxide	74.71	green, grey or black crystals	6.67	1984	-	1.0-1.3. 10^{-3} (c) 'insoluble'	about 2.10^{-3} (d)	sol.in acids, NH_4OH
-(III)oxide 1314-06-3* (Monohydrate?)	-sesquioxide $Ni_2O_3.H_2O$	183.44	black crystals α, β and γ form	3.2- 3.9 (e)	decomp.	-	'insoluble'	n.a.	
-(IV)oxide 12035-36-8	NiO_2	90.71	Not isolated. Occurs in the active mass of nickel positive plates when these are charged						
-hydroxide 12054-48-7	$Ni(OH)_2$	92.72	green, crystalline or amorphous	4.15	230 decomp.	-	13 x 10^{-3} 'insoluble'	n.a.	Sol. in acids, NH_4OH
-sulphate 7786-81-4 (Hexahydrate: 10101-97-0)	$NiSO_4$	154.78	yellow crystals (Hexahydrate: α-form blue, β-form green) (b)	3.68 (b)	848 decomp.	-	29.3	n.a.	Heptanydrate sol.in alcohol
-sulphide 16812-54-7*	(Millerite: crystalline) NiS	90.77	black crystals or amorphous solid	5.3- 5.65	797	-	$3.6.10^{-4}$ 'insoluble'	n.a.	sol.in HNO_3, KHS
-subsulphide 12035-72-2*	(Heazlewoodite) Ni_3S_2	240.26	Yellowish metallic solid, $\alpha$and β-forms	5.82	790	-	α-form: about 0.7 (d) 'insoluble'	α-form about 5 (d)	sol.in HNO_3
-carbonyl 13463-39-3	Nickeltetra-carbonyl $Ni(CO)_4$	170.75	colourless highly flammable liquid	1.32	-19 (b) -25	43	$1.8.10^{-2}$ 'insoluble'	n.a.	sol.in some org. solvents HNO_3

(a) Greenwood & Earnshaw, 1984 (b) Windholz, 1983 (c) Landolt-Boernstein, 1962 (d) Andersen et al, 1980
(e) Gmelin, 1966 (f) CEC, 1987

* All the different forms have been allocated to the same CAS Number, although differences in appearance, physical data and sometimes toxicological behaviour exists.

n.a. : no data available

The names of the naturally occurring minerals are given in brackets.

TABLE 2
ACUTE TOXICITY (Oral)

(Fairhurst and Illing, 1987, unless otherwise stated)

Compound	Species	LD50 mg/kg	Expressed as Ni	Remarks
nickel metal	rat	>9000	>9000	powder (Mastromatteo 1986)
nickel(II)oxide	rat	>5000	>3930	50%(w/v)suspension in mineral oil; diarrhoea
(green)	rat	>5000	>3930	(Mastromatteo 1986)
(black)	rat	>5000	>3930	(Mastromatteo 1986)
nickel(III)oxide	rat	>5000	>3548	50%(w/v) suspension in mineral oil; decreased activity, ataxia, diarrhoea
nickel(IV)oxide				no relevant data
nickel hydroxide	rat M	1500	915	50%(w/v) suspension in water
	F	1700	1037	decreased activity, ataxia, diarrhoea
nickel carbonate ($NiCO_3$. x H_2O)	rat M	1305		50%(w/v) suspension
	F	840		in mineral oil; decreased activity, ataxia, diarrhoea; 18.8% H2O (Mastro-matteo 1986)
nickel subsulphide (crystalline)	rat	>5000	>3663	50%(w/v)suspension in mineral oil; diarrhoea
(amorphous)	rat	>5000	>3663	aqueous slurry; no signs of intox-ication
nickel sulphide (amorphous)	rat	>5000	>3233	(Mastromatteo 1986)
nickel sulphate	rat	500	112	50% aqueous solution
	rat M	325	73	50% aqueous solution
	F	275	61	50% aqueous solution
(hexahydrate)	rat	300	67	U.S.1987
nickel chloride	rat M	430	105	vehicle not given;
	F	529	129	excitation and increased motor activity, followed by depression of the nervous system
	rat M	210	51	50%(w/v) aqueous solution;
	F	175	42	decreased activity, ataxia, salivation, swollen limbs

TABLE 2 continued (Inhalation)

Compound	Species	LC50 mg/m3	Expressed as Ni	Remarks
nickel carbonyl	rat	240		exposure duration: 30 min. pneumonitis with atelectasis and necrosis; spleens had focal necrosis and degeneration of the reticulum; glomerular and tubular degeneration of kidneys; degeneration of acinar cells and islets of Langerhans in the pancreas (Kincaid et al, 1953)
	rat	250		no further details.
	rat	400		30 min. exposure; (Kincaid et al, 1953)
	rat	100		20 min. exposure (Ghiringhelli 1957)
	mouse	67		30 min. exposure; (Kincaid et al, 1953)
	mouse	100		10 min. exposure; (Kincaid et al, 1953)
	cat	1900		30 min. exposure; (Kincaid et al, 1953)

TABLE 3

SHORT TERM TOXICITY (Fairhurst and Illing 1987, unless otherwise stated)

Compound	Dose and route of administration	Duration	Species	Results
Ni-carbonate	0, 250, 500 & 1000 ppm in the diet	8 weeks	rat	no significant effect on bodyweight
Ni-carbonate	0, 62.5, 250, & 1000 ppm in the diet	8 weeks	dairy calves	reduced feed consumption & reduced bodyweight gain at 250 & 1000 ppm, reduced lung, spleen liver, gall bladder & testis weights at 1000 ppm, histopathology showed progressive kidney lesions, culminating in pyelonephritis
Ni-carbonate	0, 250, 500 & 1000 ppm in the diet	24 weeks	monkey	no effect on bodyweight or haematological parameters
Ni-carbonyl	from 0.016 increasing to 0.19 mg/l by inhalation	10 exposures during 48 days, 30 min. each	rat mouse	one death, following 9th exp.; no changes in haematology (Kincaid et al, 1953) no deaths, although exp. 6 & 7 were equal to LC50 for mice, cumulative dose neither caused any deaths (Kincaid et al, 1953)

TABLE 3 continued

Compound	Dose and route of administration	Duration	Species	Results
Ni-carbonyl	from 0.016 increasing to 0.19 mg/l by inhalation	10 exposures during 48 days 30 min. each	cat	1 animal ill after 1st exp., but signs of intoxication after further exp. (Kincaid et al, 1953)
Ni-chloride	0 & 20 ppm Ni in the diet	28 days) 42 days)	rat) rat)	decreased weight gain & slightly lowered haemoglobin levels at day 42 (NOTE: in these studies groups of rats were given additional copper in the diet; only effects pertinent to the nickel-only groups are reported on here)
Ni-chloride	0,5 & 25 ppm Ni on dry weight basis in milk (after day 21 in dry diet	21 days))) 21 + 28 days)	pig (1 day old)	no effect on weight gain, & no biologically significant effects as indicated by clinical chemical or haemotological parameters
Ni-chloride	0, 2.5, 5 & 10 ppm Ni in drinking water	28 days	rat	water consumption increased, body-weight gain decreased at all dose levels; most important was elevated serum glucose at all dose levels
Ni-chloride	0 & 225 ppm Ni in drinking water	4 months	rat	signif. lower final bodyweight, lowered serum cholesterol & triglycerides, urinary volume, zinc & calcium

TABLE 3 continued

Compound	Dose and route of administration	Duration	Species	Results
Ni-chloride	5 ppm in drinking water	10, 20 & 40 weeks) 20 weeks)	rat (12 wk old) rat (10 m old))	no gross or histological changes of prostate, zinc content of the nuclei of the prostate was increased, plasma testosterone level not significantly altered
Ni-chloride	0,0.2, 1, 5 & 50 µg Ni/m^3 inhalation as aqu. aerosol, 1-5 µm	6 months continuously	rat	weight gains were depressed at the 5 & 50 µg levels & increased at 1 µg; haemotology & bone marrow cytology normal; biochemistry indicated effects on various enzyme concentrations, mainly at 5 & 50 µg levels; morphological changes were observed in lung and thyroid gland, no details given
Ni-chloride	0 & 0.3 ± 2 mg Ni/m^3 inhalation by aerosol 81% 0.1-2.0 µm	6h/d, 5d/wk, 4-6 weeks	rabbit	reduced lyosome levels in lung lavage fluid
Ni-chloride	0, 0.43 ± 0.23 & 0.23 ± 0.16 mg Ni/m^3 inhalation by aerosol 0.1-2.0 µm	6h/d, 5d/wk, 4-6 weeks	rabbit	effects on lung macrophages both functional and morphological; thickened alveolar septa
Ni-oxide	0.001, 0.005, 0.05 & 0.5 mg Ni/m^3 by inhalation, 84% < 3.5 µm	3 months continuously	rat	clinical chemical & haemotological parameters measured, changed during the study but most returned to normal values; histology revealed dust foci & fatty degeneration in the lung & renal calculi in the kidney; minimal effect level : 0.005 mg/m^3

TABLE 3 continued

Compound	Dose and Route of administration	Duration	Species	Results
Ni-oxide	0, 0.8, 1.6, & 3.2 mg Ni/m^3 by inhalation, < 1 um	21 days continuously	rat	bodyweight gain & liver weight reduced, lung weight increased at all levels, most signif. changes in haemotology were decreased numbers of erthrocytes but elevated haemoglobin levels in the 1.6 & 3.2 mg/m^3 groups; increased numbers of leucocytes at 0.8 & 1.6 mg/m^3 & lowered at the 3.2 mg/m^3 level urea in urine was elevated in the 0.8 mg/m^3 group
Ni-oxide	0, 0.2, 0.4, & 0.8 mg Ni/m^3, < 1 um, by inhalation	28 days continuously	rat	reduced bodyweight gain & increased lung & liver weights at all dose levels; from the mainly minor haematological changes, the reduction in leucocyte numbers at the 0.8 level only is noteworthy; no significant biochemical changes
Ni-oxide	0, 0.2, 0.4, & 0.8 mg Ni/m^3 by inhalation	120 days continuously	rat	reduced body & relative kidney weights increased lung weight at all dose levels increased number of erythrocytes at the 0.8 level and decreased number of leucocytes at 0.4 & 0.8 level; minor biochemical changes; histopathology revealed fibrosis of the lung and granular degeneration of kidney tubules, dose levels not given
Ni-oxide	0, 1.1, & 5.5 mg Ni/m^3, 1.2 ± 2.2 um, by inhalation	6h/d, 5d/wk, 1 month	rat	only hisopathological changes were dose-related macrophage exudates in alveoli of the lung & interstitial pneumonitis; on electron microscopy macrophages were found to contain NiO particles

TABLE 3 continued

Compound	Dose and Route of administration	Duration	Species	Results
Ni-oxide	0, 0.5 & 6.3 mg Ni/m^3, 1.2 ± 2.2 µm, by inhalation	6h/d, 5 d/wk, 1 mth, 12 mth recovery	rat	histopathology indicated interstitial pneumonia/squamous metaplasia in 2/5 of the 6.3 mg/m^3
Ni-oxide	0, 0.5 & 6.3 mg Ni/m^3, 1.2 ± 2.2 µm, by inhalation	6h/d, 5 d/wk, 1 mth, 24 mth recovery	rat	histopathology indicated interstitial pneumonia amd bronchial gland hyperplasia in all test animals, & squamous metaplasia in 3/8 of the 6.3, 3/6 of the 0.5 mg/m^3 & 2/5 of the control group. (See also Chapter H.)
Ni-oxide	0, 0.9, 2.0, 3.9, 7.0 mg Ni/m^3 calcined at 1350 °C by inhalation	6h/d, 5 d/wk, 12 days	rat and mouse	no mortality; lesions of the lung primarily at the highest concentration; Ni burden in lung increased with concentration (Dunnick et al, 1988)
Ni-oxide	0, 0.6, 1.2, 2.5, 5 & 10 mg/m^3, NiO calcined at 1350 °C by inhalation	6h/d, 5d/wk, 13 weeks	mouse	weight gain depressed; histopathology, lung lesions: alveolar macrophage hyperplasia & perivascular lymphocytic infiltration at 2.5 mg/m^3 and greater; inflammation at 10 mg/m^3 (Hobbs et al, 1988)
Ni-oxide	0, 0.6, 1.2., 2.5, 5 & 10 mg/m^3, NiO calcined at 1350 °C by inhalation	6h/d, 5d/wk 13 weeks	rat	no signif. change in weight gain; histopathology, lung lesions : alveolar macrophage hyperplasia & perivascular lymphocytic infiltration at 1.2 mg/m^3 and greater; inflammation at 2.5 mg/m^3 and greater (Hobbs et al, 1988)

TABLE 3 continued

Compound	Dose and Route of administration	Duration	Species	Results
Ni-subsulphide	0, 0.4, 0.9, 1.8, 3.6 & 7.3 mg Ni/m^3	6h/d, 5d/wk, 12 days	rat and mouse	depresson of body weight gain; mortality at 7.3 mg/m^3 in mice not rats, at 0.9 mg/m^3 and higher inflammatory lesions of lungs and nasal cavity; nickel burden of lungs increased with concentration (Dunnick et al, 1988)
Ni-subsulphide	0, 0.15, 0.3, 0.6 1.2 & 2.5 mg/m^3 by inhalation, mmd 2.4 µm	6h/d, 5d/wk, 13 weeks	rat	histopathology, inflammatory lung lesions : at 0.15 mg/m^3 and higher; further dose-related lesions in nose (atrophy of olfactory epithelium), lung-associated lumph nodes, forestomach & thymus (Hobbs et al, 1987)
Ni-subsulphide	0, 0.15, 0.3, 0.6 1.2 & 2.5 mg/m^3 by inhalation, mmd 2.4 µm	6h/d, 5d/wk, 13 weeks	mouse	histopathology, inflammatory lung lesions : at 0.6 mg/m^3 & higher; further dose-related lesions in nose (atrophy of olfactory epithelium), lung-associated lymph nodes, forestomach & thymus (Hobbs et al, 1987)
Ni-sulphate	100 mg/kg/day & 250 mg/kg/day by oral gavage	20 days on day 21	rat	animals ceased to gain weight, clinical chemistry revealed 35% reduced blood cholinesterase activity, on from wk 2, 40% elevated blood glucose & 19% reduced serum proteins; histopathology showed parenchymal dystrophy in liver & kidney, & focal thickening of interalveolar septa of lung

TABLE 3 continued

Compound	Dose and Route of administration	Duration	Species	Results
Ni-sulphate	0, 0.0005, 0.005, 0.05, 0.5 & 5.0 mg Ni/kg/day by oral gavage	7 months	rat	significant lack of weight gain at 5.0 mg/kg the only histopathological changes were in the intestines at the 5.0 mg/kg dose, consisting of extensive proliferation of lymphoid cells & histiocytes & micronecrosis
Ni-sulphate	5.0 & 10.0 mg/m^3 dust inhalation	4h/d, 7d/wk, 9 months	rat	less bodyweight gain at 5.0 mg/m^3, histological effects in lung, liver & kidney, which were minimal at 5.0 mg/m^3 level. Poorly reported study.
Ni-sulphate	0, 3.5, 7.0, 15, 30 & 60 mg hexahydrate/m^3 by inhalation	6h/d, 12 days	rat	10/15 died during exposure to 15, 30, & 60 mg/m^3; laboured respiration, emaciation, dehydration & lethargy, red discharge from nose; lung weights of animals that died during exposure increased, lung/brain weight ratios at 3.5 mg/m^3 & above were increased; thymus/brain ratios at 7.0 mg/m^3 & above increased; histopathology of the lung revealed inflammation, less severe in survivors, nasal lesions incl. degeneration of respiratory epithelium & atrophy of the olfactory epithelium were present at all dose levels; lymphocytes in bronchial & mediastinal nodes in survivors either decreased (high exp.) or increased (lower exp.); male survivors at 60 mg/m^3 level showed degeneration of germinal epithelium of the testis (Benson et al, 1988a; Dunnick et al, 1988)

TABLE 3 continued

Compound	Dose and Route of administration	Duration	Species	Results
Ni-sulphate	0, 3.5, 7.0, 15, 30 & 60 mg hexahydrate/m^3 by inhalation	6h/d, 12 days	mouse	all died during exposure to 7.0, 15, 30, & 60 mg/m^3; laboured respiration, emaciation, dehydration & lethargy; lung weights of animals that died during exposure were increased, lung/brain weight ratios at 3.5 mg/m^3 & above were increased; thymus/brain ratios at 7.0 mg/m^3 & above increased; histopathology of the lung revealed inflammation, less severe in survivors, olfactory lesions only at 0, 3.5 & 7.0 mg/m^3 levels (Benson et al, 1988a; Dunnick et al, 1988)
Ni-sulphate	0, 0.12, 0.25, 0.50, 1.0 & 2.0 mg hexahydrate/m^3 by inhalation	6h/d, 5d/wk, 13 wk	rat	histopathology: lung lesions included necrotising pneumonia & degeneration of bronchiolar epithelium; atrophy of olfactory epithelium of the nose (Benson et al, 1988b)
Ni-sulphate	0, 0.12, 0.25, 0.50, 1.0 & 2.0 mg hexahydrate/m^3 by inhalation	6h/d, 5d/wk, 13 wk	mouse	histopathology: lung lesions included focal chronic inflammation with focal fibrosis, chronic active pneumonia infiltrates in the interstition, alveolar macrophage hyperplasia; atrophy of olfactory epithelium of the nose (Benson et al, 1988b)

TABLE 4

SUMMARY OF ANIMAL CARCINOGENICITY STUDIES WITH NICKEL COMPOUNDS

Compound	Route of administration	Species	Results with Respect to Carcinogenicity	Authors
Ni-metal	Subcutaneous implants	Rat	Sarcomas at implantation site	Mitchell et al (1960)
Ni-metal	Intra-muscular	Rat	Rhabdomyosarcomas at injection site	Heath and Daniel (1964)
Ni-metal	Intra-femoral and subcutaneous	Rat	Sarcomas at injection site	Heuper (1952 and 1955)
Ni-metal	Intra-venous, intra-peritoneal and intra-muscular	Mouse	No tumours induced	Heuper (1955)
Ni-metal	Inhalation	Rat, Mouse Guinea pig	Proliferative lung lesions in rats and guinea pig - inconclusive with respect to carcinogenicity	Heuper (1958)
Ni-metal	Inhalation	Rat	No tumours induced	Kim (1969)
Ni-metal	Intra-thoracic	Rat	Mesotheliomas	Furst and Cassetta (1973); Furst, Cassetta and Sasmore (1973)
Ni-metal	Intra-peritoneal	Rat	Tumours (unspecified)	Furst and Cassetta (1973)
Ni-metal	Intra-peritoneal	Rat	Sarcomas of abdominal cavity	Pott et al (1987)

TABLE 4 continued

Compound	Route of administration	Species	Results with Respect to Carcinogenicity	Authors
Ni-metal	Intra-muscular	Rat and Hamster	Sarcomas at injection site	Furst and Schlauder (1971)
Ni-metal	Intra-tracheal	Rat	Carcinomas of the lung	Pott et al (1987)
Ni-metal	Inhalation	Rat and Hamster	No tumours induced	Heuper and Payne (1962)
NiO	Intra-muscular	Rat and Mouse	Sarcomas at injection site	Gilman (1962)
NiO (black)	Intra-muscular	Rat	Sarcomas at injection site	Sunderman (1987)
NiO (green)	Intra-muscular	Rat	No tumours induced	Sunderman (1987)
NiO (green	Intra-peritoneal	Rat	Sarcomas of abdominal cavity	Pott et al (1987)
NiO (green)	Intra-tracheal	Rat	Carcinomas of the lung	Pott et al (1987)
NiO (black)	Inhalation	Hamster	No tumours induced	Wehner et al (1975, 1979, 1984)
NiO	Inhalation	Rat	Inconclusive - design inadequate	Horie et al (1985)
NiO**	Inhalation	Rat	No tumours induced but poor survival	Glaser et al (1986)
$Ni(OH)_2$	Intra-muscular	Rat	Sarcomas, mainly rhabdomyosarcomas at injection site	Kasprazak et al (1983)
$NiSO_4$	Diet	Rat	No tumours induced, poor survival	Ambrose et al (1976)

TABLE 4 continued

Compound	Route of administration	Species	Results with Respect to Carcinogenicity	Authors
$NiSO_4$	Intra-muscular	Rat	No tumours induced	Kasprazak et al (1983)
$NiSO_4$	Inhalation	Rat	No tumours induced but duration too short	Kosova (1979)
$NiSO_4 6H_2O$	Intra-muscular	Rat	No tumours induced	Gilman (1962)
Ni_3S_2	Intra-muscular	Rat	Sarcomas, mainly rhabdomyosarcomas at injection site	Kasprazak et al (1983)
Ni_3S_2	Intra-muscular	Rat	Sarcomas at injection site	Daniel (1966)
Ni_3S_2	Intra-testicular	Rat	Testicular sarcoma	Damjanov et al (1978)
Ni_3S_2	Intra-tracheal	Mouse	No tumours induced	Fisher et al (1986)
Ni_3S_2	Intra-muscular	Rat	Rhabdomyosarcomas at injection site	Gilman et al (1966)
Ni_3S_2	Intra-muscular implant	Rabbit	Rhabdomyosarcomas at implantation site	Hildebrand and Biserte (1979)
Ni_3S_2	Intra-muscular implant	Rat	Rhabdomyosarcomas at implantation site	Hildebrand and Biserte (1978)
Ni_3S_2	Intra-muscular implant	Rat	Rhabdomyosarcomas at injection site	Kasprazak et al (1985)
Ni_3S_2	Intra-muscular implant	Rat	Sarcomas at implantation site	Lunde et al (1985)
Ni_3S_2 (+3,4-Benz-pyrene)	Intra-muscular implants	Rat	Sarcomas at implantation site	Maenza et al (1971)

TABLE 4 continued

Compound	Route of administration	Species	Results with Respect to Carcinogenicity	Authors
Ni_3S_2	Intra-ocular	Japanese common newt	Malignant melanoma-like tumours of the eye	Okamoto (1987)
Ni_3S_2	Intra-muscular, subcutaneous	Mouse	Sarcomas at injection sites	Oskarsson et al (1979)
Ni_3S_2	Intra-muscular	Rat and Mouse	Sarcomas at injection site	Gilman (1962)
Ni_3S_2	Intra-muscular, cheek pouch, oral cavity and GI tract	Hamster	Tumours after intra-muscular injection only	Sunderman et al (1978)
Ni_3S_2	Subcutaneous	Rat	Malignant tumours at injection site	Lumb et al (1987)
Ni_3S_2	Intra-peritoneal	Rat	Sarcomas of abdominal cavity	Pott et al (1987)
Ni_3S_2	Intra-testicular	Rat	Testicular sarcomas	Sunderman et al (1978)
Ni_3S_2	Intra-hepatic	Rat	No tumours induced	Sunderman et al (1978)
Ni_3S_2	Intra-renal	Rat	Renal tumours (anaplastic, spindle cell and rhabdomyosarcomas)	Sunderman et al (1979)
Ni_3S_2	Intra-ocular	Rat	Ocular melanomas	Sunderman et al (1980)
Ni_3S_2	Tracheal implants	Rat	Sarcomas and carcinomas at implantation site	Yarite and Wettesheim (1978)
Ni_3S_2	Intra-tracheal	Rat	Carcinomas of the lung	Pott et al (1987)

TABLE 4 continued

Compound	Route of administration	Species	Results with Respect to Carcinogenicity	Authors
Ni_3S_2	Inhalation	Rat	Carcinomas of the lung	Ottolenghi et al (1974)
'Ni-sulphide'	Intra-muscular	Rat	Rhabdomyosarcomas at injection site	Jasmin (1963)
'Ni-sulphide'	Intra-muscular	Rat	Rhabdomyosarcomas at injection site	Basrur et al (1970)
'Ni-sulphide'	Intra-muscular implant	Rat	Rhabdomyosarcoma at implantation site	Herchen and Gilman (1964)
'Ni-sulphide'	Intra-muscular injection	Rat	Rhabdomyosarcoma at injection site	Noble and Capstick (1963)
'Ni-sulphide'	Intra-muscular and subcutaneous	Rat	Sarcomas at injection site	Mason (1972)
$Ni(CO)_4$	Intra-venous (multiple)	Rat	Various sarcomas	Lau et al (1972)
$Ni(CO)_4$	Inhalation	Rat	Inconclusive	Sunderman et al (1957, 1959)
$Ni(CO)_4$	Inhalation	Rat	Inconclusive	Sunderman and Donnelly (1965)

TABLE 5
SUMMARY OF EPIDEMIOLOGICAL STUDIES

Location	First Author	Year Published	Industry	Start of Process (Year)	No. of Workers	Findings - Comments
INCO Clydach Wales	Morgan	1958	Refining of matte, production of Ni pellets Ni&Cu salts	1900	2094	Increased incidence of nasal and lung cancers in those beginning before 1925. Risk area : calcination furnace, $CuSO_4$ & $NiSO_4$
	Doll	1958	Refining of matte, production of Ni pellets Ni&Cu salts	1900		Increased lung & nasal cancers
	Doll	1970	Refining of matte, production of Ni pellets Ni&Cu salts		845	Nasal 1900-24 SMR 36448 1925-29 SMR - 1930-44 SMR - Lung 1900-24 SMR 750 1925-29 SMR 176 1930-44 SMR 152
	Doll	1977	Refining of matte, production of Ni pellets Ni&Cu salts	1900	967	Nasal 1900-24 SMR 24852 1925-29 SMR - 1930-44 SMR - Lung 1900-24 SMR 697 1925-29 SMR 249 1930-44 SMR 146
	Morgan	1979	Carbonyl workers	1933	84	Nasal nil cases No excess of pulmonary cancer

TABLE 5 continued

Location	First Author	Year Published	Industry	Start of Process (Year)	No. of Workers	Findings - Comments
	Cuckle	1980	Soluble Nickel & Cobalt salts	1939	297	No nasal cancer Lung SMR 172 (Local rates)
	Peto	1983	Refining of Matte Production of Ni Pellets Ni & Cu salts	1939	967	Nasal 1900-24 SMR 28000 1925-29 SMR - 1930-44 SMR - Lung 1900-24 SMR 507 1925-29 SMR 200 1930-44 SMR 121
INCO Canada	Sutherland Port Colborne	1959	Nickel refining Ni & Cu Sulphides	1930	2355	Nasal SMR 3684 Lung SMR 225
	Sutherland Copper Cliff	1969	Sinter plant	1948	483	Nasal 1 case Lung SMR 897
Canada Sudbury	Roberts	1984	Sinter plant	1944	2482	Nasal SMR 2174 Lung SMR 462
			Non sinter plant	circa 1900	47954	Nasal SMR 144
		1988				Lung SMR 108
			Miners			Lung SMR 112
Port Colborne	Roberts	1984	Leaching, calcining, and sintering	1930)	4288	Nasal SMR 9412 Lung SMR 298
			Non leaching, calcining and sintering	1930)		Nasal SMR 625 (1 case) Lung SMR 78
FALCO Canada	Shannon	1984	Mining & refining	1930	11594	Nasal nil cases Lung SMR 123

TABLE 5 continued

Location	First Author	Year Published	Industry	Start of Process (Year)	No. of Workers	Findings - Comments
FALCO Norway	Pedersen	1973	Refining and electrolysis	1930	1916	Nasal SMR 800 Lung SMR 475
	Magnus	1982	Refining and electrolysis	1930	2247	Nasal SMR 4000) Roasting Lung SMR 360) Nasal SMR 2670) Electrolysis Lung SMR 550)
SHERIT GORDON Canada	Egedahl	1984	Hydrometallurgical refining	1954	1643	Nasal 0 Cases Lung SMR 83
HANNA USA	Cooper	1981	Refining of lateritic ores	1954	1307	Nasal 0 Cases Lung SMR 112
INCO USA.	Enterline	1982	Refining and manufacture of Ni alloy	1922	1855 (266 Refinery)	Nasal SMR 2443 Lung SMR 139 Nasal 0 Cases Lung SMR 105
USA	Redmond	1984	Production high nickel alloys	-	28261	Nasal nil cases Lung SMR 120 (Maint. Wkrs.)
INCO Hereford UK	Cox	1981 1986	Production of nickel alloys	1952	1925	Nasal 1 case Lung SMR 98 Nasal 1 case Lung SMR 87
USA Hertford	Bernacki	1978	Production of aero engines	?	42	Nasal nil cases Lung SMR <100 (Case control study)

TABLE 5 continued

Location	First Author	Year Published	Industry	Start of Process (Year)	No. of Workers	Findings - Comments
USA	Cornell	1984	Production of stainless steel & Ni foundry workers	-		Nasal nil cases Lung SMR 105
USA	Cragle	1971	Nickel powder in barrier manufacture	1948	814	Nasal nil cases Lung SMR 59
UK	Sorahan	1983	Nickel-Cadmium battery manufacture (joint exposure)	1983	3025	Nasal nil cases Lung SMR 127
Sweden	Sjogren	1980	Stainless steel welders	-	234	Lung SMR 440
SLN New Caledonia	Lessard	1978	Lateritic mining & refining	1850	-	Nickel workers relative risk lung cancer 3 (significant)
	Goldberg	1987	Lateritic mining & refining	1850	-	Nickel workers relative risk URT cancer 1.4 (not significant) (3 cases) lung cancer 0.9 (not significant)
UK	Burgess	1988	Chrome & Nickel platers	1946	2689	Lung SMR 1500

TABLE 6
COMMENTS ON CARCINOGENIC HAZARD OF REFINING PROCESSES
INVOLVING MIXED EXPOSURES TO NICKEL COMPOUNDS *

Process	Remarks	Compounds present	"Classification" of processes **
Matte roasting	Several positive epidemiology studies	Nickel sulphides including nickel subsulphide, copper sulphides, nickel/copper oxides, sulphur dioxide and minor quantities of nickel arsenate, nickel arsenide, arsenic trioxide, nickel sulphate and copper sulphate	Proven human carcinogen
Hybinette process	Single positive epidemiology study	Same compounds as above, additionally nickel chloride and copper chloride	Proven human carcinogen
Manufacture of nickel sulphate from nickel carbonyl process residues (prior to 1936)	Single positive epidemiology study (new data, Easton 1988)	Nickel sulphate, copper sulphate, nickel/copper oxides, nickel metal, cobalt sulphate, cobalt hydroxide, minor quantities of nickel arsenate, copper arsenate and possibly precious metals	Probable human carcinogen
Manufacture of nickel sulphate and nickel metal	Case reports only	$NiSO_4$, Ni, others ?	Possible human carcinogen

* In the nickel user industries and other refining processes epidemiology studies do not indicate a hazard (see Table 5).

** Conclusions reached by the Task Force on the basis of epidemiological data for the "classification of processes", if this was possible

TABLE 7
POSSIBLE CLASSIFICATION OF NICKEL COMPOUNDS FOR CARCINOGENICITY

Compound	Classification	Remarks
Nickel metal (CAS No. 7440-02-0)		
- massive	No classification	No data
- powder	Category 3	Negative epidemiology and negative inhalation studies, in rats, mice, hamsters and guinea pigs. Late onset of lung tumours in the rat after repeated intra-tracheal instillation. No genotoxicity data.
Nickel (II) oxide (NiO) (CAS No. 1313-99-1)	Category 3	Non-specific epidemiology in view of mixed exposure, inhalation studies negative in hamsters and inadequate in rats. Late onset of lung tumours in the rat after repeated intra-tracheal instillation. Inadequate genotoxicity data. A long-term inhalation study in rats and mice is in progress.
Nickel (IV) oxide (NiO_2) (No CAS No.)	No classification	No data. This compound has never been isolated.
Nickel (III) oxide (Ni_2O_3) (CAS No. 1314-06-3)	No classification	No data.
Nickel subsulphide (Ni_3S_2) (CAS No. 1203-72-2)	Category 2	Non-specific epidemiology in view of mixed exposure. Lung tumours induced by inhalation in the rat and by repeated intra-tracheal injection. Inadequate genotoxicity data. A long-term inhalation study in rats and mice is in progress.

TABLE 7 continued

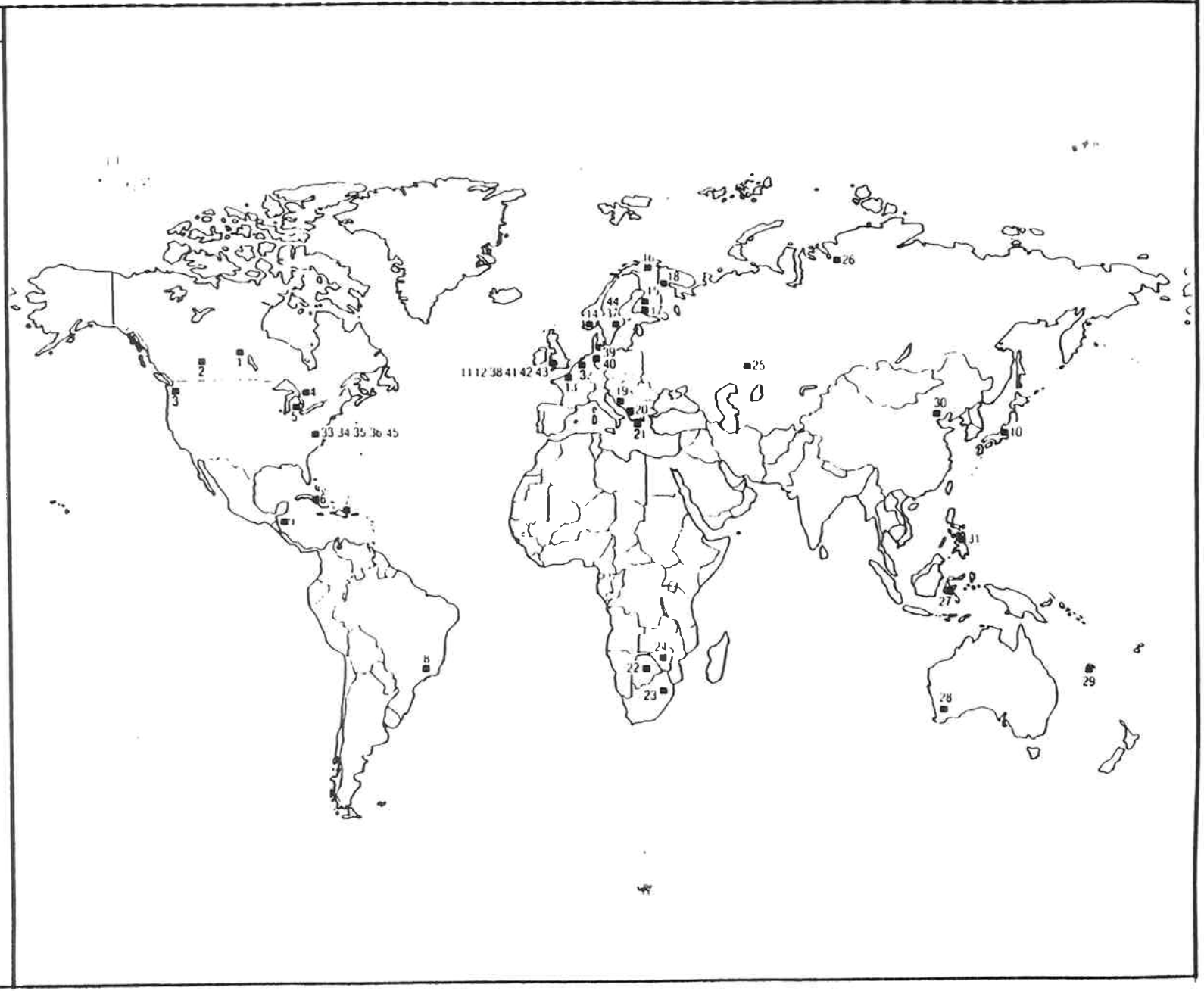
Compound	Recommended Classification	Remarks
Nickel sulphide (NiS) (CAS No. 16812-54-7)	No classification	No relevant data. Sometimes confused with Ni_3S_2 (see Table 4).
Nickel carbonyl ($Ni[CO]_4$) (CAS No. 13463-39-3)	No classification	Inadequate epidemiology. Inadequate evidence of lung tumours following inhalation in the rat. Note that this compound is acutely toxic.
Nickel sulphate ($NiSO_4$) (CAS No. 7786-81-4) - hexahydrate (CAS No. 10101-97-0)	No classification	Non-specific epidemiology in view of mixed exposure (see Table 6). The animal and other supportive data are insufficient alone to warrant a classification. A long-term inhalation study in rodents is in progress.
Nickel chloride ($NiCl_2$) (CAS No. 7718-54-9) - hexahydrate (CAS No. 7791-20-0)	No classification	No relevant data
Nickel nitrate ($NiNO_3$) (CAS No. 13138-45-9) - hexahydrate (CAS No. 13478-00-7)	No classification	No relevant data
Nickel hydroxide ($Ni[OH]_2$) (CAS No. 12054-48-7)	No classification	No relevant data
Nickel carbonate (CAS No. 3333-67-3) and - hydroxycarbonates ($xNiCO_3.yNi[OH]_2.zH_2O$) (CAS No. 39430-27-8 12667-70-4 65404-96-1)	No classification	No relevant data

THE NICKEL MAP

MINES · REFINERIES AND EPIDEMIDLOGICAL STUDIES

KEY

1	Thompson	Canada	M R
2	Fort Saskatchewan	Canada	R
3	Riddle	U S A	M R
4	Sudbury	Canada	M R
5	Port Colborne	Canada	R
6	Moabay	Cuba	M
7	Bonao	Dominican Republic	M
8	Miguel & Paulista	Brazil	M
9	Eximbal	Guatemala	G M
10	Matsusaka	Japan	R
11	Clydach	U K	R
12	Hereford	U K	O
13	Le Havre	France	R
14	Kristiansand	Norway	R
15	Harjavathalla	Finland	R
16	Pechanga	U S S R	M
17	Kotalamti	Finland	M & R
18	Monchegorsk	U S S R	R
19	Kosovo	Yugoslavia	M
20	Tirana	Albania	M
21	Laryinna	Greece	M & R
22	Selebwi-Phikwe	Botswana	M
23	Rustenburg, Springs	South Africa	M & R
24	Bindura	Zimbabwe	M
25	Orsk	U S S R	M & R
26	Nonilsk	U S S R	M & R
27	Soroako	Sulawesi, Indonesia	M & R
28	Kalgoorlie	Australia	M & R
29	Noumea	New Caledonia	M & R
30	Beijing	China	M & R
31	Surigao	Philipines	M
32	Hoboken	Belgium	R
33	Huntington	U S	O
34	Bernacki	U S	O
35	Cornell	U S	O
36	Godbold & Tomkins	U S	O
37	Kjellstrom	Sweden	O
38	Sorohan	U K	O
39	Raithel	Germany	O
40	Becker	Germany	O
41	Jones	U K	O
42	Burgess	U K	O
43	Silverstein	Sweden	O
44	Sjogren	Sweden	O
45	Polednak	U S A	O



M M ... R R ... O Other

Fig. 2

EXTRACTION AND REFINING OF NICKEL AND COMPOUNDS FROM SULPHIDE ORES

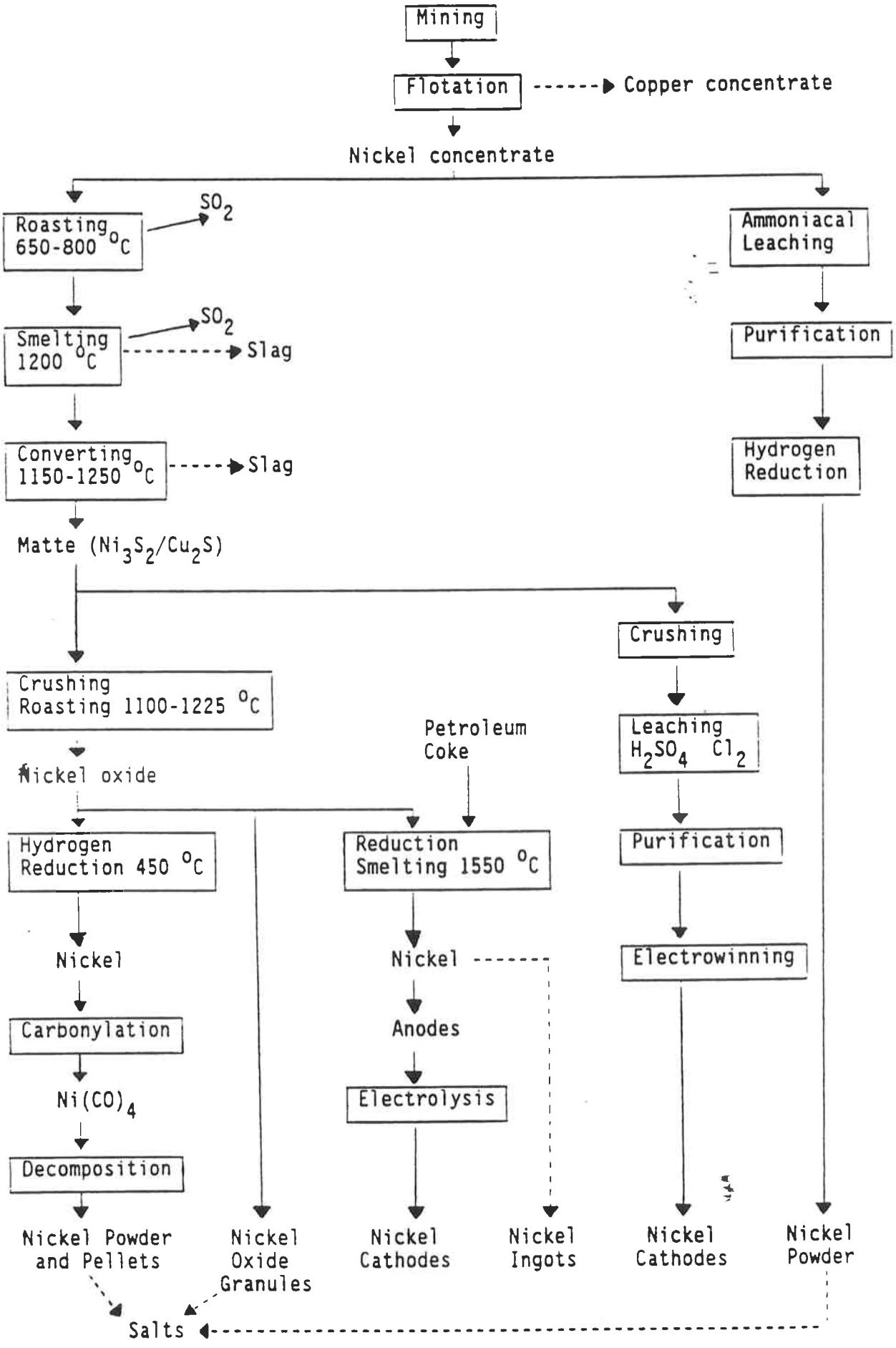


Fig. 3

EXTRACTION AND REFINGING OF NICKEL AND COMPOUNDS FROM LATERITE ORES

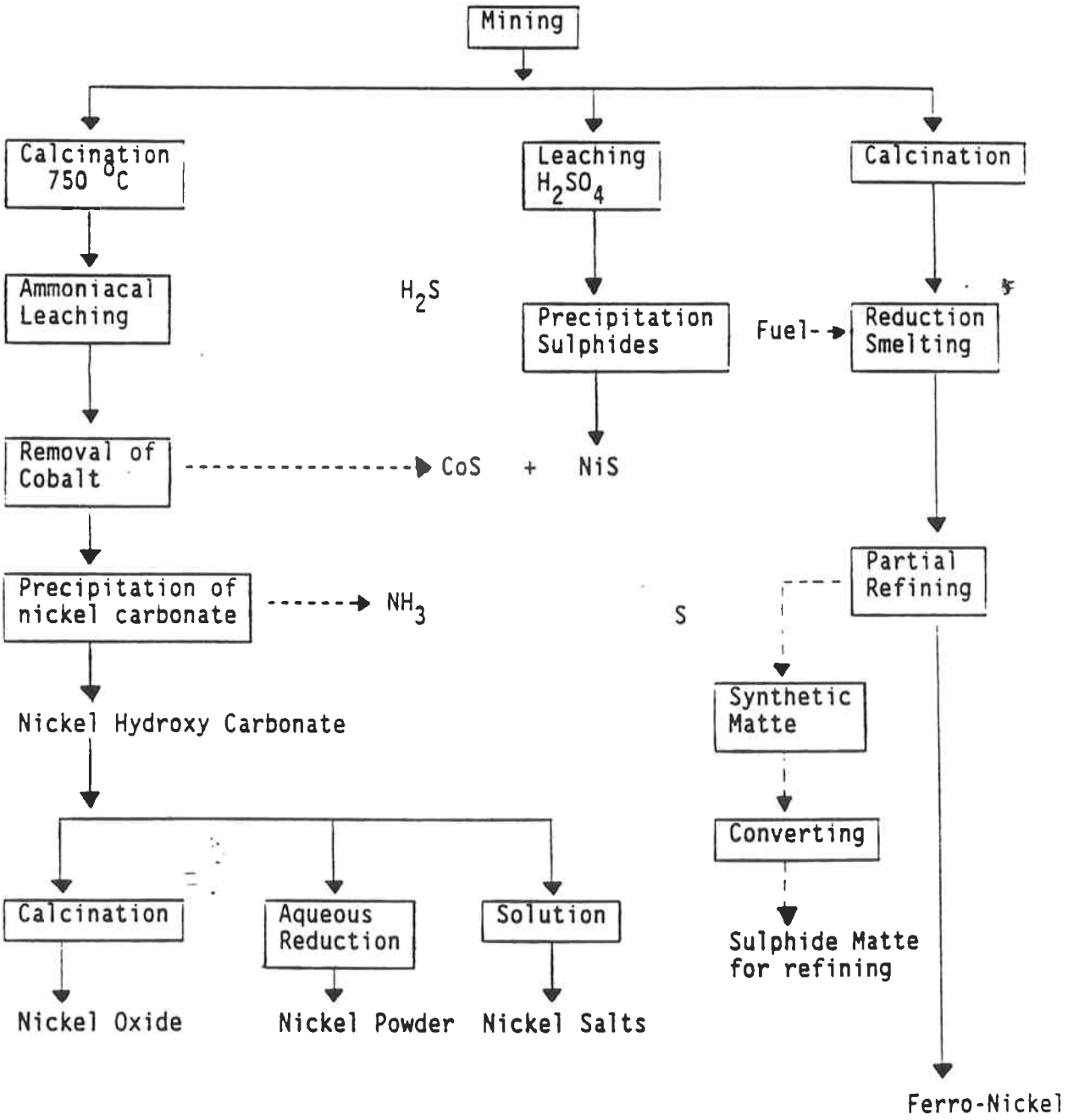
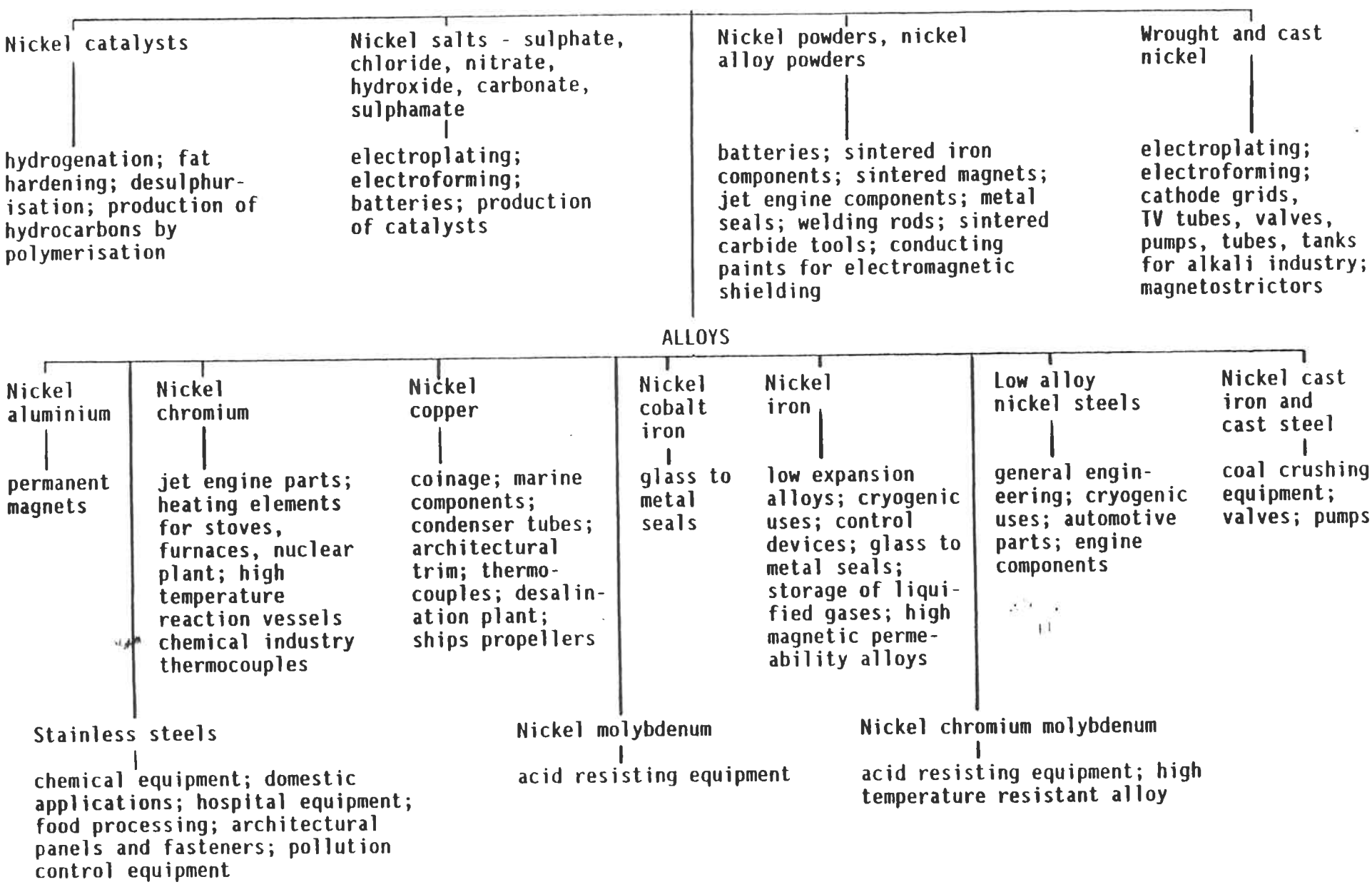


Fig. 4

USAGE OF NICKEL IN INDUSTRY



APPENDIX 1

E.E.C. Criteria for the Classification of Carcinogenic Substances

Category 1

Substances known to be carcinogenic to man. There is sufficient evidence to establish a causal relationship between human exposure to a substance and the development of cancer.

Category 2

Substances which should be regarded as if they are carcinogenic to man. There is sufficient evidence to provide a strong presumption that human exposure to a substance may result in the development of cancer, generally on the basis of :

- appropriate long-term animal studies;
- other relevant information.

Category 3

Substances which cause concern for man owing to possible carcinogenic effects but in respect of which the available information is not adequate for making a satisfactory assessment. There is some evidence from appropriate animal studies, but this is insufficient to place the substance in Category 2.

Recently, a new definition of category 3 has been elaborated (E.E.C., 1988) :

"Category 3 :

Substances which cause concern for man owing to possible carcinogenic effects :

- substances for which some evidence of possible carcinogenic effects exist but this is insufficient to place the substance in Category 2;

- substances in respect of which the available information is not adequate to make a satisfactory assessment, but a carcinogenic potential is suspected. For these substances further research is urgently required.

==========

Comments regarding the categorisation of carcinogenic substances *

The placing of a compound into category 1 is done on the basis of epidemiological data; placing into categories 2 and 3 is based primarily on animal experiments.

For classification as a category 2 carcinogen either positive results in two animal species should be available, or clear positive evidence in one species, together with supporting evidence such as genotoxicity data, metabolic or biochemical studies, induction of benign tumours, structural relationship with other known carcinogens, or data from epidemiological studies suggesting an association.

Category 3 actually comprises two sub-categories :

(a) substances which are well investigated but for which the evidence of a tumour-inducing effect is insufficient for classsification in category 2. Additional experiments would not be expected to yield further relevant information with respect to classification;

(b) substances which are insufficiently investigated. The available data are inadequate, but they raise concern for man. This classification is provisional; further experiments are necessary before a final decision can be made.

For a distinction between categories 2 and 3 the arguments listed below are relevant which reduce the significance of experimental tumour induction in

---

* These comments have been made by the Specialized Experts. The document is still under discussion.

view of possible human exposure. These arguments, especially in combination, would lead in most cases to classification in category 3, even though tumours have been induced in animals :

- carcinogenic effects only at very high dose levels exceeding the "maximal tolerated dose". The maximal tolerated dose is characterized by toxic effects which, although not yet reducing lifespan, go along with physical changes such as about 10% retardation in weight gain;

- appearance of tumours, especially at high dose levels, only in particular organs of certain species known to be susceptible to a high spontaneous tumour formation;

- appearance of tumours, only at the site of application, in very sensitive test systems (e.g., i.p. or s.c. application of certain locally active compounds), if the particular target is not relevant to man;

- lack of genotoxicity in short-term tests in vivo and in vitro;

- existence of a secondary mechanism of action with the implication of a practical threshold above a certain dose level (e.g. hormonal effects on target organs or on mechanisms of physiological regulation, chronic stimulation of cell proliferation);

- existence of a species-specific mechanism of tumour formation (e.g. by specific metabolic pathways) irrelevant for man.

For a distinction between category 3 and no classification the following arguments are relevant which exclude a concern for man :

- A compound should not be classified in any of the categories if the mechanism of experimental tumour formation is clearly identified, with good evidence that this process cannot be extrapolated to man.

- If the only available tumour data are liver tumours in certain sensitive strains of mice, without any other supplementary evidence, the substance may not be classified in any of the categories.

- Particular attention should be paid to cases where the only available tumour data are the occurrence of neoplasms at sites and in strains where they are well known to occur spontaneously with a high incidence."

APPENDIX 2

Nickel Working Party on Epidemiology

In order to try to establish whether it was possible to differentiate between the carcinogenicity of different nickel compounds from the epidemiological data a special working party was set up in January 1985. The Chairman is Sir Richard Doll, the members were the authors of the principle epidemiological studies already carried out and the sponsors' representatives. The working party was sponsored by the EPA (USA), the Canadian Ministry of Health, the Ontario Ministry of Labour, National Health and Welfare Canada, the Directorate-General V of the Commission of the European Communities, and the Nickel Producers' Environmental Research Association. The objective was to update and review all the known studies in a manner in which they could be compared.

APPENDIX 3

Glossary of Terms

Hybinette Process = Process for the electrowinning of nickel involving leaching of calcined matte and electrolysis using impure anodes. It results in a higher proportion of insoluble nickel and copper oxides and sulphides in the tank house atmosphere and the formation of a larger proportion of anode slimes than other nickel electrowinning processes.

Matte = Impure metal sulphide

mmd = mass median diameter (aerodynamic), where aerodynamic means that the diameter of a sphere of density 1 is calculated which has the same sedimentation velocity in air as a median particle of the probe.

PMR = Proportional Mortality Rate: A ratio of the number of deaths from a given cause to the total number of deaths in the same population.

$$PMR = \frac{\text{No. of deaths due to cause}}{\text{Total deaths}} \times 100$$

Sinonasal cancer = Cancer occurring in the nasal passages and in the adjacent sinuses

Sintering = Heating a powder to produce a solid mass. In the nickel refining industry the term was applied to heating a matte powder to produce an oxide in lumpy form.

SMR = Standardised Mortality Ratio: A ratio of the observed number of cases in a given population to the number of cases to be expected from national figures for a population of the same size matched for age and sex (and any other stated variable)

$$SMR = \frac{\text{No. of observed cases}}{\text{No. of expected cases}} \times 100$$

The significance of SMR is dependent upon the number of deaths being studied. A number of confounding factors such as smoking, local variations and habits, social status all tend to influence the SMR. However, a relative risk of 1.5 in a population with 30 deaths would be significant, whereas 400 deaths are needed if a relative risk of 1.1 is to be considered statistically significant.

TRK = Technische Richtkonzentration = technical guiding concentration. It is defined as "that concentration of gas, vapour or airborne particulates which is the minimum possible with current technology ....and which serves as a guidance for necessary protective measures and monitoring of the workplace. TRK values are assigned only for hazardous materials for which MAK values confirmed by toxicological or industrial medical experiences cannot be established at the present time. Adherence to TRK values is intended to reduce the risk of health hazard but cannot completely eliminate it." (DFG, 1988).

APPENDIX 4

Occupational Exposure Limits in Various Countries *

	Ni (mg/m^3)		
Country	Water Insoluble	Water Soluble	Ni-Carbonyl
Australia	1	-	0.007
Belgium	1 (oxides, sulphides)	-	0.7
Bulgaria	0.5	-	-
Canada	1	0.01	0.007
GDR	1 (30') 0.5 (8.75 h)	-	-
Finland	1 (oxides, sulphides)	-	0.007
France	1 (metal - as dust)	-	-
FRG	0.5 **	0.05 respirable droplets **	0.7 **
Italy	1	0.1	0.07
Japan	1	-	0.07
Netherlands	1 (oxides, sulphides)	-	0.007
Norway	0.4	0.4	-
Poland	-	-	0.007
Rumania	-	0.5	-
Sweden	0.01	-	0.007
Switzerland	1 (oxides, sulphides)	-	0.007
UK	0.5	0.1	0.13 (10 mins)
USA	1 (metal) ***	0.1 ***	0.007 ***
USSR	0.05	0.005	0.0005
Yugoslavia	-	0.5	0.007

* Based upon "Forschungsbericht Nickel", 1987, Hauptverband der gewerblichen Berufsgenossenschaft

** "TRK"-values (see Glossary of Terms, p. 107)

*** Presently under revision

APPENDIX 5

Members of the Task Force

J. ISHMAEL (Chairman)	ICI PLC, Alderley Park, UK
J.C. AUBRUN	RHONE-POULENC, Courbevoie, F
E. BOELSMA-VAN HOUTE	SHELL INTERNATIONALE PETROLEUM MIJ, The Hague NL
G. CREMER	VEBA ÖL, Gelsenkirchen-Buer, D
J. GORDON	ICI PLC, Wilton, UK
L. MORGAN	INCO, Swansea, UK
M. RICHOLD	UNILEVER RESEARCH, Sharnbrook, UK
H.J. NIESSEN (Secretary)	ECETOC, Brussels, B

The Task Force wishes to thank Dr. R. Jäckh, BASF, Ludwigshafen, Federal Republic of Germany, for his valuable contributions to Chapter G: Metabolism - Toxicokinetics - Intracellular Availability.

APPENDIX 6

Members of ECETOC Scientific Committee

I.F.H PURCHASE (Chairman), Director, Central Toxicology Laboratory	ICI, Alderley Park UK
M. SHARRATT, (Vice-Chairman), Senior Toxicologist	BP, Sunbury UK
B. BROECKER, Coordinator, Product-Related Environmental Problems	Hoechst, Frankfurt D
H. DE HENAU, Professional and Regulatory Services	Procter and Gamble B
H.O ESSER, Vice Director, Product Safety	Ciba-Geigy, Basel CH
P. GELBKE, Head of Toxicology Department	BASF, Ludwigshafen D
P.A. GILBERT, Environmental Relations Manager	Unilever, Port Sunlight UK
I.J. GRAHAM-BRYCE, Head of Environmental Affairs Division	Shell, The Hague NL
J.R. JACKSON, Director, Medicine and Health Science	Monsanto Europe, Brussels B
S. LUNDBERG, Chief Toxicologist	Nobel Industries, Karlskoga S
R. MILLISCHER, Chief Toxicologist	Atochem, Paris La Defense F
H.G. NÖSLER, Head, Coordination Centre for Environmental Protection and Consumer Safety	Henkel, Düsseldorf D
S. PAGLIALUNGA, Scientific Director Toxicology	Unipro, Milan, I
W.F. TORDOIR, Head of Occupational Health and Toxicology Division	Shell, The Hague NL
H. VERSCHUUREN, Head of Toxicology Department	Dow Chemical, Horgen CH

Responsible editor : D.A. Stringer, ECETOC
Avenue Louise 250, Bte 63
B-1050 Brussels, Belgium