ARBETE OCH HÄLSA vetenskaplig skriftserie

1995:26

The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals

119. Nickel and Nickel Compounds

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Arbetslivsinstitutet
National Institute for Working Life

National Institute for Working Life

The Swedish National Institute for Working Life is the national center for research and development on labour market, working life and work environment. Diffusion of information, training and teaching, local development and international collaboration are other important issues for the Institute.

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Arbete och Hälsa

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ISBN 91-7045-362-4
ISSN 0346-7821
Tryckt hos Graphic Systems

Preface

The Nordic Council is an intergovernmental collaborative body for the five countries, Denmark, Finland, Iceland, Norway and Sweden. One of the committees, the Nordic Senior Executive Committee for Occupational Environmental Matters, initiated a project in order to produce criteria documents to be used by the regulatory authorities in the Nordic countries as a scientific basis for the setting of national occupational exposure limits.

The management of the project is given to an expert group. At present the Nordic Expert Group consists of the following member:

Vidir Kristjansson	National Board of Occupational Health, Iceland
Petter Kristensen	National Institute of Occupational Health, Norway
Per Lundberg (chairman)	National Institute for Working Life, Sweden
Vesa Riihimäki	Institute of Occupational Health, Finland
Adolf Schaich Fries	National Institute of Occupational Health, Denmark

For each document an author is appointed by the Expert Group and the national member acts as a referent. The author searches for literature in different data bases such as Toxline, Medline, Cancerlit and Nioshtic. Information from other sources such as WHO, NIOSH and the Dutch Expert Committee is also used as are handbooks such as Patty's Industrial Hygiene and Toxicology. Evaluation is made of all relevant scientific original literature found. In exceptional cases information from documents difficult to access are used. The draft document is discussed within the Expert Group and is eventually accepted as the Group's document.

An editorial work is performed by the Group's Scientific Secretary, Brita Beije/Gregory Moore, and the technical editing is performed by Ms Karin Sundström, all at the National Institute for Working Life in Sweden.

Only literature judged as reliable and relevant for the discussion is referred to in this document. Concentrations in air are given in mg/m^3 and in biological media in mol/l. In case they are otherwise given in the original papers they are if possible recalculated and the original values are given within brackets.

The documents aim at establishing a dose-response / dose-effect relationship and defining a critical effect based only on the scientific literature. The task is not to give a proposal for a numerical occupational exposure limit value.

The evaluation of the literature and the drafting of this document on Nickel and Nickel Compounds was made by Dr Antero Aitio at the Finnish Institute of Occupational Health in Helsinki. The final version was accepted by the Nordic Expert Group 23 May, 1995, as its document.

Brita Beije/Gregory Moore
Scientific Secretary

Per Lundberg
Chairman

Contents

Nickel and nickel compounds

1. Introduction

Contact dermatitis from nickel exposure was described already in 1889. Other relatively early reports concern nickel carbonyl poisoning in an exposed worker in 1890, two fatalities due to exposure to nickel carbonyl in 1903, and nasal cancer in 1933. Since then the toxicity of nickel and nickel compounds has been extensively studied. Also, several reviews and authoritative national and international evaluations have been published, such as those by the MacMaster University (152) and International Agency for Research on Cancer (IARC) (202) in 1984, British Health and Safety Executive (58) in 1987, U.S. ATSDR in 1991 and 1993 (227, 228) and International Programme on Chemical Safety (IPCS) in 1991 (87) and IARC in 1990 (85). Further important sources of information include Nriagu's review (157), and the series of IUPAC nickel subcommittee meeting proceedings (26, 27, 151). The present review is an effort to update the IPCS and IARC evaluations[1], using the Nordic Expert Group general scheme for criteria documents. Thus, in this document only studies published after the IPCS/IARC working groups have been described in detail. For studies described by the working groups, their descriptions and assessments have been accepted as valid and reference is generally made to the review and not to the original papers.

As with many elements, the terminology used to identify the chemical tends to be imprecise. For instance the word nickel is used, when in fact the data discussed refer not to metallic nickel but rather to various nickel compounds. The generally held view today is that most of nickel toxicity is caused by the nickel ion, and therefore, exact definition of the nickel species is not absolutely required. However, conerning the toxic potency of nickel compounds it is apparent that the exact chemical identity and physical chemical form of the compound are very important.

2. Substance identification

Chemical formula, atomic mass, together with CAS and EINECS numbers, of some nickel compounds are listed in Table 1.

[1]Evaluations and conclusions from IARC and IPCS have been reproduced by permission

Table 1. Substance identification of nickel compounds that may be important concerning occupational health.

Chemical	Chemical formula	Atomic mass	CAS-number(s)	EINECS-number(s)
Metallic nickel	Ni	58.69	7440-02-0	231-111-4
Nickel carbonyl	$Ni(CO)_4$	170.73	13463-39-3	236-669-2
Nickel monoxides	NiO	74.69	1313-99-1, 11099-02-8	215-215-7, 234-323-5
Nickel hydroxide	$Ni(OH)_2$	92.70	12054-48-7	235-008-5
Nickel acetate	$Ni(OOCCH_3)_2$	176.78	373-02-4, (tetrahydrate: 6018-89-9)	206-761-7
Nickel chloride	$NiCl_2$	129.60	7718-54-9, (hexahydrate: 7791-20-0)	231-743-0
Nickel nitrate	$Ni(NO_3)_2$	182.70	13138-45-9, (hexahydrate: 13478-00-7)	236-068-5
Nickel sulphate	$NiSO_4$	154.75	7786-81-4, (hexahydrate: 10101-97-0; heptahydrate: 10101-98-1)	232-104-9
Nickel sulphides	NiS	90.75	11113-75-0, 16812-54-7, 1314-04-1	234-349-7, 240-841-2
Nickel disulphide	NiS_2	122.81	12035-51-7, 12035-50-6	-
Nickel subsulphides	Ni_3S_2	240.19	12035-72-2, 12035-71-1	234-829-6

3. Physical and chemical properties

Nickel is a white, lustrous, hard metal, or grey powder. Its melting point is 1455 °C and boiling point 2730. It is insoluble in water but soluble in dilute nitric acid and slightly soluble in hydrochloric and sulphuric acids. Metallic nickel is resistant to air and water, but as a finely divided powder, it is oxidised by air, and may even spontaneously ignite (85, 227).

Nickel acetate, chloride, nitrate and sulphate are soluble in water, whereas hydroxides, oxides, carbonate, sulphides, disulphides and subsulphides are practically insoluble in water. Nickel oxide (NiO) occurs in two different crystalline forms, green and black nickel oxide. The former is generated by firing nickel at approximately 1000 °C producing a very refractory material which is very insoluble in water. Black nickel oxide is generated by calcining nickel acetate at a temperature of approximately 600 °C producing a less refractory than the green nickel oxide.

Nickel carbonyl is a colourless volatile liquid, which is insoluble in water. It decomposes upon heating to yield carbon monoxide and finely divided metallic nickel.

4. Occurrence, production and use (85, 239)

Nickel forms about 0.008% of the earth's crust (0.01% in igneous rocks) and ranks as the 24th most abundent element. The core of the earth contains about 8.5% nickel. Meteorites contain 5-50% nickel, and deep-sea nodules typically comprise of approximately 1.5% nickel.

Nickel is a component of several minerals (breithauptite, niccolite, zaratite, bunsenite, morenosite, millerite, vaesite, polydomite, haezlewoodite, pentlandite, pyrrhotite, garnierite). The commercially important nickel containing ores are either oxidic (laterite), or sulphidic (pentlandite).

Sulphide ores are extracted by flotation and magnetic separation. Most processes of refining begin with oxidation of iron and sulphur, followed by smelting, to remove rock and sulphur as slag, leaving ferrous nickel-copper matte. Further, iron and copper are removed by roasting, cooling, magnetic concentration and froth flotation. The product, nickel subsulphide, is usually oxidised to nickel oxide. This is reduced to (crude) metallic nickel, and further refined by either the nickel carbonyl (Mond) process or electrolysis. The sulphide matte can also be purified without roasting by a combination of hydrometallurgy and electrolysis or by hydrometallurgy alone.

Silicate ores are processed either by pyrometallurgy or hydrometallurgy. Hydrometallurgy may proceed with sulphuric acid leaching and precipitation of nickel sulphide with hydrogen sulphide, or selective reduction by hydrogen and

carbon monoxide, followed by ammoniacal leaching, removal of cobalt as sulphide, and precipitation of nickel as nickel hydroxycarbonate by ammonia treatment. Pyrometallurgy consists of drying, calcining and reduction/smelting to give crude ferronickel. After further refining by thermic processes, the ensuing ferronickel may be used for stainless steel production, or further processed to nickel sulphide matte in a furnace.

Nickel containing steels and stainless steels are produced by melting cast iron, iron scrap/steel scrap/ferrochrome and ferronickel/pure nickel in electric furnaces, and after adjustment of the carbon/additive/impurity levels, cast into ingots or continuously into casting shapes.

Nickel is a component of several commercially important alloys, such as stainless steels (nickel/chromium/iron with other metals), monels (nickel/copper alloys with good resistance), nichromes (nickel/chrome alloy with good corrosion and heat resistance), hastelloys (nickel/molybdenum alloys with resistance to oxidising environments), inconels and incoloys (iron/nickel/chromium alloys with good oxidation and corrosion resistance especially at low temperatures), nickel-based superalloys (alloys of nickel with niobium, titanium, molybdenum and others), alnico alloys (nickel/aluminium/iron, sometimes with cobalt and copper for use in permanent magnets) (134). Approximately half of all nickel produced is used to make stainless steels and 10% alloy steels. Non-ferrous applications such as high-nickel alloys, cupronickel alloys and coinage use approximately 20%, and foundry applications and electroplating 10%. Smaller uses of nickel include batteries, chemicals, pigments, welding products and catalysts (85, 239).

In Finland, the annual production of nickel concentrate from four mines was 135,000 tonnes and the amount imported 27,000 tonnes and cathode nickel production 17,000 tonnes in 1990 (88). In the same year, stainless steel export amounted to 70,000 and import to 220,000 tonnes. In Sweden, during 1993, the use of nickel and nickel oxide as catalysts amounted to 67 tonnes, of nickel salts (in metal plating) to 68 tonnes, and of antimony nickel in paints and lacquers to 73 tonnes (Ulf Rick, Kemi, personal communication). Export of nickel sulphate amounted to 481 tonnes in the same year. In Norway, during 1994, the production (expressed in tonnes) of metallic nickel was (67), nickel salts (84.5), nickel sulphide (497) and that of nickel subsulphide (87,027). The corresponding amounts imported in the same year were 32, 32.3, 364 and 43,514 tonnes (Petter Kristensen, Arbeitsmiljöinstituttet, personal communication). In Denmark, use of main groups of nickel and nickel-containing chemicals in 1994 amounted to ca 500 tonnes for metallic nickel and alloys, 300-400 tonnes for oxides, hydroxides and hydrides, 200 tonnes for minerals such as zeolite, ca 100 tonnes for hexahydrates of nickel salts, approximately 30 tonnes for pigments, and 10-20 tonnes for nickel salts such as carbonate, chloride, sulphate, nitrate (AS Fries, Danish National Institute of Occupational Health, personal communication).

5. Occupational exposure and uptake

Occupational exposure occurs mostly through the lungs. However, a significant intake may also occur by absorption via other routes, notably from the gastrointestinal tract (13, 110, 111).

Reported levels of occupational exposure to nickel as well as of nickel concentrations in the urine of the workers in different industries and trades have been listed in Tables 2 and 3. Estimates of historical exposures to different nickel species in various processes in nickel refining have been collected and listed in Tables 4-6.

6. Sampling and analysis at workplace

Traditional industrial hygiene measurements, which most often involve collection of the specimen on cellulose ester membrane filter, acid digestion, and analysis by flame atomic absorption spectrometry (149) can only measure total nickel in the air. A classification of nickel species (water soluble, sulphidic, metallic, oxidic) has been reported by consecutive leachings of the filter (85). For the analysis of low concentrations of nickel, flameless atomic absorption spectrometry or ICP mass spectrometry may be employed. X-ray diffraction procedures for the characterisation of nickel (and other metal) species in welding fumes have been published, but seem to have been little used.

7. Toxicokinetics (85, 87)

7.1. Uptake

7.1.1 Humans

When nickel sulphate was given to volunteers orally, 1-5% of the dose was absorbed, whereas 4-20% of the dose was absorbed when given to fasted volunteers. Gastrointestinal absorption of nickel from food items rich in nickel is approximately 1%.

Elevation of plasma and urinary nickel concentrations after occupational exposure mainly via inhalation (see "Biological monitoring", Section 8), indicate that nickel species are absorbed effectively through the lungs. In electroplaters (exposed mainly by inhalation to soluble nickel salts), the urinary excretion of nickel was faster than in glass workers (see "Elimination", Section 7.4) or welders indicating rapid pulmonary absorption of the water soluble nickel species from the lungs. The less readily soluble nickel species are more slowly absorbed. Very high nickel concentrations were observed in nasal mucosal biopsies and autopsy specimens obtained from the lungs of workers in the Kristiansand nickel refinery.

Table 2. Occupational exposure to nickel (Ni) in different industries (adapted and updated from Ref. 108)

Industry	Ni in air µg/m³ mean (SD) or range	Ni in urine mean (SD) or range	Country	Ref.
Mines	6-40		USA, Canada	178
Ferronickel production	2-274		New Caledonia	239
	5-420		U.S.A	"
Nickel refinering				
Smelter	37-1160[a]		Canada	54
	230-860[a]	44.6-129 µg/L[a]	Norway	84
		22-73 [a]	Norway	218
	10-5000	24-39 µg/L[a]	UK	144
	0.13 (0.26)	15.6 (9.1) µg/g creat.	China	243
	0.0034-1.276	3.645-36.47		
Smelter, fluid bed roaster	80-1570[a]		Canada	54
Electrolytic refinery	20-2 200	8.6-813 µg/g creat.	USA	15
	20-130[b]		Canada	89
	100-390		Finland	3
	86-1 265	125-450 µg/L	Czechoslovakia	178
	50	2.5-63 µg/g creat.	BRD	170
	5-481[a]	3.48-98.55 µg/L	Czechoslovakia	226
	0.1 -500	49.9-117.5 µg/L	Finland	99
	0.4-2.4[c]	5.3-75 µg/L[d]	Finland	111
	1.3-71[e]			
Hydro-metallurgical refining	1-1630		Canada	239
	140-1090		USA	
	9->10000		USA	
			USA	42
			USA	214
Nickel carbonyl refinery				
Kiln	10-5000		UK	144
Powder plants	9-1530		"	"
Wet treatment	30-4180		"	"
Hydrogen	10-20		"	"
Engineering	10-400		"	"
Stainless steel production/ foundries				
	<1-189		Canada	239
	1-60 000		Canada	"
	<4-900		United States	189
	<DL[f]-710		Canada	239
	2-141		France	115
		5.0-38.6 µg/L	Poland	12
Cast cleaning	50-1100		Finland	67
High nickel alloy production	1-4 400		Canada	239
	10-1420	0.5-97 µg/g creat.	BRD	222
	300[a]	0.5-52 µg/L	BRD	173
Nickel salt production	<10-12 070	<10-210 µg/g creat.[g]	UK	144
	9-590		Canada	239
Nickel battery production		3.4-25 µg/L	USA	15
	12.3-33.0	23.7-26.6 µg/g creat.	USA	2
	20-1910		Canada	239
		0.4-121 µg/g creat.	Germany	171
		1.9-10.9 µg/L	Germany	170

Table 2. (contd.)

Industry	Ni in air µg/m³ mean (SD) or range	Ni in urine mean (SD) or range	Country	Ref.
Nickel catalyst production		0.1-5.8 µg/g creat.	USA	15
	<1000-5870	8-301 µg/g creat.	The Netherlands	250
	10-600		USA	239
Electroplating		11-26 µg/L	India	210
		3.6-65 µg/L	USA	15
	30-160	25-120 µg/L[h]	Finland	216
	0.5-21.2	5-262 µg/L[a]	USA	19
	20-170	12-109 µg/L	Finland	220
	<2-<16		USA	239
		1.7-3.6 µg/L	BRD	66
	0.1-42	0.7-50 µg/L	Italy	13
		0.02-0.05 µg/L[i]	Finland	110
Hollow glass industry	3-3800	3.6-42.1 µg/L[j]	BRD	170
	3.4-623	1.7-107.5 µg/g creat[j]	BRD	173
Flame and plasma spraying, cutting				
Flame spraying	0.04-6.5	1.4-26 µg/L	USA	15
	3-600	8.5-81.5 µg/L[j]	BRD	170
Flame spraying +mechanical work	300-410	4.9-53.9 µg/L[j]	BRD	"
Plasma spraying	200	3.4-12.5 µg/L	BRD	66
Spark eroding	<10	0.7-2.1 µg/L	BRD	"
Plasma cutting	<100	1.1-6.5µg/L	BRD	"
	<1-240	1.7-4.3 µg/L	New Zealand	48
Grinding	0.05-129	0.5-9.5 µg/L	USA	15
	18-3800	2.9-24.3 g/L[j]	BRD	170
	140	0.7-9.9 µg/L	BRD	66
	10-10 000[g]	3-7 µg/L[k]	BRD	77
	25-65		The Netherlands	237
Painting		<0.5-9.2 µg/L	USA	65
		6-39 µg/L	USA	210
Hard metal industry		<0.78 µg/g urine	Italy	150
	<1-86		Japan	119
Electrical resistance manufacture	0.2-332	0.2 - 100.6 µg/g creat.	Belgium	182
Miscellaneous exposure	0.01-252	1.4-41 µg/L	USA	15
		1.1-13.5 µg/L	USA	65
Welding				
High nickel alloy	70-1070	8.1-38 µg/L	Sweden	5
MMA/SS		2-14 µg/L	Finland	94
	30-1780	7.8-26.5 µg/g creat.	Finland	169
	0.6-77.8[i]	0.6-8.8 µg/g creat[j]	BRD	247
	10-210		The Netherlands	236
	<50-10	2.50-144.00 µg/L	BRD	247
	12.3-70.6[g]	2.5-12 µg/g creat[j]	BRD	249
	<50-260	0.6-164.7 µg/L	BRD	7
	<2-<5	1.1-4.4 µg/L	New Zealand	48
	3-70	1.3 - 18.7 µg/g creat.	Czechoslovakia	233

Table 2. (contd.)

Industry	Ni in air µg/m³ mean (SD) or range	Ni in urine mean (SD) or range	Country	Ref.
Welding (cont.)				
MMA/MS	<10-20	0.40-78.4 µg/L	BRD	247
MMA+MIG/SS		0.1-85.2 µg/L	BRD	7
MMA/SS + flame cutting	50-1100		Finland	67
MMA+TIG/SS		1-18 µg/L	Finland	94
	11.7 (12.9)	2.5 (2.3) µg/g creat.	Denmark	116
MIG/SS	30		The Netherlands	236
	150		BRD	247
	66[k]	3.5-21.4 µg/g creat.[j]	BRD	249
	<50-320	1.2-209.4 µg/L	BRD	7
	<1-2	1.2-6.0 µg/L	New Zealand	48
	11.6 (9.2)	1.6 (2.4) µg/g creat.	Denmark	116
MAG/SS	<10-500		BRD	247
TIG/SS		1-6 µg/L	Finland	94
	10-40		The Netherlands	236
	20		BRD	247
		5.2 (1.8) µg/L	USA	112
	<2-1	0.7-4.2 µg/L	New Zealand	48
	15.2 (17.3)	2.0 (1.9) µg/g creat.	Denmark	116
PC/SS	<10-260		The Netherlands	237
PW/SS	1-20		The Netherlands	"

a = range of individual mean values; *b* = range for yearly geometric means; *c* = range of averages inside the protecting mask; *d* = range of averages in different parts of the plant; *e* = range of averages outside the protecting mask; *f* = detection limit; *g* = corrected to 1.6 µg/L creatinine; *h* = adapted from figures; *i* = median; *j* = 68th percentile range; *k* = 90th percentile range.

creat. = creatinine.

MMA/SS = manual metal arc stainless steel welding; MMA/MS = manual metal arc mild steel welding; MMA+MIG/SS = manual metal arc & metal inert gas stainless steel welding; MMA+TIG/SS = manual metal arc & tungsten inert gas stainless steel welding; MIG/SS = metal inert gas stainless steel welding; MAG/SS = metal active gas stainless steel welding; TIG/SS = tungsten inert gas stainless steel welding; PC/SS = plasma cutting of stainless steel; PW/SS = plasma welding of stainless steel.

Table 3. Nickel concentrations (µmol/L) in urine in different trades in Finland in 1980-1989 (107).

Job title	N (workers)	n (work-places)	Mean	Median	Maximum
Grinders	154	7	0.20	0.19	0.82
Metal sprayers	97	12	0.26	0.24	0.99
Moulders	121	5	0.39	0.20	6.83
Painters	10	3	0.30	0.31	0.61
Plumbers	24	4	0.14	0.14	0.29
Platers	635	9	0.32	0.21	22.9
Plasma cutters	29	5	0.27	0.23	0.72
Preparers	32	1	0.15	0.12	0.37
Sheet metal workers/welders	850	22	0.19	0.16	2.40
Welders	708	21	0.19	0.16	2.40

Table 4. MOND/INCO (Clydach, South Wales, UK) nickel refinery - average nickel exposure levels and cancer risks in 'high-risk' departments in workers with 15 or more years since first exposure[a] (reproduced by permission from Ref. 85)

Department	Estimated airborne concentration (mg/m³ Ni) [b]				Duration in department									
					Ever				≥5 years					
					Lung cancer		Nasal cancer		Lung cancer		Nasal cancer			
	Metallic nickel	Oxidic nickel	Sulphidic nickel	Soluble nickel	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)		
Furnaces, 1905-63	5.6	6.4	2.6	0.4	9	409	3	24781	1	370	3	1000		
Linear calciners, 1902-30; milling and grinding, 1902-36	5.3	18.8	6.8	0.8	16	725	7	44509	12	1244	6	78280		
Copper plant, before 1937	-	13.1	0.4	1.1	17	317 (185-507)	5	13912 (4507-32415)	8	541 (233-1066)	2	14541 (1759-52493)		
1938-60	-	0.4	0.01	0.01	-		-		-		-			
Hydrometallurgy 1902-79	0.5	0.9	0.05	1.3	7	196 (79-404)	4	18779 (5108-48074)	5	333 (108-776)	4	36363 (9891-93089)		

a = From Doll et al. (45). Estimated airborne concentrations of nickel species and mortality from lung cancer and nasal cancer by department. In each row, observations are restricted to men with <1 year employment in other high-risk departments. Standardised mortality ratio (SMR) and 95% confidence interval (CI).

b = The working group expressed reservations about the accuracy of these estimates, as discussed on page 391 in Ref. 85.

Table 5. Falconbridge (Kristiansand, Norway) nickel refinery - average nickel exposure levels and cancer risks in workers with 15 or more years since first exposure[a] (reproduced by permission from Ref. 85)

Department	Estimated airborne concentration (mg/m3 Ni)[b]				Duration in department							
	Metallic nickel	Oxidic nickel	Sulphidic nickel	Soluble nickel	Ever				≥5 years			
					Lung cancer		Nasal cancer[b]		Lung cancer		Nasal cancer[b]	
					Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
Calcining, roasting, smelting; never in electrolysis	0.3-1.3	5.0-10.0	0.3	Negl.[c]	14	225 (122-377)	5	-	8	254 (109-500)	5	-
Electrolysis; never in calcining, roasting, smelting	0.3-1.3	0.3-1.3	Negl.-1.3	1.3-5.0	30	385 (259-549)	2	-	19	476 (287-744)	2	-

a = From Doll et al (45). Estimated airborne concentrations of nickel species and mortality from or incidence of lung cancer and nasal cancer by department. Standardised mortality ratio (SMR) and 95% confidence interval (CI).

b = Three deaths and four incident cases.

c = Negl., negligible exposure.

Table 6. INCO (Ontario, Canada) nickel refinery facilities - average nickel exposure levels and cancer risks in workers with 15 or more years since first exposure[a] (reproduced from Ref. 85).

Plant	Department	Estimated airborne concentration (mg/m^3 Ni)[b]					Duration in department							
		Metallic nickel	Oxidic nickel	Sulphidic nickel	Soluble nickel	Total nickel	Ever				≥5 years			
							Lung cancer		Nasal cancer		Lung cancer		Nasal cancer	
							Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)	Obs	SMR (95% CI)
Coniston	Sinter	Negl.[b]	0.1-0.5	1-5	Negl.	1-5	8	292 (126-576)	0	-	6	492 (181-1073)	0	-
Copper Cliff	Sinter													
1948-54		Negl.	25-60	15-35	<4	40-100	63	307 (238-396)	6	3617 (1327-7885)	33	789 (543-1109)	4	13146 (3576-33654)
1955-63		Negl.	5-25	3-15	<2	8-40								
Port Colborne	Leaching, calcining, sinter													
1926-35		Negl.	20-40	10-20	<3	30-80	72	239 (187-302)	19	7776 (4681-12144)	38	366 (259-502)	15	18750 (10500-30537)
1936-45		Negl.	3-15	2-10	<3	5-25								
1946-58		Negl.	5-25	3-15	<3	8-40								
	Electrolysis	<0.5	<0.2	<0.5	<0.3	<1	19	88[d] (53-137)	0[c,d]	-	10[d,e]	89	0[c,d]	-

a = From Doll et al. (45). Estimated airborne concentrations of nickel species and mortality from lung cancer and nasal cancer by department. Standardised mortality ratio (SMR) and 95% confidence interval (CI); b = Negl., negligible exposure; c = Two nasal cancer deaths occurred in men with >20 years in electrolysis and only short exposure (three months and seven months) in leaching, calcining and sintering; d = Never worked in leaching, calcining and sintering; e = Workers with ≥10 years in electrolysis.

This was most marked in workers that had worked in the roasting/smelting department. Some of the specimens with high nickel concentrations had been collected from workers more than ten years after they had retired - this indicates that dissolution from the nasal mucosa very slow (85). Similarly, grossly elevated nickel concentrations were observed in the lungs of welders, plasma sprayers, and especially nickel refinery workers in an autopsy study (172). Some of the autopsy samples had been collected from workers years after exposure had ceased.

Overt toxicity, and elevated tissue nickel concentrations after inhalation exposure to nickel carbonyl indicate effective pulmonary absorption; however, quantitative data are lacking.

Nickel salts are slowly absorbed in the skin in dermal exposure -chloride is more efficiently absorbed than sulphate. The amounts that reach the systemic circulation are very small.

7.1.2 Experimental animals

The oral LD_{50} of nickel acetate (a soluble nickel salt) was 360-420 mg/kg in male and female mice and rats, while the intraperitoneal LD_{50} was 23-32 mg/kg. This indicates that approximately 1/10 of the dose was absorbed from the gastrointestinal tract in these rodents. For nickelocene, a similar finding has been reported.

After intratracheal instillation of nickel sulphate in rats, there was a rapid excretion of nickel in the urine, with a half time of 4.6 to 23 h (the higher the dose, the shorter the half time). Rapid clearance from the lungs has also been observed after intratracheal instillation of nickel chloride to rats. In line with these findings, the nickel content of the lungs reached a steady state within 5 days in rats exposed to nickel chloride aerosols for 2 h/day for 14 days (85). After inhalation exposure to nickel sulphate, or after intratracheal instillation, the lung nickel content decreased monoexponentially with a half time of approximately 30 h in rats (79).

When rats were given a single intratracheal instillation of black nickel oxide, elevated concentrations of nickel could be observed for mediastinal lymph nodes, heart, bone, gastrointestinal tract, kidney and other tissues. The clearance of nickel was faster from tissues other than the lung. In three months, 60% of the dose had been excreted, half of it in the urine. Slow clearance of nickel from the lungs has also been demonstrated after inhalation exposure to nickel monoxide aerosols. Several consecutive half times were observed for the disappearance of nickel from the lungs of mice given an intratracheal instillation of nickel subsulphide. After 35 days, 10% of the dose was still retained in the lungs.

After nose-only inhalation exposure of Fischer 344/N rats to green nickel oxide (calcined at 1200 °C, MMAD 1.3 µm, 9.9 mg/m^3, 70 min), or nickel subsulphide (5.7 mg/m^3, MMAD 1.3 µm, for 120 min), the fraction deposited in the lungs was 5% for both aerosols (15). Inhaled nickel oxide was cleared slowly from the lungs, with a half time of approximately 120 days. The oxide could not be observed in extrarespiratory tissues indicating clearance via the gastrointestinal tract only. In contrast, nickel subsulphide was cleared relatively rapidly, with a

clearance half time of four days. Nickel subsulphide was also distributed in extrapulmonary tissues.

The difference in the clearance between green nickel oxide and nickel subsulphide was apparent also in a long-term experiment (51): When rats were exposed by inhalation to nickel sulphate, nickel subsulphide or green nickel oxide for 13 weeks (6h/d, 5d/w), the concentrations of nickel in the lung had reached a plateau by 4 weeks (earlier time-points were not studied) in rats treated with nickel sulphate or nickel subsulphide, whereas in the rats treated with nickel oxide the nickel concentration continued to rise until the end of the experiment.

After inhalation exposure of rats for 6 months to green nickel oxide (generated at 1030° C, black nickel oxide (generated at 550 °C, and nickel subsulphide, the clearance during the following 12 months amounted to 82, 73, and 98% of the amount deposited, respectively (117). For nickel subsulphide, the finding is thus well in line with the previous studies (15, 51), and is in line with its water solubility. For nickel oxides, the clearance is remarkably more effective than predicted from the short-time experiments (15, 51). Also it is difficult to explain, why the green oxide was cleared more rapidly than the black oxide: the black oxide is 70 times more soluble in water, and ten times more soluble in saline than the green oxide.

7.2. Distribution

7.2.1 Humans

In autopsy specimens, highest nickel concentrations have been observed in the lungs, followed by bone, thyroid, adrenals, kidney, heart, liver, brain, spleen and pancreas. The disappearance half time of nickel in serum was 11 hours in volunteers after ingestion of nickel sulphate. After inhalation exposure to soluble nickel salts, the plasma disappearance half time was 20-34 h.

Tissue levels of nickel were similar in foetuses and mothers, indicating free permeation of nickel through the placenta.

7.2.2 Experimental animals

Nickel salts are rapidly distributed in the organism after absorption. Accumulation has been observed in the lung, spleen and kidney after parenteral administration in rats and mice[2]. After intratracheal instillation of black nickel oxide to rats, nickel was accumulated in the mediastinal lymph nodes, and distributed widely in the organism. After an intratracheal instillation nickel subsulphide, highest concentrations (outside the lungs) were observed in the kidneys. After subcutaneous or intramuscular administration, nickel subsulphide was accumulated in regional lymph nodes.

[2]Note added in print: A further study on the distribution of nickel sulphate after long-term administration in drinking water in rats was reported in: Severa J, Vyskocil A, Fiala Z, Cizkova M. Distribution of nickel in body fluids and organs of rats chronicall exposed to nickel sulphate. *Human Exp Toxicol* 1995;14:955-958.

Elevated concentrations of nickel were detected in foetuses after intramuscular administration of nickel subsulphide to rats. Several studies have demonstrated that nickel reaches the foetus after the administration of nickel chloride to dams.

7.3. Biotransformation

Nickel carbonyl is metabolised to metallic nickel and carbon monoxide.

7.4. Elimination

7.4.1 Humans

In electroplaters (exposed mainly by inhalation to soluble nickel salts), the urinary excretion of nickel immediately after the exposure showed a half time of 17-30 h. The apparent half times were longer in glass workers (30-50 h) and welders (53 h); this is most likely due to the fact that the nickel species in these trades, which are less readily soluble in water, are more slowly absorbed than those encountered in electroplating. However, even for exposure to soluble nickel compounds (electrolytic refining and electroplating), elevated urinary concentrations of nickel were observed after a 1-5 week vacation, indicating a slow phase of excretion after the first short half time (110, 111).

Small amounts of nickel are excreted in pancreatic juice, bile and sweat.

7.4.2 Experimental animals

After an intratracheal injection of black nickel oxide to Wistar rats, about half of the dose was excreted in the urine, and half in the faeces. One sixth of the dose was excreted within three days and three fifths in 90 days.

After intratracheal administration of radiolabelled nickel subsulphide powder to mice, 100% of the dose was recovered in excreta within 35 days, the proportion in the urine being 60%. After intramuscular injection of nickel subsulphide to rats, 67% of the dose was excreted in the urine and 7% in the faeces within 8 weeks.

After a single intravenous injection of nickel chloride to rats, 87% of the dose was excreted in the urine within 24 h and 90% within four days. The cumulative excretion in the faeces within four days amounted to 3%. Over 60% of nickel chloride instilled intratracheally in rats was excreted in the urine within 6 days, while the faecal excretion amounted to 5%. During the following three months, the cumulative proportions of the dose excreted in the urine and faeces increased to 64 and 6%, respectively.

After intratracheal instillation of nickel sulphate to rats, the routes of excretion were dependent on the dose. Faecal excretion amounted to 30% after a dose of 1 and 11 µg/rat, but was 13% after a dose of 106 µg/rat. Urinary excretion was the predominant route of excretion. The half time of the urinary excretion was also dose-dependent: 23 h for the lowest and 4.6 h for the highest dose. Urine was the most important route of excretion also after intratracheal administration of nickel carbonate to mice.

After intravenous administration of nickel carbonyl to rats, 38% of the dose was exhaled during the first 6 hours. Thereafter, urine was the major route of excretion (23% of the dose within 12 h and 31% in four days). Total faecal excretion was 2.4%.

7.5. Relevant kinetic interactions

None known

8. Biological monitoring

Analysis of both plasma/serum nickel and urinary nickel have been used in the biological monitoring of exposure to nickel. Because of the ease of sample collection, and of the higher concentrations observed, urine is usually preferred (4, 204, 205).

Use of analysis of nickel in fingernails has also been suggested as a means of biological monitoring (160), but external contamination diminishes the value of such measurements.

A literature survey on the reference values of nickel concentrations in blood, serum, and urine was performed within the TRACY project in 1994 (211). From published studies, six were deemed suitable for assessing the reference values in urine, and five gave upper reference limits. In four of the studies, the upper reference limit was 6 µg/L (102 nmol/L) or less. A re-evaluation of the fifth study (by excluding specimens with a relative density less than 1.010) gave 60 nmol/L as the upper reference limit (109). For serum, six studies could be used, and five of them reported upper reference values equal to or below 1.1 µg/L (18.7 nmol/L).

A good correlation was observed between the time-weighted-average nickel concentration in the air, and the urinary excretion of nickel among nickel platers, exposed to soluble nickel salts (216). In an afternoon-shift urine specimen ($r = 0.82$), exposure to 100 µg/m^3 corresponded to an urinary nickel concentration of 1.35 µmol/L. In a morning specimen after the exposure ($r = 0.96$), the corresponding value was 1.0 µmol/L. These data fit well with the prediction of Norseth, based on a summary of three studies on workers exposed to soluble nickel salts (100 µg/m^3 exposure corresponded to an after-shift urinary nickel concentration of 67.4 µg/L = 1.15 µmol/L) (152, 156). In a further study with electroplers, an equally good correlation was obtained (226). The corresponding value was 0.70 µmol/L in an after-shift specimen.

From studies performed at lower exposure levels, higher urinary nickel concentrations have been calculated to arise from exposure to soluble nickel salts. Using a linear intrapolation ($r = 0.74$), 24.2 µg/L was considered as the post-shift urinary nickel concentration corresponding to an 8-h TWA exposure to 20 µg/m^3 (241). An even higher value was obtained in a study in which the correlation between the exposure and the urinary nickel concentration was lower. Using a logarithmic equation, exposure to 20 µg/m^3 was calculated to correspond to a

urinary nickel concentration of 47 µg/L (0.80 µmol/L) in an after-shift specimen (62).

The correlation between nickel in the air and urine is much weaker in exposure to slightly soluble nickel compounds (4, 5, 7, 18, 84, 143, 201, 205, 246, 248).

In a nickel-cadmium battery plant, where exposure to the practically insoluble nickel hydroxide occurs, a correlation was observed between weekly average nickel concentrations in the breathing zone, and weekly average urinary nickel concentrations. From the values presented, it can be roughly estimated that an exposure to 100 µg/m^3 would lead to an urinary nickel concentration of 15 - 60 µg/gramme creatinine (73).

On a group basis, Morgan and Rouge reported a correlation of 0.86 between exposure to insoluble nickel and urinary nickel concentration in different departments of a nickel refinery (144). An air nickel concentration of 0.5 mg/m^3 corresponded to an urinary nickel concentration of 36.9 µg/L (0.64 µmol/L).

Angerer and Lehnert estimated that in stainless steel welders an 8-h TWA exposure to 500 µg/m^3 nickel (The German TRK) would induce an urinary concentration of nickel of 30 -50 µg/L (7). The German Senate Commission has published an EKA value of 45 µg/L (0.77 µmol/L), which corresponds to the German TRK-value of 500 µg/m^3 for an exposure to slightly soluble nickel compounds, such as metallic nickel, nickel carbonate, nickel oxide, and nickel sulphides (41).

In exposure to nickel carbonyl, data on the relationships between exposure and the urinary nickel concentration have not been published. However, the Sunderman family has published a guideline on the predictive value of urinary nickel levels (203): if the urinary nickel during the first 8 hours after the exposure does not exceed 100 µg/L, the poisoning will be mild; when the level is 100-500 µg/L, the poisoning is predicted to be moderately severe, and; severe when the level of 500 µg/L is exceeded.

Early effects of nickel have also been studied as an approach for biological monitoring. The work of Torjussen and Boysen (85, 87) has demonstrated that nickel induces dysplastic lesions in the nasal mucosa of workers both in the smelting-roasting and electrolysis departments of the nickel refinery. However, it was estimated that 30-50% of dysplastic changes remained undetected, mainly because of the small size of the biopsy specimen, and the method could therefore not be recommended for the assessment of the health risk of the individual worker (23). Nasal brush samples did not provide a better sensitivity: The detection probability for both histological and cytological specimens was estimated to be below 60% (47). Image cytometry correctly identified 89% of the nondysplastic cases, and 75% of the dysplastic cases (176).

For exposure to water soluble nickel salts, it is apparent that most nickel is rapidly excreted in the urine, and that the urinary nickel concentration in an after-shift specimen mainly reflects exposure over the working day. Less soluble nickel salts are retained in the body, and urinary nickel concentrations are affected by both the body burden and the immediately preceding exposure.

9. Mechanisms of toxicity

9.1. Dissolution and cellular uptake

Dissolution and cellular uptake of different nickel species has been extensively studied in an attempt to explane why there are large differences in the carcinogenic potency in experimental animals between different nickel species (see "Carcinogenicity", Section 10.5). However, one should bear in mind that these studies have been performed in vitro or using parenteral administration, the target cells are different than those in human cancer, the concentrations applied are often excessively high and, the prevailing concept of nickel carcinogenesis in humans does not support the notion that the less soluble nickel species are more potent carcinogens (see "Carcinogenic effects", Section 11.4). Thus the validity of the data and models described in this section should be carefully considered when making extrapolations to the human exposure situation.

Nickel compounds that are practically insoluble in water, are not necessarily insoluble in body fluids. It has been shown that the dissolution half time for six nickel oxides prepared at different temperatures, as well that of four nickel copper oxides with different nickel-copper ratios was >11 years in water. However, it was <1 year for a nickel oxide calcined at a low temperature, and 2.7 - 7.2 years for three of the nickel-copper oxides in rat serum and renal cytosol. The oxides that had shorter half times in biological fluids, were also more avidly phagocytized in C3H/10T1/2 cells. Same oxides were also more carcinogenic in rats after intramuscular injection (207). An inverse relationship between carcinogenicity after intramuscular injection in rats and dissolution rate in human serum or artificial lung fluid was also observed for nickel subsulphide, crystalline nickel hydroxide, air-dried nickel hydroxide gel, colloidal nickel hydroxide, and nickel sulphate (103). However, no such relationship existed between dissolution half time and phagocytosis on the other hand, and carcinogenicity, as tested by intramuscular injection in rats, for nickel selenide, subselenide, telluride, sulpharsenide, arsenide, arsenide tetragonal, arsenide hexagonal, antimonide, ferrosulphide matte, a ferronickel alloy and nickel titanate (85).

Crystalline (carcinogenic) nickel sulphides were phagocytised by Syrian hamster embryo cells and Chinese hamster ovary cells, whereas particles of amorphous (non-carcinogenic) sulphides were not. Less nickel chloride than insoluble nickel sulphides was taken up by CHO. Treatment of Chinese hamster ovary cells with ß-nickel sulphide (crystalline, carcinogenic) resulted in a binding of nickel to DNA, RNA and protein that was 300-2000 times higher than the binding of the soluble nickel sulphate.

Nickel subsulphide particles were internalised in rat tracheal epithelial cells in culture within 24 h of culture, while nickel oxide particles were internalised only after 5-7 weeks (158).

9.2. Mechanisms of genetic toxicity

As indicated by the studies cited in the IARC Monograph on nickel, nickel is mostly nonmutagenic in bacterial mutagenicity assays, but induces chromosomal aberrations, sister chromatid exchanges, DNA single strand breaks, and crosslinks of DNA-nuclear proteins in mammalian cells (85). Nickel effects are usually observed only at high concentrations, and therefore, mechanisms other than direct DNA damage have been sought as explanations for nickel carcinogenicity (71).

Nickel has been suggested to induce DNA damage through generation of active oxygen species (100, 114). This view was supported by the finding (215) that nickel ion, in the presence of hydrogen peroxide, induced tandem double CC⇒TT mutations in single-stranded M13G1 DNA, a "hallmark" for oxygen radical- (or UV-light)- induced DNA damage. The mutation frequency was further enhanced in the presence of the tripeptide glycine-glycine-histidine (215), which is a potent stimulator of the production of hydroxyradicals from H_2O_2 in the presence of nickel (219). This mechanism of action of nickel ions was further strengthened by the finding that H_2O_2 and glycine-glycine-histidine enhanced the mutagenesis of nickel in a forward mutation assay using the M13mp2 single-stranded DNA, and that free radical scavengers inhibited the mutagenesis (215). The glycyl-glycyl-histidine complex of nickel also mediated protein-protein crosslinks in the presence of oxidants such as ozone or peroxyphthalic acid (25). Nickel compounds also induced bulky DNA-adducts in vitro. This reaction was inhibited by hydroxyl free-radical scavengers and by sodium azide, a scavenger of singlet oxygen. DNA-adducts with similar chromatographic behaviour in a post-labelling assay could also be detected in the kidney after treatment of the animals with nickel acetate in vivo (28). Nickel chloride induced DNA cleavage in human c-Ha-ras-1 proto-oncogene in the presence of H_2O_2 in vitro. This reaction was inhibited by some (sodium azide, dGMP, dimethylsulphoxide, sodium formate), but not all (1,4-diazabicyclo(2.2.2)octane, dimethylfuran, ethanol, mannitol) singlet oxygen or hydroxyl radical scavengers (105).

Nickel has also been reported to induce oxidation of deoxyguanosine bases in vitro in the presence of hydrogen peroxide (104). Concentration of 8-hydroxy-2'-deoxyguanosine was elevated in DNA extracted from kidneys of rats treated with a single intraperitoneal injection of nickel acetate (101). These data are consistent with the finding of GGT to GTT mutations in the codon 12 of K-ras-oncogene in seven out of nine renal tumours induced by treatment with nickel subsulphide plus iron (78). Oxidation of deoxyguanosine to 8-hydroxydeoxyguanosine would promote misincorporation of dATP opposite the oxidised guanine residue. However, this mutation was observed in only one out of 12 tumours induced by nickel subsulphide alone.

In several experimental systems, nickel ions have been shown to potentiate the effects of other mutagenic chemicals. Nickel enhanced the transformation of Syrian hamster embryo cells by benzo(a)pyrene (but not that by methylcholanthrene) (179), the mutagenicity of methyl methane sulphonate in polymerase proficient strains of E. coli (49) and that of UV-light (but not of

methyl methane sulphonate) in Chinese hamster cells (30, 70, 71, 129). Nickel also potentiates the SCE-inducing capacity of UV light in V79 and CHO K1 cells (71, 129). Nickel inhibits the repair of DNA damage induced by UV-light and X-ray irradiation (30, 70, 122, 199) and induces chromosome deletions in lymphocytes during repair after γ-irradiation (11). The mechanism of the inhibition of the DNA-repair in HeLa cells after UV-light seems to involve both inhibition of the incision step of the nucleotide excision and the ligation of the repair patches (72, 199). These findings were made at high (>0.25 mmol/L) nickel concentrations, which, however, were not cytotoxic to the cells studied. The post-incision events in the repair phenomenon were similar to those observed after X-ray irradiation in HeLa and CHO cells (30, 199). Lee-Chen and co-workers (122) reported that nickel (1 mmol/L) inhibited DNA ligation and postreplication repair in CHO-K1 cells after UV-irradiation, but had no effect on the incision step of excision repair.

Primary human kidney epithelial cells were immortalised by treatment with nickel sulphate, and they became capable of growing in soft agar, but did not undergo malignant transformation (223). However, when they were transfected with v-Ha-ras, the cells became tumorigenic in athymic mice (75). The nickel-immortalised epithelial cells contain a mutant p53-gene and a 17p deletion, which render the tumour suppressing gene inoperative, and thus support the concept of mutagenicity as the basis of nickel carcinogenicity (130). However, nickel-induced inactivation of gpt-expression in transgenic gpt+ Chinese hamster cell line was accompanied by increased DNA methylation while reversion to 6-thioguanine sensitivity was induced via demethylation by 5-azacytidine indicating an epigenetic mechanism for the nickel-induced mutagenesis (120).

Human osteoblast cells, which had been transformed by treating them with crystalline NiS, were able to grow on soft agar in contrast to the original HOST cell line. The retinoblastoma protein of these transformed cells was hypophosphorylated, but did not form a complex with simian virus 40 large antigen - a phenomenon considered to be an indication of lack of functional activity. When the cells were transfected with a plasmid containing a normal retinoblastoma gene, a normal phosphorylation pattern (phosporylated unphosphorylated) of the Rb protein was restored, and the cells lost the capacity of anchorage-independent growth (127).

Treatment with nickel sulphate (36 µmol/L) transformed the human osteoblast cell line HOST TE-85, which is immortal but not tumorigenic, to a phenotype that was tumorigenic in nude mice (174).

Treatment of Chinese hamster embryo cells with nickel induced transformants which were immortal, anchorage-independent and tumorigenic in nude mice (35); they also exhibited non random deletions of the heterochromatic long (q) arm of the X-chromosome. When an intact mouse X-chromosome was introduced to these cells, senescence was introduced in a large percentage of the recipients (113).

At high nickel concentrations, nickel may replace magnesium, the native DNA counter ion leading to a distortion of the spatial arrangement of the DNA molecule, i.e., to the B to Z transition (128). In line with this finding, it has been observed that coadministration of magnesium with nickel inhibits nickel-induced carcinogenesis in rat kidney (102). Nickel leads to decreased DNA replication fidelity. This has been explained by its effects on DNA polymerases which in the absence of magnesium, nickel may substitute (although inefficiently) magnesium as the cofactor of DNA polymerases, but in the presence of magnesium it inhibits DNA polymerases and causes misincorporation. However, at low concentrations nickel may also increase the fidelity of DNA replication with some DNA polymerases. Different DNA polymerases exhibit remarkably different sensitivity toward nickel (198).

10. Effects in animals and in vitro studies

10.1. Irritation and sensitisation

Single application of 50% nickel sulphate did not induce irritation in intact skin in rabbits, but repeated application induced skin erythema, eschar, acanthosis, hyperkeratinisation and atrophy in rats. No data are available on skin or eye irritation by insoluble nickel compounds or nickel carbonyl (58).

Nickel sulphate and chloride were weakly positive in guinea pig maximisation tests (58).

10.2. Effects of single exposure

Selected numeric data on the acute toxicity of different nickel compounds is given in Table 7 (123). The description of the acute toxicity of nickel compounds below is adapted from Refs. 58 and 87.

The target organ for the acute toxicity of nickel carbonyl is the lungs: it induces pulmonary hyperaemia, and oedema and haemorrhages. At high exposure levels pulmonary oedema may ensue within one hour, at lower exposure levels it may develop after several days. Histopathological findings after nickel carbonyl exposure include centrilobular necrosis of the liver, tubular degeneration of the kidney, haemorrhagies and degeneration of pancreatic acini and Langerhans islets, as well as of adrenal glands.

Diffuse lung fibrosis was observed in rats killed 1-4 months after a single sub-lethal dose of nickel carbonyl. This effect was much less extensive at later time points. Lesions were not observed in the liver, kidney, brain or spleen.

After oral administration of lethal or near-lethal doses of soluble nickel salts, central nervous system effects (excitation, ataxia, depression, convulsions) have been described. In some, but not all studies, histological damage in the liver and

Table 7. Values of acute toxicity for nickel compounds (123).

Compound	Species	Route of exposure	Parameter	Numeric value
Nickel	Rat	oral	LD_{Lo}	5 g/kg
		intratracheal	LD_{Lo}	12 mg/kg
Nickel carbonyl	Human	inhalation	LC_{Lo}	30 cm^3/m^3, 30 min
	Rat	inhalation	LC_{50}	35 cm^3/m^3, 30 min
	Mouse	inhalation	LC_{50}	67 mg/m^3, 30 min
Nickel monoxides	Rat	intratracheal	LD_{Lo}	20 mg/kg
Nickel hydroxide	Rat	oral	LD_{50}	1500 mg/kg
Nickel acetate	Rat	oral	LD_{50}	350 mg/kg
		intraperitoneal	LD_{50}	23 mg/kg
Nickel chloride hexahydrate	Mouse	intraperitoneal	LD_{50}	48 mg/kg
Nickel sulphate	Mouse	intraperitoneal	LD_{50}	55 mg/kg
Nickel subsulphide	Guinea pig	intraperitoneal	LD_{Lo}	102 µg/kg

LD_{Lo} = lowest lethal dose; LC_{50} = concentration in inhaled air causing a 50% mortality within a specified time; LD_{50} = dose causing a 50% mortality.

kidney has been reported. After parenteral administration, hepatic and renal damage has been observed, as well as effects on the immune system (decreased thymus weight, decreased response of T lymphocyte to mitogens in vitro, decreased response to injected sheep erythrocytes and clearance of injected tumour cells from the lung, decreased natural killer cell activity in vitro).

After intratracheal instillation of nickel subsulphide to rats, histopathological changes were not observed after 24 h, but after 7 days, a multifocal alveolitis, with type II cell hyperplasia and interstitial fibroplasia, developed. Nickel oxide produced hyperplastic changes at a 10 times higher dose level.

10.3. Effects of repeated exposure

10.3.1 Systemic and organ effects (85, 87)

All mice died after inhalation exposure (6h/d, 5 d/w for 12 days, i.e. 2 weeks + 2 days) to nickel sulphate when the concentration was 1.6 mg/m^3 or more whereas some rats died after exposure to 13 mg/m^3. No mortality was observed in rats or mice after similar exposure to green nickel oxide at the highest concentration tested, 24 mg/m^3. All mice died after similar exposure to nickel subsulphide at a concentration of 7.3 mg/m^3, but none at 3.6 mg/m^3 (50). No exposure-related mortality, and only minor effects on body weight gain were observed in mice or

rats after a 13-week inhalation exposure (6h/d, 5d/w, for 13 weeks) to nickel sulphate hexahydrate (0.04 mg/m^3), nickel subsulphide (1.8 mg/m^3) or green nickel oxide (7.9 mg/m^3) (16, 51). Life-time inhalation exposure to 53 mg/m^3 nickel monoxide (unspecified) induced mortality in Syrian golden hamsters.

Oral administration of 22 mg/kg of nickel sulphate for three weeks was reported to give rise to hepatic and renal damage in rats. At 5.6 mg/kg testicular damage was observed. Hepatic and renal damage was also observed in rats after 90 daily i.p. injections of nickel sulphate (3 mg/kg).

Urinary albumin excretion was elevated, and kidney weight increased in rats after 6 months exposure to nickel sulphate in the drinking water (100 mg/L). Urinary total protein, lactate dehydrogenase, N-acetyl-β-glucosaminidase or β2-microglobulin were not changed (234).

10.3.2 Respiratory effects

Pulmonary effects of nickel and nickel compounds after different procedures of administration have been studied extensively in different rodent species. Below a summary is given on studies in which inhalation exposure was used. Unless otherwise stated, the descriptions are taken from Refs. 85 and 87.

Exposure to metallic nickel dust (1 mg/m^3, 4 weeks to 6 months) induced alveolar proteinosis in rabbits. Alveolar proteinosis was also observed in rats after exposure to black nickel oxide. The oxide inhibited the clearance of ferrous oxide particles from the lungs after 7 days of exposure at 50 µg/m^3.

Pulmonary (and other) effects of inhalation exposure to nickel sulphate, nickel subsulphide and green nickel oxide were studied in a 12-day and 13-week studies (6h/d, 5d/w) (16, 17, 50, 51). In the 12-day study, the concentrations of different nickel compounds used were (expressed as mg nickel/m^3): nickel sulphate (0.8, 1.6, 3.3, 6.7, and 13.3); nickel subsulphide (0.4, 0.9, 1.8, 3.6, and 7.3) and; nickel oxide (0.9, 2.0, 3.9, 7.9, and 23.6). For the 13-week study the concentrations used were: (0.02, 0.05, 0.1, 0.2 and 0.4) for nickel sulphate; (0.11, 0.2, 0.4, 0.9 and 1.8) for nickel subsulphide, and; (0.4, 0.9, 2.0, 3.9 and 7.9) for nickel oxide.

In the 12-day study nickel sulphate induced lung inflammation and atrophy of olfactory epithelium in rats at all dose levels. All mice at dose levels of 1.6 mg/m^3 and higher died of pneumonia, those at the lowest dose level had lung inflammation, and atrophy of olfactory epithelium. In the 13-week study, chronic active inflammation of the lungs and olfactory epithelial atrophy were observed in rats at the two highest dose levels. In mice, inflammation was less marked but olfactory epithelial atrophy was observed at the highest dose level. In addition, pulmonary fibrosis was also seen in mice at this dose level.

Nickel subsulphide induced inflammation (≥0.4 mg/m^3), olfactory atrophy (≥0.9 mg/m^3) but also pulmonary emphysema (≥3.6 mg(m^3) in rats in the 12-day study. In mice, lung inflammation (≥0.9 mg/m^3) and olfactory atrophy (≥0.9 mg/m^3), and occasionally, lung fibrosis were observed. Qualitatively similar

findings were obtained also in the 13-week study i.e. chronic active inflammation and olfactory atrophy both in rats and mice, and fibrosis in mice[3].

Nickel oxide induced lung inflammation in rats (≥7.9 mg/m^3) and in mice (23.6 mg/m^3 in the 12-day study. Chronic active inflammation was observed also in the 13-week study in rats (≥3.9 mg/m^3).

Life-time exposure of Syrian golden hamsters to an unspecified nickel oxide (53 mg/m^3) resulted in emphysema in animals that died early in the experiment.

Inhalation exposure to nickel carbonyl (30-60 mg/m^3, 90 min thrice a week for 52 weeks) induced extensive inflammatory lesions in the lungs, and contiguous pericarditis and suppurative lesions of the thoracic walls.

10.3.3 Immunological effects

Administration of nickel salts induced a suppression of the formation of antibodies to T1 phage in rats, of the antibody response to sheep erythrocytes, interferon production in vitro and in vivo in mice, and increased the susceptibility to pulmonary infection in mice (87).

A single high intramuscular dose (18.3 mg/kg) caused a significant reduction in murine splenic natural killer cell activity. The same phenomenon was observed when the dose was divided over a period of 14 days. The decrease in natural killer cell activity was accompanied by a reduction in the clearance of YAC-1 tumour cells from the lungs of the mice, as well as enhanced pulmonary tumour induction after injection of the mice with B16-F10 melanoma cells (195). Decreased natural killer cell activity was also observed in rats treated with 10 mg/kg nickel chloride or more. This was accompanied with increased mortality from injection with MADB106 tumour cells (196).

Decreased lymphoproliferative response to lipopolysaccharide antigen was the only indication of systemic immunotoxicity in mice given nickel sulphate in drinking water (5 g/L) for 180 days. At this dosage, the animals also showed nephrosis and thymic and splenic atrophy (43).

When mice were exposed by inhalation to nickel sulphate (0.027-0.45 mg/m^3), nickel subsulphide (0.11-1.8 mg/m^3), or green nickel oxide (calcined at 1350 °C, 0.47-7.9 mg/m^3) for 65 days, only the highest exposure to nickel subsulphide decreased the splenic natural killer cell activity. Nickel subsulphide or oxide had no effect on the pulmonary tumour yield after i.v. injection of B16F10 tumour cells, the effect of the highest concentration of nickel sulphate was borderline (68).

Nickel subsulphide, and to a lesser extent also nickel sulphate decreased the cytotoxicity of cultured human monocytes, and the numbers of CD4- and natural killer cells in vitro (245). Nickel subsulphide, sulphate and acetate also decreased hydrogen peroxide production by human monocytes in vitro (244).

[3]Note added in print: Effects of 2-6 mo exposure to nickel oxide and nickel sulphate on lung histopathology and clearance mechanisms was reported in: Benson JM, Chang I-Y, Cheng YS, et al. Particle clearance and histopathology in lungs of F344/N rats and B6C3F1 mice inhaling nickel oxide or nickel sulfate. *Fundam Appl Toxicol* 1995;28:232-244.

10.4. Mutagenicity and genotoxicity

A summary of the studies on the mutagenicity and genotoxicity of nickel and nickel compounds, as written by the IARC working group (85), is given below.

In one study, metallic nickel did not induce chromosomal aberrations in cultured human cells, but it transformed animal cells in vitro. Nickel oxides induced anchorage-independent growth in human cells in vitro and transformed cultured rodent cells, but in one study did not induce chromosomal aberrations in cultured human cells.

Crystalline nickel subsulphide induced anchorage-independent growth and increased the frequency of sister chromatid exchange but did not cause gene mutation in human cells in vitro. Crystalline nickel sulphide and subsulphide induced cell transformation, gene mutation and DNA damage in cultured mammalian cells. The sulphide also induced chromosomal aberrations and sister chromatid exchange. Amorphous nickel sulphide did not transform or produce DNA damage in cultured mammalian cells. In one study, crystalline nickel sulphide and crystalline nickel subsulphide produced DNA damage in Paramoecium.

Nickel chloride and nickel nitrate were inactive in assays in vivo for induction of dominant lethal mutations and micronuclei, and nickel sulphate did not induce chromosomal aberrations in bone marrow cells; however, nickel chloride induced chromosomal aberrations in Chinese hamster and mouse bone-marrow cells.

Soluble nickel compounds were generally active in the assays of human and animal cells in vitro in which they were tested.

Nickel sulphate and nickel acetate induced anchorage-independent growth in human cells in vitro. Nickel sulphate increased the frequency of chromosomal aberrations in human cells, and nickel sulphate and nickel chloride increased the frequency of sister chromatid exchange. Nickel sulphate did not induce single-strand DNA breaks in human cells. Nickel sulphate and nickel chloride transformed cultured mammalian cells. Chromosomal aberrations were induced in mammalian cells by nickel chloride, nickel sulphate and nickel acetate, and sister chromatid exchange was induced by nickel chloride and nickel sulphate. Nickel chloride and nickel sulphate also induced gene mutation, and nickel sulphate inhibited intercellular communication in cultured mammalian cells.

Nickel sulphate induced aneuploidy and gene mutation in a single study with Drosophila. Nickel chloride and nickel nitrate did not cause gene mutation. However, in yeast nickel chloride induced gene mutation and recombination.

In a single study, nickel acetate produced DNA damage in bacteria, while nickel nitrate did not; however, the results obtained with nickel chloride were inconclusive. In bacteria, neither nickel acetate, sulphate, chloride nor nitrate induced gene mutation.

Nickel carbonate induced DNA damage in rat kidney in vivo. Crystalline nickel subselenide transformed cultured mammalian cells, and nickel potassium cyanide increased the frequency of chromosomal aberrations. Nickelocene did not induce

bacterial gene mutation. DNA damage was induced in calf thymus nucleohistone by nickel(III)-tetraglycine complexes.

Insoluble particles of crystalline nickel sulphide, but not soluble nickel sulphate, induced a strong mutation response in an inserted E coli gpt gene in a hprt-deficient V79 cell line (121). Nickel sulphate induced DNA damage in isolated human and rat gastric mucosal cells, but only at concentrations that were cytotoxic (164).

Nickel chloride, nickel acetate and a nickel complex ($(C_2H_5)_4N_2)(NiCl_4)$) produced 2-6 fold increases of the control in the average number of 6-thioguanine resistant colonies in FM3A cells in suspension culture (145).

Nickel chloride induced chromosome aberrations in cultured CHO cells (81) and nickel sulphate induced chromosomal aberrations and micronuclei in cultured human lymphocytes (22).

Chinese hamster embryo cells were transformed to anchorage independence by high concentrations of ß-crystalline nickel sulphide or nickel chloride; chromosomal alterations were non-random, and were frequent in the long (heterochromatic) arm of the X-chromosome (35).

Crystalline nickel sulphide, nickel subsulphide and black and green nickel oxide were strongly mutagenic toward the gpt gene in two transgenic V79 cell lines while the response to nickel chloride was weak. Nickel sulphide, black nickel oxide and nickel chloride were not mutagenic to the hprt gene in the parent cell line (98).

Nickel subsulphide induced primarily point mutations or frameshift/small deletions, while soluble nickel sulphate induced primarily larger deletions in the transfected gpt gene in a Chinese hamster ovary cell line (183) Nickel hydroxide, a compound of limited solubility, was intermediate.

Nickel nitrate at concentrations up to 10 µmol/L did not induce mutations in Salmonella in an Ames test in the presence or absence of the S9-mix; nor was it positive in a rec-assay in Bacillus subtilis (212).

Nickel subsulphide, nickel oxide and nickel sulphate induced transformation of rat tracheal endothelial cells to enhanced growth variants. Nickel subsulphide was more potent than nickel oxide and sulphate. Further transformation to immortal growth variants took place after nickel subsulphide or sulphate treatment, but seldom after nickel oxide treatment (158).

Nickel sulphate induced an increase in sister chromatid exchange rates in cultured human lymphocytes, but only at concentrations (0.25 µmol/L) that also caused a cell cycle delay (184).

Further studies on nickel mutagenicity and genotoxicity are described in Section 9.2 "Mechanisms of genetic toxicity".

10.5. Carcinogenicity

A large number of carcinogenicity studies have been performed in several animal species using different nickel compounds and different routes of administration. Below, the summary of these studies, as documented by IARC (85) is given.

Metallic nickel was tested by inhalation exposure in mice, rats and guinea pigs, by intratracheal instillation in rats, by intramuscular injection in rats and hamsters, and by intrapleural, subcutaneous, intraperitoneal and intrarenal injection in rats. The studies by inhalation exposure were inadequate for an assessment of carcinogenicity. After intratracheal instillation, it produced significant numbers of squamous-cell carcinomas and adenocarcinomas of the lung. Intrapleural injections induced sarcomas. Subcutaneous administration of metallic nickel pellets induced sarcomas in rats, intramuscular injection of nickel powder induced sarcomas in rats and hamsters, and intraperitoneal injections induced carcinomas and sarcomas. A significant increase in the incidence of local kidney tumours was not observed following intrarenal injection.

Nickel alloys were tested by intramuscular, intraperitoneal and intrarenal injection and by subcutaneous implantation of pellets in rats. A ferronickel alloy did not induce local tumours after intramuscular or intrarenal injection. Two powdered nickel alloys induced malignant tumours following intraperitoneal injection, and one nickel alloy induced sarcomas following subcutaneous implantation in pellets.

Nickel monoxide was tested by inhalation exposure in rats and hamsters, by intratracheal instillation in rats, by intramuscular administration in two strains of mice and two strains of rats, and by intrapleural, intraperitoneal and intrarenal injection in rats. The two studies by inhalation exposure in rats were inadequate for an assessment of carcinogenicity. Lung tumours were not induced in the study in hamsters. Intratracheal instillation resulted in a significant incidence of lung carcinomas. Local sarcomas were induced at high incidence after intrapleural, intramuscular and intraperitoneal injection. No renal tumour was seen following intrarenal injection.

Two studies in rats in which nickel trioxide was injected intramuscularly or intracerebrally were inadequate for evaluation.

In a study in which nickel hydroxide was tested in three physical states by intramuscular injection in rats, local sarcomas were induced by dry gel and crystalline forms. Local sarcomas were induced in one study in which nickel hydroxide was tested by intramuscular injection in rats.

Nickel subsulphide was tested by inhalation exposure and by intratracheal instillation in rats, subcutaneous injection in mice and rats, by intramuscular administration to mice, rats, hamsters, and rabbits, by intrapleural, intraperitoneal, intrarenal, intratesticular, intraocular and intra-articular administration in rats, by injection into retroperitoneal fat in rats, by implantation into rat heterotopic tracheal transplants, and by administration to pregnant rats.

After exposure by inhalation, rats showed a significant increase in the incidence of benign and malignant lung tumours (adenocarcinomas, squamous-cell carcinomas ad mixed tumours).

A high incidence of local sarcomas was observed in rats after intrapleural administration. Subcutaneous injection induced sarcomas in mice and rhabdomyosarcomas and fibrous histiocytomas in rats. Nickel subsulphide has been shown consistently to induce local sarcomas following intramuscular administration, and dose-response relationships were demonstrated in rats and hamsters. The majority of the sarcomas induced were of myogenic origin, and the incidences of metastases were generally high. In rats, strain differences in tumour incidence and local tissue responses were seen. After intramuscular implantation of Millipore diffusion chambers containing nickel subsulphide, a high incidence of local sarcomas was induced.

Mesotheliomas were included among the malignancies induced by intraperitoneal administration. Intrarenal injections resulted in a dose-related increase in the incidence of renal-cell neoplasms. A high incidence of sarcomas (including some rhabdomyosarcomas) was seen after intratesticular injection, and a high incidence of eye neoplasms (including retinoblastomas, melanomas and gliomas) after intraocular injection. Intra-articular injection induced sarcomas (including rhabdomyosarcomas and fibrous histiocytomas), and injection into retroperitoneal fat induced mainly fibrous histiocytomas. Implantation of pellets containing nickel subsulphide into rat heterotopic tracheal transplants induced both carcinomas and sarcomas. In the group given the highest dose, sarcomas predominated. The study in which pregnant rats were injected with nickel subsulphide early in gestation was inadequate for evaluation.

Nickel disulphide was tested by intramuscular and intrarenal injection in rats. High incidences of local tumours were induced.

Nickel monosulphide was tested by intramuscular and intrarenal injection in rats. The crystalline form induced local tumours, but the amorphous form did not.

Nickel ferrosulphide matte induced local sarcomas after administration by intramuscular injection in rats.

Nickel sulphate was tested for carcinogenicity by intramuscular and intraperitoneal injection in rats. Repeated intramuscular injections did not induce local tumours; however, intraperitoneal injections induced malignant tumours in the peritoneal cavity.

Nickel chloride was tested by repeated intraperitoneal injections in rats, inducing malignant tumours in the peritoneal cavity.

Nickel acetate was tested by intraperitoneal injection in mice and rats. After repeated intraperitoneal injections in rats, malignant tumours were induced in the peritoneal cavity. In Strain A mice, lung adenocarcinomas were induced in one study and an increased incidence of pulmonary adenomas in two studies.

Studies in rats, in which nickel carbonate was tested for carcinogenicity by intraperitoneal administration and nickel fluoride and nickel chromate by intramuscular injection could not be evaluated.

Nickel carbonyl was tested for carcinogenicity by inhalation exposure and intravenous injection in rats. After inhalation exposure, a few lung carcinomas were observed two years after the initial treatment. Intravenous injection induced an increase in the overall incidence of neoplasms, which were located in several organs.

Nickelocene induced some local tumours in rats and hamsters following intramuscular injection.

One sample of dust collected in nickel refineries, containing nickel subsulphide and various proportions of nickel monoxide and nickel sulphate, induced sarcomas in mice and rats following intramuscular injection. Intraperitoneal administration of two samples of dust, containing unspecified nickel sulphides and various proportions of nickel oxide, soluble nickel and metallic nickel, induced sarcomas in rats. In a study in which hamsters were given prolonged exposure to a nickel-enriched fly ash by inhalation, the incidence of tumours was not increased.

Intramuscular administration to rats of nickel sulpharsenide, two nickel arsenides, nickel antimonide, nickel telluride and tow nickel selenides induced significant increases in the incidence of local sarcomas, whereas administration of nickel monoarsenide and nickel titanate did not. None of these compounds increased the incidence of renal-cell tumours in rats after intrarenal injection.

After the IARC evaluation, following studies on the carcinogenicity of different nickel compounds in experimental animals have become available:

In 1992, Haratake and co-workers (69) exposed male Wistar rats to green nickel oxide (mass median aerodynamic diameter ± geometric standard deviation 4.1 ± 2.2 µm), black nickel oxide (3.6 ± 2.3) or nickel subsulphide (2.6 ± 1.9) at air concentrations of 1.1, 1.3 or 0.5 mg/m^3, respectively, 6h/d, 5d/w for six months. After a clearance period of 12 months, the animals were killed, and autopsy and histopathological examination of the lungs, liver, pancreas, kidneys, spleen and of the head and neck organs en block were performed. The survival was not different and no increase was observed in the tumour rates in treated or control rats. The short duration of exposure and follow-up, together with the low dose level, hamper the interpretation of this study.

A non-specified nickel oxide was included in an extensive study on the pulmonary carcinogenicity of particulate and fibrous matters, in which the materials were administered by intratracheal instillation to female Wistar rats (167). Nickel oxide (10 x 3 mg) induced a low frequency of adenocarcinomas and squamous cell carcinomas, together with a high frequency of "cystic keratinizing squamous cell tumours (benign)".

When different nickel oxides and nickel copper oxides were administered to Fischer 344 rats intramuscularly, the following tumour rates were observed: 6/15 for black nickel oxide, calcined at <650 °C; 0/15 for green nickel oxide, calcined at 735 °C; 0/15, green nickel oxide, calcined at 1045 °C; 13/15 for nickel-copper oxide at a ratio of 2.5:1: and; 15/15 for nickel-copper oxide at a ratio of 5:1. Nickel subsulphide was used as the positive control and induced 15/15 tumours in rats (207).

After intramuscular implantation of rods of different materials, high nickel alloy (96.2% Ni) induced a high frequency of implantation site sarcomas in mice, while the other materials tested, including a stainless steel (17.8% Cr, 12.51% Ni) did not induce implantation-site-tumours (209).

In a short-term carcinogenicity study in strain A mice, increase in the number of animals with pulmonary adenomas or the number of pulmonary adenomas per animal was not observed after intraperitoneal or intratracheal treatment with nickel subsulphide (137).

Five out of 16 rats developed injection site sarcomas after a subcutaneous injection of nickel acetate 22-66 weeks after the administration (212).

In an initiation-promotion experiment, nickel(II)acetate was injected intraperitoneally into rats as an initiator, followed by promotion with phenobarbital (101). Induced renal cortical adenomas and/or carcinomas were observed in 16/24 animals.

The US National Toxicology program has performed 104-week inhalation carcinogenicity studies with nickel(II) oxide, nickel sulphate hexahydrate and nickel subsulphide using male and female Fischer 344 rats and female and male B6C3F1 mice. When the present review was being written, these studies were in the "with post peer review, final technical report in progress" stage, and only the conclusions of the results, reported below, were available (Internet: http://ntp-server.niehs.gov/)[4]

For nickel(II)oxide, the air nickel concentrations were 0, 0.62, 1.25 or 2.5 mg/m^3 for rats and 0, 1.25, 2.5 or 5.0 mg/m^3 for mice. The conclusion was that there was "some evidence" of carcinogenicity in male and female rats, "no evidence" in male and "equivocal evidence" of carcinogenicity in female mice (Internet: http://ntp-server.niehs.gov/htdocs/Results_status/ResstatN/1198-D.ht).

For nickel sulphate hexahydrate, the concentrations used were 0, 0.125, 0.25 or 0.5 mg/m^3 for rats and 0, 0.25, 0.5 or 1.0 mg/m^3 for mice. There was "no evidence" of carcinogenicity in either male or female rats or mice (Internet: http://ntp-server.niehs.gov/htdocs/ Results_status/ResstatN/1027-X.ht).

For nickel subsulphide, the nickel concentrations used were 0, 0.075 or 0.15 mg/m^3 for rats and 0, 0.6 or 1.2 mg/m^3 for mice. There was "clear evidence" of carcinogenicity in male and female mice, and "no evidence" in male or female mice (Internet: http://ntp-server.niehs.gov/htdocs/ Results_status/ResstatN/11234-V.ht).

10.6. Reproductive and developmental toxicity (85, 87)

Nickel chloride (1.2 - 6.9 mg/kg), administered intraperitoneally caused increased resorption, decreased foetal weight, delayed skeletal ossification and malformations mainly in the brain and the skeletal system in ICR mice. Mortality of dams was observed at dose levels of 4.6 mg/kg or more. In Wistar rats, nickel chloride induced hydrocephalus, haemorrhage, hydronephrosis and skeletal retardation after intraperitoneal administration. The occurrence of malformations was highest at dose levels that were toxic to the dams. No malformation were

[4]Note added in print: This study has been published: Dunnick JK, Elwell MR, Radovsky AE, et al. Comparative carcinogenic effects of nickel subsulfide, nickel oxide, or nickel sulfate hexahydrate exposures in the lung. Cancer Res 1995;55:5251-5256.

observed in Fischer rats after treatment with similar doses of nickel chloride intramuscularly.

Three studies have reported increase in embryonic mortality in rats after administration of soluble nickel salts in drinking water (0.1 mg/L or more).

Nickel carbonyl has been shown to induce malformations, increase foetal mortality and decrease the weight of the pups in rats after intravenous and inhalation exposure, and in hamsters after inhalation exposure, in the absence of maternal toxicity. In rats, the malformations include anophthalmia, microphthalmia, cystic lungs and hydronephrosis, in hamsters cystic lungs, exencephaly, fused ribs, anophthalmia, cleft palate, hydronephrosis and haemorrhage into serous cavities.

Nickel subsulphide, administered intramuscularly to rats, reduced the number of live pups. Malformations were not observed.

Nickel chloride in drinking water (10, 50 or 250 ppm) throughout the gestation induced an increase in the proportion of dead pups in rats, whereas no overt toxicity was observed in the dams (except a decrease of the weight gain at the highest dose level) (197).

Nickel chloride was teratogenic and embryotoxic to the frog Xenopus laevis, inducing malformations mainly in the eyes, skeleton, and gastrointestinal tract. Malformations were found in >95% of the embryos at concentrations in excess of 5.6 µmol/L (76, 80). Malformations were also observed in tadpoles after treatment of the embryos by nickel (162).

11. Observations in man

11.1. Acute effects by contact and systemic distribution

Nickel carbonyl causes a chemical pneumonitis which may be fatal. The immediate symptoms after exposure include headache, vertigo, nausea, vomiting, insomnia and irritability. The initial symptoms are followed by a symptomless interval and thereafter, symptoms reminiscent of a pneumonia develop: chest pain, cough, dyspnoe, cyanosis, tachycardia, sweating and weakness. Death is caused by pulmonary oedema and haemorrhages (87).

A fatal case of nickel poisoning by the oral route has been described. A two and a half year old girl died after ingesting an estimated dose of 15 g of nickel sulphate (40). Nausea, vomiting, abdominal discomfort, diarrhoea, giddiness, lassitude, head ache, cough and shortness of breath were reported by a group of workers who accidentally drank water contaminated with nickel sulphate and nickel chloride. The estimated dose of nickel was 0.5 to 2.5 g. All recovered uneventfully within 1-2 days (206). A similar array of symptoms was reported in dialysis patients, when leaching from a nickel-plated tank contaminated the dialysate. The serum concentration of nickel in these patients with acute symptoms was approximately 3 mg/L (240).

A case of fatal adult respiratory distress syndrome caused by inhalation of fine nickel fume at a high concentration has been described (177). A simulation of the exposure situation suggested that the peak concentration of nickel in the air had been 382 mg/m^3. An incident involving 13 workers with a similar illness - with one ending fatally - that occured after exposure to fine particulate nickel in 1943, has also been described (185).

11.2. Effects of repeated exposure on organ systems

11.2.1 Cardiovascular diseases

Mortality from circulatory disease was not elevated in the Falconbridge refinery cohort (191, 192) or in the INCO Ontario cohort (181). There was an excess mortality from circulatory disease (SMR 115) in the Clydach cohort; however, this disappeared in comparison to local rather than national rates, and the excess was largest among those that were least exposed (161). The SMR from circulatory diseases was 0.78 among the gaseous diffusion plant workers (39), 0.93 ($p<0.01$) among white and 0.82 ($p<0.01$) among non-white male high nickel alloy workers (175), 0.99 (SPMR) among nickel/chromium alloy foundry workers (36), 0.74 ($p<0.05$) among nickel alloy welders (163), but 1.16 ($p<0.01$) among workers engaged in stainless steel and nickel alloy steel production (36) and 1.25 (NS) among nickel alloy manufacture workers in Hereford, UK (38).

11.2.2 Skin diseases

Nickel-induced occupational dermatitis was described already in 1889, when Blaschko described the disease among "metal galvanisers", and noted that among the metals used in galvanising, nickel seemed to be most potent cause of skin disorders (20).

Nickel allergy is the most frequent contact allergy both in the general female population and among female patients evaluated by dermatologists for eczematous skin disease. It affects 8-30% of females and 0.8-3% of males (46, 59, 106, 139, 153, 159). Primary sensitisation to nickel from e.g. consumer items, such as earrings, metal buttons, etc., is usually a minor event and is not considered sufficiently serious to entail contact with a doctor. However, nickel allergy increases the risk of hand eczema (139, 155, 242).

Alloys releasing more than 1 µg nickel/cm^2/week in synthetic sweat gave a strong patch test reaction in nickel sensitive persons, while alloys releasing less than 0.5 µg/cm^2/week usually gave only a weak reaction (140). Enough nickel to induce an allergic reaction in sensitised people may occasionally also leach from stainless steel. Nickel release is greater from stainless steels with high sulphur content (74, 96, 97).

Some studies have reported that people with atopic dermatitis were more prone to react to nickel in a patch test (46, 82) while no such susceptibility has been observed in several other studies (55, 59, 136, 154, 238). Sensitivity to nickel does not seem to be associated with any specific HLA type (56).

Patients sensitive to nickel are often also sensitised to cobalt. Positive patch tests to cobalt in the absence of a positive reaction to nickel is unusual (133). Based on experimental studies in guinea pigs, it has been considered likely that this is due to concomitant exposure rather than to cross reaction (126). In comparison, nickel and palladium produce a "true" cross-reaction (95, 235).

Patients with psoriasis had a lower frequency of allergic patch test reactions to nickel than healthy controls (59).

In a study on 1140 consecutive patients, referred to by a Danish department on occupational dermatology, 8% of male and 30% of female patients were positive in the standard patch-test to nickel. In investigating the occupational exposure of these patients, the dimethylglyoxime (DMG) leach test was used to identify sources of nickel exposure. Positive items included a large variety of different tools (e.g., screw-drivers, tongs, forceps, drills and bits, screws, nuts, spanners, vices, pipes, keys and roller handles), but also the inside of protecting gloves, as well as tables, handles and banisters outside the plating hall in a nickel plating facility. Further, DMG-positive items included black-nickel plated instruments, and aluminium sheets of different colours, sealed with nickel (124, 125). Nickel has also induced dermatitis in exposure to coins (64). Nickel was the most common chemical to which workers in ceramic workers with hand eczema were sensitised (190).

Some nickel-allergic patients with hand eczema benefit from reduction of nickel in the diet (60, 93, 229, 230). However, at least a part of nickel-sensitive patients with hand or other eczema tolerate well a long-treatment with oral nickel sulphate (187, 188)

Ear piercing is a significant risk factor for nickel sensitisation (46, 106, 136, 138, 154, 168).

Nickel is a very uncommon cause of immediate allergy (57). A few cases of chronic urticaria caused by oral intake of nickel have also been described (1, 242).

11.2.3 Respiratory diseases

In early Russian studies, chronic rhinitis, nasal septal erosions, ulcerations and perforations have been described in workers exposed to high concentrations of nickel-containing fumes (among other chemicals, such as sulphuric acid). Hypo- and anosmia has also been reported in these workers. The work of Torjussen demonstrated frequent epithelial dysplasia in nasal biopsy specimens from workers in roasting/smelting as well from the electrolysis department of a Norwegian nickel refinery (87).

Elevated mortality (20 observed, 11.1 expected) from non-malignant respiratory diseases was reported among the most heavily exposed workers of the Welsh nickel refinery hired before 1925. Less heavily exposed workers suffered no such excess (43 observed, 51.2 expected) (161). Similarly, a statistically significant excess mortality (standardised proportional mortality ratio, 1.40, $p < 0.01$) from respiratory (non-cancer) diseases was observed among nickel/chromium foundry workers. This excess was related to the length of foundry employment. However,

no nasal cancer was observed in this cohort (0.8 expected), and the lung cancer mortality was not elevated (36).

No excess mortality from non-cancer respiratory diseases was observed among workers in the INCO Ontario refinery (181), Falconbridge Ontario refinery (191, 192) or among workers in a nickel alloy manufacturing plant, where the estimated exposure to metallic nickel and nickel oxide was 0.5-0.9 mg/m^3 (38). Mortality from non-cancer respiratory diseases was not elevated in the Oak Ridge Gaseous Diffusion Plant workers, exposed to low levels, (see "Long-term exposures", Section 12.2) of metallic nickel (39), in welders of these facilities exposed to nickel oxides (welders of nickel-alloy pipes) (163), or among high nickel alloy production workers in the U.S.A. (175).

Cases of pulmonary fibrosis and pneumoconiosis have been described among workers exposed to nickel dusts and fumes (87). In the Falconbridge Ontario cohort, mortality from pneumoconiosis was grossly elevated (SMR 877, $p<0.001$), but the cohort included miners known to be exposed to silica dust (192). No radiological evidence of fibrosis was observed in a study on 745 nickel sinter plant workers. For 80% of the workers, the duration of exposure had been < 5 years and for 65% of the workers, the follow-up study was 30 years or more (148).

Nickel may cause asthma, but this seems to be very rare (21, 31, 57, 132, 135); all reported cases so far have been due to occupational exposure to nickel. Seven out of eight patients with hard-metal asthma also reacted to nickel sulphate inhalation with a drop in FEV (193).

A few cases of eosinophilic pneumonia, considered to be caused by nickel have been published (87, 221)

11.2.4 Renal diseases

A transient increase in the urinary excretion of albumin was observed in three workers (out of 32 exposed) who accidentally ingested an estimated dose of 0.5 to 2.5 g of nickel sulphate (206). Proteinuria was not observed among 17 workers in a nickel electroforming facility, where there was an outbreak of nickel dermatitis (238).

Urinary excretion of β_2-microglobulin was elevated in an exposure-related fashion in nickel refinery workers, whose average urinary nickel concentration was 231 (SD 490) µg/L. No elevation of β_2-microglobulin excretion was observed among electroplaters who showed an average urinary nickel excretion of 6.1 (SD 6.0) µg/L (208).

Serum creatinine, urinary total protein and β_2-microglobulin were within the normal range among workers exposed to nickel in two electrolytic refining plants. The average concentration of urinary nickel was 28 (SD 6) and 60 (SD 30) µg/L (186).

No difference was observed in the urinary excretion of lactate dehydrogenase, albumin or transferrin among workers in a chemical plant, where they were exposed to soluble salts of nickel at levels reported to exceed 4 to 26 times the occupational exposure limit of 50 µg/m^3. The urinary excretion of nickel

(5 - 10.3 µg/g creatinine) correlated with that of β_2-microglobulin both in men and women, and with N-acetyl-β-D-glucosaminidase in men (232).

No difference in the levels of several markers of kidney damage in the urine (such as total protein, albumin, protein 1, transferrin, retinol binding globulin, lactate dehydrogenase, lysozyme, N-acetylglucosamine of β-aminoisobutyric acid) was observed between welders of stainless steel and referents (217, 233). A minor elevation of β_2-microglobulin was observed among welders with highest urinary chromium levels (233).

11.3. Genotoxic effects

The International Agency for Research on Cancer summarised the data on genotoxicity of nickel/nickel compounds in humans in vivo as follows:

In four studies, the frequency of sister chromatid exchange did not appear to be increased in peripheral blood lymphocytes of nickel workers exposed during various processes. Enhanced frequencies of chromosomal gaps and/or anomalies were observed in single studies in peripheral blood lymphocytes of employees engaged in: (i) crushing, roasting and smelting (exposure mainly to nickel oxide and nickel subsulphide); (ii) electrolysis (exposure mainly to nickel chloride and nickel sulphate); and (iii) electroplating (exposure to nickel and chromium compounds). Enhanced frequencies were also seen in lymphocytes from retired workers who had previously been exposed in crushing, roasting and smelting and/or electrolysis.

Elevated frequencies of sister chromatid exchanges were observed in lymphocytes from workers exposed to metallic chromium, cobalt, iron and nickel dust in a metal powder producing factory, when compared to age- and smoking habit- matched referents. Nickel exposures ranged from 31 to 336 µg/m^3 (medians of two plants at two different time points, three years apart), those for chromium between 32 and 3818, and for cobalt, between 10 and 164 µg/m^3 (61).

No increase was observed in the frequency of micronuclei in oral mucosal epithelial cells in workers from the electrolytic department of a nickel refinery (111).

The International Agency for Research on Cancer summarised the data on genotoxic effects observed among stainless steel welders, who are exposed to both chromium and nickel:

One of three studies showed increased levels of sister chromatid exchange and chromosomal aberrations in peripheral blood lymphocytes of workers exposed during stainless-steel welding. The greater frequencies of sister chromatid exchanges were found in exposed workers who smoked.

The frequency of chromosomal aberrations was elevated among welders employing the metal active gas welding technique. These welders also had elevated levels of nickel and manganese both in serum and urine. However, no correlation was observed between the frequency of chromosomal aberrations and blood/urine nickel concentrations. Other welders of either stainless steel or mild

steel showed neither elevated chromosome aberration frequencies nor elevated nickel or manganese levels (53).

In a German study (165, 166), SCE's were less frequent in the lymphocytes from welders than in those from controls, but their frequency showed a significant positive correlation with the urinary chromium concentration. Slower alkaline elution of DNA among welders was interpreted as indicating increased DNA-protein cross links. No elevation of SCE frequencies were seen in a Danish study either, where tungsten inert gas (TIG), metal inert gas (MIG) and manual metal arc (MMA)+TIG welders were studied separately. Similarly, unscheduled DNA synthesis in lymphocytes did not differ between welders and referents. On the other hand, stainless steel (SS)-welders, and MMA+TIG welders showed elevated chromosomal aberration frequencies in lymphocytes - TIG and MIG welders showed no such elevation (116).

A Norwegian study reported an elevated frequency of chromatid breaks in MMA welders of stainless steel, when compared to a non-exposed referent group. The difference was most marked in non-smokers (90) No such change was observed in welders using MIG, TIG or metal active gas (MAG)-techniques (91).

11.4. Carcinogenic effects

Carcinogenicity of nickel was first suspected in 1920's, when there was a query in the British Parliament on the high rates of nasal cancer among the workers of the Clydach nickel refinery in Wales. In 1933, a report was published in which the high frequency of nasal cancer mortality was verified, in 1939 a formal epidemiological study was performed confirming the same findings plus adding lung cancer among the nickel-induced cancers; however, the study was not published. In 1949 cancer of the lung and of the nose among workers in nickel refineries was prescribed as an industrial diseases in UK, and in 1958 two epidemiological studies were published that unequivocally showed that the risk of nasal and lung cancer were elevated among the nickel refinery workers (44, 142).

Similar findings have also been occurred in Norway, Ontario Canada and Oregon, USA. Several of these cohort studies were updated starting in 1984, and published in 1990 (45). In addition to the combined report (45), reports on some of the individual cohorts have also been published (180, 181, 192). This reanalysis profoundly changed the prevailing views concerning the identity of which nickel species are carcinogenic to humans. Earlier it had been thought that the carcinogenicity was limited to insoluble nickel species, notably nickel sulphides. This was likely to be present in the different departments in nickel refineries where the highest cancer risks were observed, and also where the highest exposures occurred. The evaluations of the carcinogenicity of nickel and its compounds by IARC, and IPCS, were very much based on the results of this study. The IARC summary of these studies is given below, followed by a description of more recent relevant studies. The data are also depicted in Tables 4-6, reproduced from IARC (85).

Increased risks for lung and nasal cancers were found to be associated with exposures during high-temperature oxidation of nickel matte and nickel-copper matte (roasting, sintering, calcining) in cohort studies conducted in Canada, Norway (Kristiansand) and the UK (Clydach). In the Norwegian study exposure occurred during electrolytic refining and in the UK study during leaching of nickel-copper oxides in acidic solution (copper plant) and extraction of nickel salts from concentrated solution (hydrometallurgy) (see Table 26 in Ref. 85).

The substantial excess risk for lung and nasal cancer among Clydach hydrometallurgy workers seems likely to be due, at least partly, to their exposure to 'soluble nickel'. Their estimated exposures to other types of nickel (metallic, sulphidic and oxidic) were up to an order of magnitude lower than those in several other areas in the refinery, including some where cancer risks were similar to those observed in hydrometallurgy. Similarly, high risks for lung and nasal cancers were observed among electrolysis workers at Kristiansand. These men were exposed to high estimated levels of soluble nickel and to lower levels of other forms of nickel. Nickel sulphate was the only or predominant soluble nickel species present in these areas.

The highest risks for lung and nasal cancers were observed among calcining workers, who were heavily exposed to both sulphidic and oxidic nickel. A high lung cancer rate was also observed among nickel plant cleaners at Clydach, who were heavily exposed to these insoluble compounds, but with little or no exposure to soluble nickel. The separate effects of oxides and sulphides cannot be estimated, however, as high exposure was always either to both, or to oxides together with soluble nickel. Workers in calcining furnaces and nickel plant cleaners were also exposed to high levels of metallic nickel.

Among hard-rock sulphide nickel ore miners in Canada, there was some increase in the risk for lung cancer, but exposure to other substances could not be excluded. In studies of open-cast miners of silicate-oxide nickel ores in the USA and in New Caledonia, no significant increase in risk was observed, but the numbers of persons studied were small and the levels of exposure were reported to be low.

No significant excess of respiratory tract cancer was observed in three studies of workers engaged in the manufacture of high-nickel alloy or in a small study of users of metallic nickel powder. An increased risk for lung cancer was not observed in one small group of nickel electroplaters in the UK with no exposure to chromium.

In a case-control study, an elevated risk for lung cancer was found among persons exposed to nickel together with chromium-containing materials.

The results of epidemiological studies of stainless-steel welders are consistent with the finding of excess mortality from lung cancer among other workers exposed to nickel compounds, but they do not contribute independently to the evaluation of nickel since welders are also exposed to other compounds.

Elevated lung or nasal cancer risk was not observed in a cohort study on hydrometallurgical nickel refinery workers in Canada. However, the cohort size

was rather small (716 workers), the mean duration of the follow-up was only 18 years, and the total mortality of the cohort only 57% of the expected (indicating less than complete follow-up) (52). The risk of nasal and lung cancer in workers with more than five years of exposure at the sintering operations in Copper Cliff or in sintering, leaching, calcining and sintering in Port Colborne remained very similar during the years after the cessation of exposure: very little change could be observed even 30 years later (147). This emphasises the importance of long-term follow-up study in order to fully realise the total extent of the cancer risk.

In Port Colborn there were also pockets of increased lung cancer risk in areas where nickel exposure was low, one of them being the copper refinery (SMR = 137). There, the lung cancer mortality was highest among lead welders, tank house crane men, and arc furnace workers. The exposure to sulphur dioxide and arsenic also were considered to be low, and the most likely cause of this cancer was thought to be exposure to polycyclic aromatic hydrocarbons (231).

A Finnish study detected one case of nasal cancer (vs. 0.02 expected) among workers of a nickel refinery, where the exposure had been mostly to soluble nickel salts between 0.1 and 0.5 mg/m^3. Shortly after the studies end, two further cases of sinonasal cancer were diagnosed, and although the expected numbers have not been calculated, it is apparent that the SIR must be grossly elevated (99).

No increase in lung or nasal cancer was observed in a cohort study on workers in nickel mining and refining in New Caledonia (63). However, the incidence of respiratory cancer among the New Caledonian population is considerably higher than that in the neighbouring Pacific islands, and 1/4 of the whole male population works or has worked in nickel mining or refining. The nasal cancer incidence in New Caledonia is higher even than that in western European countries. These studies therefore, are non-positive rather than negative. However, no nickel-related elevation of the incidence of lung cancer was observed, either, in a case-referent study within the cohort. A likely explanation is that the exposure is and apparently has always been low. The highest exposures have apparently been below 2 mg/m^3, and the highest exposures to sulphidic or soluble nickel seems to have been below 0.1 mg/m^3 (63).

One small study suggested that tobacco smoking and nickel exposure may interact in carcinogenesis (118). A further report on the same cohort showed that the interaction was closer to additive than multiplicative (131).

Welders of stainless steel are exposed to nickel; therefore, epidemiological studies on welders may also be used in the assessment of the cancer risks caused by nickel. IARC has evaluated the cancer risks of welding (86). The IARC summary of included studies is summarised below, followed by a description of the studies published thereafter.

Two cohort studies of lung cancer mortality among persons in various occupations did not show significant increases in risk among welders. A total of three pleural mesotheliomas was reported from one of these studies. One large cohort study conducted in the UK showed an almost two-fold excess risk for lung cancer among shipyard welders, which was not confirmed when comparison was

made with a local referent population. A moderately increased incidence of lung cancer was found in a large study of shipyard welders in Finland. Five studies conducted in the USA and Europe indicated an increased risk for lung cancer of about 30%.

A large European cohort study, including three cohorts reported previously, detected statistically significant increases in both the incidence of and mortality from lung cancer but demonstrated no consistent difference in cancer risk among stainless-steel welders as compared to mild-steel welders or to shipyard welders. In addition, five deaths were due to mesothelioma.

Of the 12 case-control studies on the association between lung cancer and exposure or employment as a welder, two detected no excess risk. Of the remaining ten, four showed a moderate excess, which was statistically significant in the largest study conducted in the USA. The other six studies, of welders in various occupations, gave risk estimates exceeding a two-fold increase, which in four of the studies was statistically significant.

Four case-control studies conducted on bladder cancer - two in Canada, one in the USA and one in the Federal Republic of Germany - addressed the possible role of exposures during welding. A significantly increased risk was only reported in one of the two Canadian studies.

Two case-control studies of leukaemia from the USA reported an elevated relative risk for myeloid leukaemia. No overall excess risk for either acute or all leukaemia was observed in a pooled analysis of data from several studies of welders.

Of the case-control studies of cancers at other sites, one on nasal cancer carried out in the Nordic countries, one on laryngeal cancer from Denmark and one on pancreatic cancer from Sweden reported elevated relative risks among welders.

In a case-referent study of lung cancer among Los Angeles county welders, the odds ratio for stainless steel welding was 0.9 (95% CI 0.5-1.8), that for manual metal arc welding of stainless steel 1.3 (0.6-2.3), and that for mild steel welding, 1.6 (0.8 -3.1) (83).

The German study on welders (which was part of the IARC cohort study (194), referred to above as "a large European study") was later updated (14) showing that mortality from lung cancer was not elevated (SMR = 113, 95% CI 67-191). In France, the cohort was also further expanded, and smoking habits were included in the analysis (146). In this study, an increase in the lung cancer mortality, which was related to duration of exposure, was observed among non-ship yard welders of mild steel. For welders of stainless steel, no such elevation was observed.

11.5. Reproductive and developmental effects

In a short report on a prevalence study of various illnesses in nickel-exposed people in an electrolytic nickel refinery in Russia, it was reported that the frequency of spontaneous abortion and threatened abortion, as well as that of structural malformations was elevated among nickel-exposed in comparison to non-exposed referents (construction workers). The authors note that there were

serious limitations in the statistical analysis and sampling details of the pregnancies and new-born (29).

No difference was observed in the semen quality between stainless steel welders and non-welders from the same plant, or non-exposed referents (92)

12. Dose-effect and dose-response relationships

12.1. Single/short-term exposure

It has been estimated (although no data to support this notion were provided) that a 30 min exposure to 30 cm^3/m^3 nickel carbonyl may be fatal to humans (24, 123, 134). For the relationship between urinary concentrations of nickel, and predicted severity of intoxication by nickel carbonyl (see "Biological monitoring", Section 8).

12.2. Long-term exposure

The International Committee on Nickel Carcinogenesis in Man, which performed the updating of major nickel refinery cohorts to assess the carcinogenicity of nickel (45) re-evaluated the exposure to nickel in different refineries. These data have been reproduced in Tables 4-6, and can be used to assess the dose-response relationships for nickel carcinogenesis. However, these exposure estimates involve major uncertainties as there are no contemporary measurements of nickel in the air. Konimeter readings were the only way to assess the dust exposure even a long time after the relevant exposures took place, and conversion of these measures to total dust concentrations is an approximation at best. Actual measurements are not available for the different nickel species, and the values shown in Tables 4-6 are estimates based on knowledge of the chemical processes involved. Therefore, the concentrations must be viewed as indications of the order of magnitude of different exposures (85).

With all these reservations in mind, it would seem that greatly elevated cancer risks were observed in facilities, where the exposure to soluble nickel was approximately 1 mg/m^3, independent of other nickel exposures. Similarly remarkably elevated cancer risks were observed, in the absence of exposure to soluble nickel species, when the exposure to sulphidic or oxidic nickel was ≥1-10 mg/m^3. Sulphidic and oxidic nickel cannot be separately evaluated because they always occurred together. Exposure to metallic nickel did not occur in the absence of clearly carcinogenic exposures to either soluble or oxidic/sulphidic nickel, its carcinogenic potency thus cannot be estimated from refinery studies.

In a small cohort of people exposed to pure metallic nickel powder in a gaseous diffusion plant no elevation of lung or nasal cancer was observed (45). The median concentration of nickel in the air was 0.13 mg/m^3, with occasional high concentrations in some areas leading to an estimated average exposure of 0.5 mg/m^3 (85).

In the study in New Caledonia (63), where the exposure was mainly to oxidic and metallic nickel, and seldom if ever exceeded 2 mg/m^3, excess lung cancer was not observed.

In the study in the Finnish electrolytic nickel refinery, elevated nasal cancer risk was observed in exposure to soluble nickel at levels of 0.1 - 0.5 mg/m^3 (99).

Considering all the data together, it would seem that soluble nickel salts will increase the risk for cancer at exposure levels exceeding 0.1 mg/m^3, for other nickel compounds such an elevation has been demonstrated at approximately 1 mg/m^3. For metallic nickel or nickel alloys, no reliable quantitative estimation of cancer risk can be performed because they have not been shown to induce cancer in humans in the absence of other nickel species.

13. Previous evaluations by international and national bodies

13.1. IARC and IPCS

International Agency for Research on Cancer has evaluated the carcinogenicity of nickel and nickel compounds in 1989 (85). The evaluation was worded as follows:

There is sufficient evidence in humans for the carcinogenicity of nickel sulphate, and of the combinations of nickel sulphides and oxides encountered in the nickel refining industry.

There is inadequate evidence in humans for the carcinogenicity of metallic nickel and nickel alloys.

There is sufficient evidence in experimental animals for the carcinogenicity of metallic nickel, nickel monoxides, nickel hydroxides and crystalline nickel sulphides.

There is limited evidence in experimental animals for the carcinogenicity of nickel alloys, nickelocene, nickel carbonyl, nickel salts, nickel arsenides, nickel antimonide, nickel selenides and nickel telluride.

There is inadequate evidence in experimental animals for the carcinogenicity of nickel trioxide, amorphous nickel sulphide and nickel titanate.

The Working Group made the overall evaluation on nickel compounds as a group on the basis of the combined results of epidemiological studies, carcinogenicity studies in experimental animals, and several types of other relevant data, supported by the underlying concept that nickel compounds can generate nickel ions at critical sites in their target cells.

Overall evaluation

Nickel compounds are carcinogenic to humans (Group 1).

Metallic nickel is possibly carcinogenic to humans (Group 2B).

The conclusion of the International Programme on Chemical Safety (IPCS) in 1989 on the carcinogenicity of nickel and nickel compounds was (87):

Although some, and perhaps all, forms of nickel may be carcinogenic, there is little or no detectable risk in most sectors of the nickel industry at current exposure levels. This includes some processes that were associated, in the past,

with very high lung and nasal cancer risks. Long-term exposure to soluble nickel at concentrations in the order of 1 mg/m^3 may cause a marked increase in the relative risk of lung cancer, but the relative risk among workers exposed to average metallic nickel levels of about 0.5 mg/m^3 is approximately one. The cancer risk at a given exposure level may be higher for soluble nickel compounds than for metallic nickel and, possibly, than for other forms as well. The absence of any marked lung cancer risk among nickel platers is not surprising, as the average exposures to soluble nickel are very much lower than those in electrolytic refining or nickel salt processing.

13.2. Other

Nickel monoxide, dioxide, trioxide, sulphide and subsulphide are listed as category 1 carcinogens, nickel, nickel carbonyl, hydroxide, sulphate and carbonate as category 3 carcinogens in the European Union (33, 34). For the purpose of protection of workers from the risks related to exposure to carcinogens at work, the category 1 carcinogens (32), as well as work involving exposure to dusts, fumes and sprays produced during the roasting and electrorefining of cupro-nickel mattes are considered carcinogenic in the European Union (37). In the legislation concerning occupational exposure to chemicals, nickel and nickel compounds are listed as carcinogens in Denmark, Finland and Norway (8, 9, 224). In Sweden, nickel compounds, but not nickel, are listed as carcinogens (10). In Germany, nickel as respirable dusts/aerosols from nickel metal, nickel sulphide and sulphidic ores, nickel oxide and nickel carbonate arising in nickel production and processing are listed as group A1 and nickel carbonyl as group A2 carcinogen (41).

In 1989, the amount of nickel leached from consumer items was limited to 0.5 µg/cm^2/week in Denmark (141). In Sweden, use of instruments containing more than 0.05% nickel (or covered by a 0.01 µm layer or more of nickel) for ear piercing have been forbidden since 1989 (200). A European Directive, which became effective as of 1 January 1995 (213), limits the amount of nickel leaching to 0.5 µg/cm^2 per week in products coming into direct and prolonged contact with the skin, and forbids use instruments containing more than 0.05% nickel for ear piercing.

Occupational exposure limits of nickel and nickel compounds have been compiled in Appendix 1.

14. Evaluation of human health risks

14.1. Groups at extra risk

There is no information on factors that might affect the individual susceptibility to nickel-induced nasal or pulmonary cancer. Whether smoking increases the risk of cancer in nickel exposure, cannot be assessed. People with atopic trait do not seem to be at elevated risk to nickel-induced eczema. Ear piercing with stainless steel instruments increases the risk of nickel hypersensitivity.

14.2. Assessment of health risks

All nickel compounds that deliver the nickel ion to susceptible cells in the organism are likely to increase the risk of nasal and pulmonary cancer. At present, no data are available to suggest that an increased risk of cancer may arise from exposures via routes other than inhalation.

Several mechanisms have been proposed as the basis of nickel carcinogenicity and alternatives exist for the genotoxic mechanism. However, nickel does induce mutations in relevant target genes and it is reasonable, for practical purposes, to base the prevention strategy on the concept that there is no threshold for the carcinogenic effects of nickel.

The relative potency of various nickel species to induce cancer apparently varies greatly, most potent seem to be the soluble nickel salts. Exposure to soluble nickel compounds at levels of approximately 0.1 mg/m^3 and over, have lead to elevated incidence of nasal cancer. For insoluble nickel compounds cancer risk elevation has been observed at levels of approximately 1 mg/m^3 and higher. No elevated risk of lung cancer has been demonstrated in exposure to metallic nickel. Lung cancer risk among stainless steel welders does not seem to exceed that of welders of mild steel.

Airborne nickel may in very rare instances induce asthma. Dermal contact is the most frequent cause of allergic skin reactions, and often leads to serious eczemas. Although it is clear that occupational exposure to nickel causes sensitivity, by far the larger proportion of nickel allergy is induced by nickel leaching from consumer items.

Nickel is embryotoxic in rodents, and also causes malformations in experimental animals. Reproductive effects have not been demonstrated in humans.

14.3. Scientific basis for an occupational exposure limit

The most significant health effect of airborne nickel and nickel compounds is their carcinogenicity to the respiratory epithelium. The critical effect should thus be regarded as carcinogenicity.

15. Research needs

The most pressing problem in nickel toxicology is the question of the carcinogenic potency of nickel, and the relative potencies of different nickel compounds. It is apparent that the approaches that are most likely to solve these questions are first, epidemiological studies on population groups with defined exposures, both qualitatively and quantitatively, and second, basic research into the mechanisms of nickel carcinogenesis, using experimental systems that are relevant for the carcinogenesis in humans and levels of nickel that human cells may have encountered during occupational exposure.

Assessment of exposure to nickel by biological monitoring is reasonably well studied in exposure to water soluble nickel compounds. By contrast, for exposure to less water-soluble nickel species, the relationships between exposure and the concentrations observed in the urine need to be further study.

16. Summary

Aitio, A. Nickel and nickel compounds. The Nordic Expert Group for Criteria Documentation of Health Risks from Chemicals. *Arbete och Hälsa* 1995;26:1-61.

Inhalation exposure to soluble nickel and nickel oxides/sulphides has caused nasal and pulmonary cancer in workers in nickel refineries. Metallic nickel and several nickel compounds are carcinogenic in experimental animals after several different exposure regimes. There is a marked discrepancy in the carcinogenic potency of nickel compounds between animals and humans. In humans, soluble nickel salts are carcinogenic but in animals the less soluble nickel compounds seem to be most potent. In nickel refineries, exposure to approximately 0.1 mg/m^3 soluble nickel salts, and approximately 1 mg/m^3 nickel oxides/sulphides seem to involve cancer hazard, whereas for metallic nickel dust, there are no convincing data on carcinogenicity in humans. Exposure to nickel or nickel compounds via routes other than inhalation has not been shown to increase the cancer risk in humans. It is unlikely that - the carcinogenic effects excluded - nickel or nickel compounds affect respiratory, cardiovascular, gastrointestinal or renal systems at present work place exposure levels. Nickel is the most common allergen in patch testing of both symptomless populations and patients at dermatological clinics. People sensitised to nickel are at an elevated risk for hand eczema. Nickel sensitivity is most often caused by nickel leached from consumer items, but nickel contact eczema may also be caused by nickel exposure at work.

Keywords: Nickel, nickel compounds, toxicology, epidemiology, occupational exposure limit, risk assessment, review

17. Summary in Swedish

Aitio, A. Nickel och nickelföreningar. Nordiska expertgruppen för kriteriedokumentation av kemiska hälsorisker. *Arbete och Hälsa* 1995;26:1-61.

Exponering via inhalation för löslig nickel och nickeloxider/sulfider har orsakat lung- och nasalcancer hos arbetare i nickelraffinaderier. Det finns en del motstridigheter i carcinogeniciteten av nickelföreningar i människa och djur. I nickelraffinaderier verkar exponering för ca 0.1 mg/m^3 lösliga nickelsalter och ca 1 mg/m^3 nickeloxider/sulfider vara förenat med en ökad cancerrisk. Det är osannolikt - exklusive de carcinogena effekterna - att nickel eller nickelföreningar inverkar på lungor, hjärta och blodkärlssystem, mag-tarmkanalen eller njurarna vid de nuvarande yrkesmässiga exponeringsnivåerna. Nickel är den mest allmäna allergenen vid "patch"-testning av både symptomfria människor och patienter vid hudkliniker. Människor som sensibiliserats för nickel har ofta en ökad risk för handeksem.

Nyckelord: Nickel, nickelföreningar, toxikologi, epidemiologi, yrkeshygieniska exponeringsgränsvärden, riskuppskattning, översikt.

18. References

1. Abeck D, Traenckner I, Steinkraus V, Vieluf D, Ring J. Chronic urticaria due to nickel intake. *Acta Derm Venereol* 1993;73:438-439.
2. Adamsson E, Lind B, Nilsson B, Piscator M. Urinary and fecal elimination of nickel in relation to airborne nickel in a battery factory. In: Brown SS, Sunderman FW Jr, eds. *Nickel Toxicology*. London: Academic Press Inc., 1980:103-106.
3. Ahlman K, Koponen M. A summary of the results of the Harjavalta biological/air monitoring program, unpublished report, July 1982, 7 pp. Outokumpu Oy, Helsinki, Finland. 1982. Quoted in: Nieboer E, Yassi A, Jusys AA, Muir DCF. *The Technical Feasibility and Usefulness of Biological Monitoring in the Nickel Producing Industry*. Hamilton, Ontario: McMaster University, 1984.
4. Aitio A. Biological monitoring of occupational exposure to nickel. In: Sunderman FW Jr, Aitio A, Berlin A, et al., eds. *Nickel in the Human Environment. IARC Scientific Publication No 53*. Lyon, France: International Agency for Research on Cancer, 1984:497-505.
5. Åkesson B, Skerfving S. Exposure in welding of high nickel alloy. *Int Arch Occup Environ Health* 1985;56:111-117.
6. American Conference of Governmental Industrial Hygienists (ACGIH). *1995-1996 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices*. Cincinnati, OH, USA: ACGIH, 1995.
7. Angerer J, Lehnert G. Occupational chronic exposure to metals II. Nickel exposure of stainless steel welders - biological monitoring. *Int Arch Occup Environ Health* 1990;62:7-10.
8. Arbeidstilsynet. *Administrative normer for forurensning i arbeidsatmosfaere 1991*. 7th ed. Oslo: Direktoratet for arbeidstilsynet, 1991.
9. Arbejdstilsynet. *Graensevaerdier for stoffer og materialer*. København: Arbejdstilsynet, 1992.
10. Arbetarskyddsstyrelsen. *Hygieniska gränsvärden. Arbetarskyddstyrelsens kungörelse med föreskrifter om hygieniska gränsvärden samt allmänna råd om tillämpningen av föreskrifterna*. Solna, Sweden: Arbetarskyddsstyrelsen, 1993 (Arbetarskyddsstyrelsens författningssamling AFS 1993:9).
11. Au WW, Heo M-Y, Chiewchanwit T. Toxicological interactions between nickel and radiation on chromosome damage and repair. *Environ Health Persp* 1994;102:73-77.
12. Baranowska-Dutkiewicz B, Rózanska R, Dutkiewicz T. Occupational and environmental exposure to nickel in Poland. *Pol J Occup Med Environ Health* 1992;5:335-343.
13. Bavazzano P, Bolognesi R, Cassinelli C, Gori R, Li Donni V, Martellini F, et al. Skin contamination and low airborne nickel exposure of electroplaters. *Sci Total Environ* 1994;155:83-86.
14. Becker N, Chang-Claude J, Frentzel-Beyme R. Risk of cancer for arc welders in the Federal Republic of Germany: results of a second follow up (1983-88). *Br J Ind Med* 1991;48:675-683.
15. Benson JM, Barr EB, Bechtold WE, et al. Fate of inhaled nickel oxide and nickel subsulphide in F344/N rats. *Inhal Toxicol* 1994;6:167-183.
16. Benson JM, Burt DG, Cheng YS, et al. Subchronic inhalation toxicity of nickel subsulphide to rats and mice. *Inhal Toxicol* 1990;2:1-19.
17. Benson JM, Burt DG, Cheng YS, et al. Biochemical responses of rat and mouse lung to inhaled nickel compounds. *Toxicology* 1989;57:255-266.
18. Bernacki EJ, Parsons GE, Roy BR, Mikac-Devic M, Kennedy CD, Sunderman FW Jr. Urine nickel concentrations in nickele-exposed workers. *Ann Clin Lab Sci* 1978;8:184-189.
19. Bernacki EJ, Zugowicz E, Sunderman FW Jr. Fluctuations of nickel concentrations in urine of electroplating workers. *Ann Clin Lab Sci* 1980;10:33-39.

20. Blaschko A. Berufsdermatosen der Arbeiter. Ein Beitrag zur Gewerbehygiene. *Disch Med Wochenschr* 1889;15:925-927.
21. Block GT, Yeung M. Asthma induced by nickel. *J Am Med Assoc* 1982;247:1600-1602.
22. Botta A, Michel MPL, Digiorgio C. Genotoxic effects of nickel sulphate in cultured human lymphocytes. *Med Sci Res* 1994;22:709-710.
23. Boysen M, Solberg LA, Andersen I, Høgetveit AC, Torjussen W. Nasal histology and nickel concentration in plasma and urine after improvements in the work environment at a nickel refinery in Norway. *Scand J Work Environ Health* 1982;8:283-289.
24. Brief RS, Blanchard JW, Scala RA, Blacker JH. Metal carbonyls in the petroleum industry. *Arch Environ Health* 1971;23:373-384.
25. Brown KC, Yang SH, Kodadek T. Highly specific oxidative cross-linking of proteins mediated by a nickel-peptide complex. *Biochemistry* 1995;34:4733-4739.
26. Brown SS, Sunderman FW Jr, eds. *Nickel Toxicology*. London: Academic Press, 1980.
27. Brown SS, Sunderman FW Jr, eds. *Progress in Nickel Toxicology*. Oxford: Blackwell Scientific Publications, 1985.
28. Chang J, Watson WP, Randerath E, Randerath K. Bulky DNA-adduct formation induced by Ni(II) in vitro and in vivo as assayed by 32P-postlabeling. *Mutat Res* 1993;291:147-159.
29. Chashschin VP, Artunina GP, Norseth T. Congenital defects, abortion and other health effects in nickel refinery workers. *Sci Total Environ* 1994;148:287-291.
30. Christie NT. The synergistic interaction of nickel(II) with DNA damaging agents. *Toxicol Environ Chem* 1989;22:51-59.
31. Cirla AM, Bernabeo F, Ottoboni F, Ratti R. Nickel induced occupational asthma: Immunological and clinical aspects. In: Brown SS, Sunderman FW Jr, eds. *Progress in Nickel Toxicology*. Oxford: Blackwell Scientific Publications, 1985:165-168.
32. Commission. Commission Directive 93/21/EEC of 1 March 1991 adapting to technical progress for the twelfth time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances (91/325/EEC). *Offic J Eur Commun* 1991 July 7;L 180:1-78.
33. Commission. Annex to Commission Directive 93/72/EEC of 1 September 1993 adapting to technical progress for the nineteenth time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Offic J Eur Commun* 1993 Oct 16;L 258 A Volume 36:1-1409.
34. Commission. Commission Directive 93/21/EEC of 27 April 1993 adapting to technical progress for the 18th time Council Directive 67/548/EEC on the approximation of the laws, regulations and administrative provisions relating to the classification, packaging and labelling of dangerous substances. *Offic J Eur Commun* 1993 May 4;L 110 Volume 36:20-21.
35. Conway K, Costa M. Nonrandom chromosomal alterations in nickel-transformed Chinese hamster embryo cells. *Cancer Res* 1990;49:6032-6038.
36. Cornell RG, Landis JR. Mortality patterns among nickel/chromium alloy foundry workers. In: Sunderman FW Jr, Aitio A, Berlin A, et al., eds. *Nickel in the Human Environment*. Lyon: International Agency for Research on Cancer, 1984:87-93. (IARC Scientific Publications; 53).
37. Council. Council Directive of 28 June 1990 on the protection of workers from risks related to exposure to carcinogens at work (Sixth individual Directive within the meaning of Article 16 (1) of Directive 89/391EEC) (93/394/EEC). *Offic J Eur Commun* 1990 July 26;L196:1-7.
38. Cox JE, Doll R, Scott WA, Smith S. Mortality of nickel workers: experience of men working with metallic nickel. *Br J Ind Med* 1981;38:235-239.

39. Cragle DL, Hollis DR, Newport TH, Shy CM. A retrospective cohort mortality study among workers occupationally exposed to metallic nickel powder at the Oak Ridge gaseous diffusion plant. In: Sunderman FW Jr, Aitio A, Berlin A, et al., eds. *Nickel in the Human Environment*. Lyon: International Agency for Research on Cancer, 1984:57-63. (IARC Scientific Publications; 53).
40. Daldrup T, Haarhoff K, Szathmary SC. Tödliche Nickelsulfatintoxikation. *Beitr gerecht Med* 1983;41:141-144.
41. Deutsche Forschungsgemeinschaft (DFG). *MAK- und BAT-Werte-Liste 1995. Senatskommission zur Prüfung gesundheitsschädlicher Arbeitsstoffe*. 31. Aufl. Weinheim, BRD: VCH Verlagsgesellschaft mbH, 1995.
42. DHEW. NIOSH Technical Report - Environmental exposure to airborne contaminants in the nickel industry, 1976-1977, Pub. No 78-178, U.S. Dept. of Health, Education, and Welfare, Washington, D.C. 1978. Quoted in: Nieboer E, Yassi A, Jusys AA, Muir DCF. *The Technical Feasibility and Usefulness of Biological Monitoring in the Nickel Producing Industry*. Hamilton, Ontario: McMaster University, 1984.
43. Dieter MP, Jameson CW, Tucker AN, Luster MI, French JE, Hong HL, Boorman GA. Evaluation of tissue disposition, myelopoetic, and immunologic responses in mice after long-term exposure to nickel sulphate in the drinking water. *J Toxicol Environ Health* 1988;24:356-372.
44. Doll R. Cancer of the lung and nose in nickel workers. *Br J Ind Med* 1958;15:217-223.
45. Doll R, Andersen A, Cooper WC, et al. Report of the international committee on nickel carcinogenesis in man. *Scand J Work Environ Health* 1990;16:1-82.
46. Dotterud LK, Falk ES. Metal allergy in north Norwegian schoolchildren and its relationship with ear piercing and atopy. *Contact Dermatitis* 1994;31:308-313.
47. Downs AM, Boysen M, Voss R, Reichborn-Kjennerud S, Abeler V, Rigaut JP, Reith A. How often is dysplasia diagnosed by biopsy or smear examination? Application of a maximum likelihood based method to the assessment of detection rates in the nasal mucosa of nickel workers. *Anal Cell Pathol* 1992;4:451-459.
48. Dryson EW, Rogers DA. Exposure to fumes in typical New Zealand welding operations. *N Z Med J* 1991;104:365-367.
49. Dubins JS, LaVelle JM. Nickel(II) genotoxicity: potentiation of mutagenesis of simple alkylating agents. *Mutat Res* 1986;162:178-199.
50. Dunnick JK, Benson JM, Hobbs CH, Hahn FF, Cheng YS, Eidson AF. Comparative toxicity of nickel oxide, nickel sulphate hexahydrate, and nickel subsulphide after twelve days of inhalation exposure to F344/N rats and B6C3F1 mice. *Toxicology* 1988;50:145-156.
51. Dunnick JK, Elwell MR, Benson JM, et al. Lung toxicity after 13-week inhalation exposure to nickel oxide, nickel subsulphide, or nickel sulphate hexahydrate in F344/N rats and B6C3F1 mice. *Fundam Appl Toxicol* 1989;12:584-594.
52. Egedahl RD, Coppock E, Homik R. Mortality experience at a hydrometallurgical nickel refinery in Fort Saskatchewan, Alberta between 1954 and 1984. *J Soc Occup Med* 1991;41:29-33.
53. Elias Z, Mur J-M, Pierre F, et al. Chromosome aberrations in peripheral blood lymphocytes of welders and characterization of their exposure by biological samples analysis. *J Occup Med* 1989;31:477-483.
54. Elliott WT. Nickel particulate and nickel urine excretion study. Unpublished report, 18 Dec 1975, 23 pp. INCO Limited, Copper Cliff, Canada. 1975. Quoted in: Nieboer E, Yassi A, Jusys AA, Muir DCF. *The Technical Feasibility and Usefulness of Biological Monitoring in the Nickel Producing Industry*. Hamilton, Ontario: McMaster University, 1984.
55. Elsner P, Burg G. Irritant reactivity is a better risk marker for nickel sensitization than atopy. *Acta Derm Venereol* 1993;73:214-216.

56. Emtestam L, Zetterquist H, Olerup O. HLA-DR, -DQ and -DP alleles in nickel, chromium, and/or cobalt-sensitive individuals: genomic analysis based on restriction fragment length polymorphisms. *J Invest Dermatol* 1993;100:271-274.

57. Estlander T, Kanerva L, Tupasela O, Keskinen H, Jolanki R. Immediate and delayed allergy to nickel with contact urticaria, rhinitis, asthma and contact dermatitis. *Clin Exp Allergy* 1993;23:306-310.

58. Fairhurst S, Illing HPA. *The Toxicity of Nickel and its Inorganic Compounds*. London: Her Majesty's Stationery Office, 1987 (Health and Safety Executive Toxicity review; 19).

59. Fedler R, Stromer K. Nickel sensitivity in atopics, psoriatics and healthy subjects. *Contact Dermatitis* 1993;29:65-69.

60. Gawkrodger DJ, Shuttler IL, Delves HT. Nickel dermatitis and diet: clinical improvement and a reduction in blood and urine nickel levels with a low-nickel diet. *Acta Derm Venereol* 1988;68:453-456.

61. Gennart JP, Baleux C, Verellen-Dumoulin C, Buchet JP, De Meyer R, Lauwerys R. Increased sister chromatid exchanges and tumor markers in workers exposed to elemental chromium- containing, cobalt-containing and nickel-containing dusts. *Mutat Res* 1993;299:55-61.

62. Ghezzi I, Baldasseroni A, Sesana G, Boni C, Cortona G, Alessio L. Behaviour of urinary nickel in low-level occupational exposure. *Med Lav* 1989;80:244-250.

63. Goldberg M, Goldberg P, Leclerc A, Chastang JF, Marne MJ, Dubourdieu D. A 10-year incidence survey of respiratory cancer and a case-control study within a cohort of nickel mining and refining workers in New Caledonia. *Cancer Causes Contr* 1994;5:15-25.

64. Gollhausen R, Ring J. Allergy to coined money: nickel contact dermatitis in cashiers. *J Am Acad Dermatol* 1991;25(Pt 2):365-369.

65. Grandjean P, Selikoff IJ, Shen SK, Sunderman FW Jr. Nickel concentrations in plasma and urine of shipyard workers. *Am J Ind Med* 1980;1:181-189.

66. Groß H. Berusbedingte krebserzeugende Wirkung von Nickel? Folgerungen aus arbeitsmedizinischen und epidemiologischen Untersuchungen, Arbeitsplatzanalysen in der stahlverarbeitenden Industrie und gesetzlichen Vorschriften. *Zbl Arbeitsmed* 1987;37:170-183.

67. Gustafsson TE, Tossavainen A, Aitio A. Scanning electron microscopic studies on flame cutting and welding fumes in a steel foundry. In: Stern RM, Berlin A, Fletcher AC, Järvisalo J, eds. *Health Hazards and Biological Effects of Welding Fumes and Gases*. Amsterdam, The Netherlands: Elsevier, 1986:93-97. (Excerpta Medica International Congress Series; 676).

68. Haley PJ, Shopp GM, Benson JM, et al. The immunotoxicity of three nickel compounds following 13-week inhalation exposure in the mouse. *Fundam Appl Toxicol* 1990;15:476-487.

69. Haratake J, Horie A, Kodama Y, Tanaka I. Histopathologic examination of rats treated by inhalation of various types of nickel compounds. *Inhal Toxicol* 1992;4:67-79.

70. Hartwig A, Beyersmann D. Comutagenicity and inhibition of DNA repair by metal ions in mammalian cells. *Biol Trace Elem Res* 1989;21:359-365.

71. Hartwig A, Beyersmann D. Enhancement of UV-induced mutagenesis and sister-chromatid exchanges by nickel ions in V79 cells: evidence for inhibition of DNA repair. *Mutat Res* 1989;217:65-73.

72. Hartwig A, Mullenders LH, Schlepegrell R, Kasten U, Beyersmann D. Nickel(II) interferes with the incision step in nucleotide excision repair in mammalian cells. *Cancer Res* 1994;54:4045-4051.

73. Hassler E, Lind B, Nilsson B, Piscator M. Urinary and fecal elimination of nickel in relation to air-borne nickel in a battery factory. *Ann Clin Lab Sci* 1983;13:217-224.

74. Haudrechy P, Foussereau J, Mantout B, Baroun B. Nickel release from nickel-plated metals and stainless steels. *Contact Dermatitis* 1994;31:249-255.

75. Haugen A, Ryberg D, Hansteen I-L, Amstad P. Neoplastic transformation of a human kidney epithelial cell line transfected with v-Ha-ras-oncogene. *Int J Cancer* 1990;45:572-577.

76. Hauptman O, Albert DM, Plowman MC, Hopfer SM, Sunderman FW Jr. Ocular malformations of Xenopus laevis exposed to nickel during embryogenesis. *Ann Clin Lab Sci* 1993;23:397-406.

77. Heidermanns G, Wolf D, Hoffmann E. Belastung durch Nickel beim Schleifen und Polieren von Nickellegierungen mit Nickelgehalten unter 80%. *Staub-Reinhalt Luft* 1983;43:374-376.

78. Higinbotham KG, Rice JM, Diwan BA, Kasprzak KS, Reed CD, Perantoni AO. GGT to GTT transversions in codon 12 of the K-ras oncogene in rat renal sarcomas induced with nickel subsulphide or nickel subsulphide/iron are consistent with oxidative damage to DNA. *Cancer Res* 1992;52:4747-4751.

79. Hirano S, Shimada T, Osugi J, Kodama N, Suzuki KT. Pulmonary clearance and inflammatory potency of intratracheally instilled or acutely inhaled nickel sulphate in rats. *Arch Toxicol* 1994;68:548-554.

80. Hopfer SM, Plowman MC, Sweeney KR, Bantle JA, Sunderman FW Jr. Teratogenicity of Ni2+ in Xenopus laevis, assayed by the FETAX procedure. *Biol Trace Elem Res* 1991;29:203-216.

81. Howard W, Leonard B, Moody W, Kochhar TS. Induction of chromosome changes by metal compounds in cultured CHO cells. *Toxicol Lett* 1991;56:179-186.

82. Huber A, Fartasch M, Diepgen TL, Bäurle G, Hornstein OP. Auftreten von Kontaktallergien beim atopischen Ekzem. *Dermatosen* 1987;35:119-123.

83. Hull CJ, Doyle E, Peters JM, Carabrant DH, Preston-Martin S. Case-control study of lung cancer in Los Angeles county welders. *Am J Ind Med* 1989;16:103-112.

84. Høgetveit AC, Barton RT, Kostøl CO. Plasma nickel as a primary index of exposure in nickel refining. *Ann Occup Hyg* 1978;21:113-120.

85. International Agency for Research on Cancer (IARC). Nickel and nickel compounds. In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Chromium, Nickel and Welding*. 49. Lyon, France: IARC, 1990:257-445.

86. International Agency for Research on Cancer (IARC). Welding. In: *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans. Chromium, Nickel and Welding*. 49. Lyon, France: IARC, 1990:447-525.

87. International Programme on Chemical Safety (IPCS). *Environmental Health Criteria 108. Nickel*. Geneva, Switzerland: World Health Organization, 1991.

88. Jaakkola J, Kokko A. *Nikkeli*. Helsinki: Työterveyslaitos; Työsuojelurahasto, 1992 (Altisteet työssä; 32) (Chemical exposure at work 32: Nickel (in Finnish)).

89. Jackson P. Personal communication, INCO Metals Company, Thompson, Canada. 1982. Quoted in: Nieboer E, Yassi A, Jusys AA, Muir DCF. *The Technical Feasibility and Usefulness of Biological Monitoring in the Nickel Producing Industry*. Hamilton, Ontario: McMaster University, 1984.

90. Jelmert Ø, Hansteen I-L, Langård S. Chromosome damage in lymphocytes of stainless steel welders related to past and current exposure to manual metal arc welding fumes. *Mutat Res* 1994;320:223-233.

91. Jelmert Ø, Hansteen I-L, Langård S. Cytogenetic studies of stainless steel welders using the tungsten inert gas and metal inert gas methods for welding. *Mutat Res Gen Toxicol* 1995;342:77-85.

92. Jelnes JE, Knudsen L. Stainless steel welding and semen quality. *Reprod Toxicol* 1988;2:213-215.

93. Kaaber K, Veien NK, Tjell JC. Low nickel diet in the treatment of patients with chronic nickel dermatitis. *Br J Dermatol* 1978;98:197-210.

94. Kalliomäki P-L, Rahkonen E, Vaaranen V, Kalliomäki K, Aittoniemi K. Lung-retained contaminants, urinary chromium and nickel among stainless steel welders. *Int Arch Occup Environ Health* 1981;49:67-75.

95. Kanerva L, Kerosuo H, Kullaa A, Kerosuo E. Allergic patch test reactions from palladium chloride in school children. *Contact Dermatitis* 1995, in press.

96. Kanerva L, Sipiläinen-Malm T, Estlander T, Zitting A, Jolanki R, Tarvainen K. Metallikoruista vapautuva nikkeli allergian aiheuttajana. *Suomen Lääkärilehti* 1994;49:917-921 (in Finnish).

97. Kanerva L, Sipiläinen-Malm T, Estlander T, Zitting A, Jolanki R, Tarvainen K. Nickel release from metals, and a case of allergic contact dermatitis from stainless steel. *Contact Dermatitis* 1994;31:299-303.

98. Kargacin B, Klein CB, Costa M. Mutagenic response of nickel oxides and nickel sulphides in Chinese hamster V79 cell lines at the xanthine-guanine phosphoribosyl transferase locus. *Mutat Res* 1993;300:63-72.

99. Karjalainen S, Kerttula R, Pukkala E. Cancer risk among workers at a copper/nickel smelter and nickel refinery in Finland. *Int Arch Occup Environ Health* 1992;63:547-551.

100. Kasprzak KS. The role of oxidative damage in metal carcinogenicity. *Chem Res Toxicol* 1991;4:604-615.

101. Kasprzak KS, Diwan BA, Konishi N, Misra M, Rice JM. Initiation by nickel acetate and promotion by sodium barbital of renal cortical epithelial tumors in male F344 rats. *Carcinogenesis* 1990;11:647-652.

102. Kasprzak KS, Diwan BA, Rice JM. Iron accelerates while magnesium inhibits nickel-induced carcinogenesis in the rat kidney. *Toxicology* 1994;90:129-140.

103. Kasprzak KS, Gabryel P, Jarczewska K. Carcinogenicity of nickel(II)hydroxides and nickel(II)sulphate in Wistar rats and its relation to the in vitro dissolution rates. *Carcinogenesis* 1983;4:275-279.

104. Kasprzak KS, Hernandez L. Enhancement of hydroxylation and deglycosylation of 2'-deoxyguanosine by carcinogenic nickel compounds. *Cancer Res* 1989;49:5964-5968.

105. Kawanishi S, Inoue S, Yamamoto K. Site-specific DNA damage by nickel(II) ioon in the presence of hydrogen peroxide. *Carcinogenesis* 1989;10:2231-2235.

106. Kerosuo H, Kullaa A, Kerosuo E, Kanerva L, Hensten-Pettersen A. Nickel allergy in adolescents in relation to orthodontic treatment and piercing of ears. *Amer J Orthodont Dent Orthop* 1995;in press.

107. Kiilunen M. Occupational exposure to chromium and nickel in Finland - analysis of registries of hygienic measurements and biological monitoring. *Ann Occup Hyg* 1994;38:171-187.

108. Kiilunen M. Occupational exposure to chromium and nickel in Finland and its estimation by biological monitoring (Dissertation). Kuopio University, Finland, 1994. 95 p.

109. Kiilunen M. Nikkeli. In: Aitio A, Luotamo M, Kiilunen M, eds. *Kemikaalialtistumisen biomonitorointi*. Helsinki: Työterveyslaitos, 1995:208-213 (In Finnish: Nickel. In: Biomonitoring of chemical exposure).

110. Kiilunen M, Tossavainen A, Aitio A. Exposure to nickel in electrolytic nickel plating. *Ann Occup Hyg* 1996; submitted for publication.

111. Kiilunen M, Utela J, Rantanen T, Norppa H, Tossavainen A, Koponen M, Aitio A. Exposure to soluble nickel in electrolytic nickel refining. *Ann Occup Hyg* 1996; submitted for publication.

112. Kilburn KH, Warshaw R, Boylen CT, Thornton JC, Hopfer SM, Sunderman FW Jr, Finklea J. Cross-shift and chronic effects of stainless-steel welding related to internal dosimetry of chromium and nickel. *Am J Ind Med* 1990;17:607-615.

113. Klein CB, Conway K, Wang XW, Bhamra RK, Lin X, Cohen MD, et al. Senescence of nickel-transformed cells by an X-chromosome: Possible epigenetic control. *Science* 1991;251:796-799.

114. Klein CB, Frenkel K, Costa M. The role of oxidative processes in metal carcinogenesis. *Chem Res Toxicol* 1991;4:592-604.

115. Klein F. Concentration du nickel et du crome dans l'atmosphere des ateliers siderurgiques. In: Brown SS, Sunderman FW Jr, eds. *Progress in Nickel Toxicology*. Oxford: Blackwell Scientific Publications, 1985:195-197.

116. Knudsen LE, Boisen T, Christensen JM, et al. Biomonitoring of genotoxic exposure among stainless steel welders. *Mutat Res* 1992;279:129-143.

117. Kodama Y, Tanaka I, Matsuno K, Ishimatsu S, Kawamoto T. Comparative deposition and clearance of various nickel compounds exposed by inhalation in rats. *Biol Trace Elem Res* 1993;36:257-269.

118. Kreyberg L. Lung cancer in workers in a nickel refinery. *Br J Ind Med* 1978;35:109-116.

119. Kusaka Y, Kumagai S, Kyono H, Kohyama N, Shirakawa T. Determination of exposure to cobalt and nickel in the atmosphere in the hard metal industry. *Ann Occup Hyg* 1992;36:497-507.

120. Lee YW, Klein CB, Kargacin B, et al. Carcinogenic nickel silences gene expression by chromatin condensation and DNA methylation: A new model for epigenetic carcinogens. *Mol Cell Biol* 1995;15:2547-2557.

121. Lee YW, Pons C, Tummolo DM, Klein CB, Rossman TG, Christie NT. Mutagenicity of soluble and insoluble nickel compounds at the gpt locus in G12 Chinese hamster cells. *Environ Mol Mutagen* 1993;21:365-371.

122. Lee-Chen SF, Wang MC, Yu CT, Wu DR, Jan KY. Nickel chloride inhibits the DNA repair of UV-treated but not methyl methane sulfonate-treated Chinese hamster ovary cells. *Biol Trace Elem Res* 1993;37:39-50.

123. Lewis RJS. *Sax's dangerous properties of industrial materials*. 8th ed. New York: Van Nostrand Reinhold, 1992.

124. Lidén C. Cold-impregnated aluminium. A new source of nickel exposure. *Contact Dermatitis* 1994;31:22-24.

125. Lidén C. Occupational contact dermatitis due to nickel allergy. *Sci Total Environ* 1994;148:283-285.

126. Lidén C, Wahlberg JE. Cross-reactivity to metal compounds studied in guinea pigs induced with chromate or cobalt. *Acta Derm Venereol* 1994;74:341-343.

127. Lin X, Dowjat WK, Costa M. Nickel-induced transformation of human cells causes loss of the phosphorylation of the retinoblastoma protein. *Cancer Res* 1994;54:2751-2754.

128. Liquier J, Bourtayre P, Pizzorni L, Sournies F, Labarre JF, Taillandier E. Spectroscopic studies of conformational transition in double stranded DNAs in the presence of carcinogenic nickel compounds and antitumoral drug (SOAZ). *Anticancer Res* 1984;4:41-44.

129. Lynn S, Yew FH, Hwang JW, Tseng MJ, Jan KY. Glutathione can rescue the inhibitory effects of nickel on DNA ligation and repair synthesis. *Carcinogenesis* 1994;15:2811-2816.

130. Machle L, Metcalf RA, Ryberg D, Bennett WP, Harris CC, Haugen A. Altered p53 gene structure and expression in human epithelial cells after exposure to nickel. *Cancer Res* 1992;52:218-221.

131. Magnus K, Andersen A, Høgetveit AC. Cancer of respiratory organs among workers at a nickel refinery in Norway. Second report. *Int J Cancer* 1982;30:681-685.

132. Malo J-L, Cartier A, Doepner M, Nieboer E, Evans SL, Dolovich J. Occupational asthma caused by nickel sulphate. *J Allergy Clin Immunol* 1982;69:55-59.

133. Massone L, Anonide A, Borghi S, Isola V. Positive patch test reactions to nickel, cobalt, and potassium dichromate in a series of 576 patients. *Cutis* 1991;47:119-122.

134. Mastromatteo E. Nickel and its compounds. In: Zenz C, Dickerson OB, Horvath EPJ, eds. *Occupational Medicine*. 3rd ed. St. Louis, Missouri, USA: Mosby-Year Books, Inc., 1994:558-571.

135. McConnel LH, Fink JN, Schlueter DP, Schmidt MG Jr. Asthma caused by nickel sensitivity. *Ann Intern Med* 1973;78:888-890.

136. McDonagh AJ, Wright AL, Cork MJ, Gawkrodger DJ. Nickel sensitivity: the influence of ear piercing and atopy. *Br J Dermatol* 1992;126:16-18.

137. McNeill DA, Chrisp CE, Fisher GL. Tumorigenicity of nickel subsulphide in Strain A/J mice. *Drug Chem Toxicol* 1990;13:71-86.

138. Meijer C, Bredberg M, Fischer T, Widström L. Ear piercing, and nickel and cobalt sensitization, in 520 young Swedish men doing compulsory military service. *Contact Dermatitis* 1995;32:147-149.

139. Menné T, Borgan Ø, Green A. Nickel allergy and hand dermatitis in a stratified sample of Danish female population: an epidemiological study including a statistic appendix. *Acta Derm Venereol* 1982;62:35-41.

140. Menné T, Brandrup F, Thestrup-Pedersen K, Andersen JR, Yding F, Valeur G. Patch test reactivity to nickel alloys. *Contact Dermatitis* 1987;16:255-259.

141. Miljöministeriet. *Bekendtgorelse om forbud mod salg af visse nikkelholdige produkter*. Miljöministeriets bekendtgörelse nr 472 af 27. juni 1989 (in Danish).

142. Morgan JG. Some observations on the incidence of respiratory cancer in nickel workers. *Br J Ind Med* 1958;15:224-234.

143. Morgan LG, Rouge PJC. A study into the correlation between atmospheric and biological monitoring of nickel in nickel refinery workers. *Ann Occup Hyg* 1979;22:311-317.

144. Morgan LG, Rouge PJC. Biological monitoring in nickel refinery workers. In: Sunderman FW Jr, Aitio A, Berlin A, et al., eds. *Nickel in the Human Environment*. IARC Scientific Publication No 53. Lyon, France: International Agency for Research on Cancer, 1984:507-520.

145. Morita H, Umeda M, Ogawa HI. Mutagenicity of various chemicals including nickel and cobalt compounds in cultured mouse FM3A cells. *Mutat Res* 1991;261:131-137.

146. Moulin JJ, Wild P, Haguenor JM, et al. A mortality study among mild steel and stainless steel welders. *Br J Ind Med* 1993;50:234-243.

147. Muir DCF, Jadon N, Julian JA, Roberts RS. Cancer of the respiratory tract in nickel sinter plant workers: effect of removal from sinter plant exposure. *Occup Environ Med* 1994;51:19-22.

148. Muir DC, Julian J, Jadon N, et al. Prevalence of small opacities in chest radiographs of nickel sinter plant workers. *Br J Ind Med* 1993;50:428-431.

149. National Institute for Occupational Safety and Health. Inorganic nickel, metal and compounds (as Ni). Method No 298. In: Taylor DG, ed. *NIOSH Manual of Analytical Methods*. Vol 7. Washington, DC: US Department of Health, Education, and Welfare, 1981:298-1 - 298-6.

150. Nicolaou G, Pietra R, Sabbioni E, Mosconi G, Cassina G, Seghizzi P. Multielement determination of metals in biological specimens of hard metal workers: A study carried out by neutron activation analysis. *J Trace Elem Electrolytes Health Dis* 1987;1:73-77.

151. Nieboer E, Nriagu JO, eds. *Nickel and human health. Current perspectives*. New York -Chichester-Brisbane-Toronto-singapore: John Wiley & Sons, Inc., 1992 (Nriagu JO, ed. Advances in Environmental Science and Technology; 25).

152. Nieboer E, Yassi A, Jusys AA, Muir DCF. *The Technical Feasibility and Usefulness of Biological Monitoring in the Nickel Producing Industry*. Hamilton, Ontario: McMaster University, 1984.

153. Nielsen NH, Menné T. Allergic contact sensitization in an unselected Danish population - The Glostrup allergy study, Denmark. *Acta Derm Venereol* 1992;72:456-460.

154. Nielsen NH, Menné T. Nickel sensitization and ear piercing in an unselected Danish population. *Contact Dermatitis* 1993;29:16-21.

155. Nilsson E, Bäck O. The importance of anamnestic information of atopy, metal dermatis and earlier hand eczema for the development of hand dermatitis in women with wet hospital work. Acta *Derm Venereol* 1986;66:45-51.

156. Norseth T. Chromium and nickel. In: Aitio A, Riihimäki V, Vainio H, eds. *Biological Monitoring and Surveillance of Workers Exposed to Chemicals*. Washington, New York, London: Hemisphere Publishing Company, 1984:49-59.

157. Nriagu JO, ed. *Nickel in the Environment*. New York: John Wiley & Sons, 1980 (Metcalf RL, Stumm W, eds. Environmental Science and Technology).

158. Patierno SR, Dirscherl LA, Xu J. Transformation of rat tracheal epithelial cells to immortal growth variants by particulate and soluble nickel compounds. *Mutat Res* 1993;300:179-193.

159. Peltonen L. Nickel sensitivity in the general population. *Contact Dermatitis* 1979;5:27-32.

160. Peters K, Gammelgaard B, Menné T. Nickel concentrations in fingernails as a measure of occupational exposure to nickel. *Contact Dermatitis* 1991;25:237-241.

161. Peto J, Cuckle H, Doll R, Hermon C, Morgan LG. Respiratory cancer mortality of Welsh nickel refinery workers. In: Sunderman FW Jr, Aitio A, Berlin A, et al., eds. *Nickel in the Human Environment*. Lyon, France: International Agency for Research on Cancer, 1984:37-46. (IARC Scientific Publications; 53).

162. Plowman MC, Grbac-Ivankovic S, Martin J, Hopfer SM, Sunderman FW Jr. Malformations persist after metamorphosis of Xenopus laevis tadpoles exposed to Ni2+, Co2+, or Cd2+ in FETAX assays. Teratogenesis *Carcinog Mutagen* 1994;14:135-144.

163. Polednak AP. Mortality among welders, including a group exposed to nickel oxides. *Arch Environ Health* 1981;36:235-242.

164. Pool-Zobel BL, Lotzmann N, Knoll M, et al. Detection of genotoxic effects in human gastric and nasal mucosa cells isolated from biopsy samples. *Environ Mol Mutagen* 1994;24:23-45.

165. Popp W, Vahrenholz C, Goch S, Muller C, Muller G, Schmieding W, Norpoth K. Erfahrungen mit der Alkalishen Filterelution beim Nachweis von DNA-Schäden durch gentoxische Verbindungen. *Zentralbl Hyg Umweltmed* 1992;193:140-149.

166. Popp W, Vahrenholz C, Schmieding W, Krewet E, Norpoth K. Investigations of the frequency of DNA strand breakage and cross-linking and of sister chromatid exchange in the lymphocytes of electric welders exposed to chromium- and nickel-containing fumes. *Int Arch Occup Environ Health* 1991;63:115-120.

167. Pott F, Dungworth DL, Heinrich U, et al. Lung tumours in rats after intratracheal instillation of dusts. *Ann Occup Hyg* 1994;38(Suppl. 1):357-363.

168. Räsänen L, Lehto M, Mustikkam%ki UP. Sensitization to nickel from stainless steel ear-piercing kits. *Contact Dermatitis* 1993;28:292-294.

169. Rahkonen E, Junttila M-L, Kalliomäki PL, Olkinuora M, Koponen M, Kalliomäki K. Evaluation of biological monitoring among stainless steel welders. *Int Arch Occup Environ Health* 1983;52:243-255.

170. Raithel HJ. *Untersuchungen zur Belastung und Beanspruchung von 837 beruflich Nickel-exponierten Personen*. St Augustin: Hauptverband der gewerblichen Berufsgenossenschaften, 1987.

171. Raithel H-J, Kress W, Schaller K-H, Weltle D, Valentin H. Toxicological and occupational medical investigations concerning nickel-exposure in different industrial areas in the FRG. In: Brown SS, Sunderman FW Jr, eds. *Progress in Nickel Toxicology*. Oxford: Blackwell Scientific Publications, 1985:219-222.

172. Raithel HJ, Schaller KH, Kraus T, Lehnert G. Biomonitoring of nickel and chromium in human pulmonary tissue. *Int Arch Occup Environ Health* 1993;65:S197-S200.

173. Raithel H-J, Schaller KH, Valentin H. Biological monitoring of nickel in different industrial areas in the Federal Republic of Germany. In: Dillon HK, Ho MH, eds. *Biological Monitoring of Exposure to Chemicals: Metals*. New York: John Wiley & Sons, 1991:27-38.

174. Rani AS, Qu DQ, Sidhu MK, et al. Transformation of immortal, non-tumorigenic ostoeblast-like human osteosarcoma cells to the tumorigenic phenotype by nickel sulphate. *Carcinogenesis* 1993;14:947-953.

175. Redmond CK. Site-specific cancer mortality among workers involved in the production of high nickel alloys. In: Sunderman FW Jr, Aitio A, Berlin A, et al., eds. *Nickel in the Human Environment*. Lyon: International Agency for Research on Cancer, 1984:73-86. (IARC Scientific Publications; 53).

176. Reith AK, Reichborn-Kjennerud S, Aubele M, Jütting U, Gais P, Burger G. Biological monitoring of chemical exposure in nickel workers by imaging cytometry (ICM) of nasal smears. *Anal Cell Pathol* 1994;6:9-21.

177. Rendall REG, Phillips JI, Renton KA. Death following exposure to fine particulate nickel from a metal arc process. *Ann Occup Hyg* 1994;38:921-930.

178. Rigaut JP. *Rapport préparatoire sur les critéres de santé pour le nickel*. Doc CCE/Lux/V/E/24/83. Luxembourg: Commission of European Communities, 1983.

179. Rivedal E, Sanner T. Synergistic effect on morphological transformation of hamster embryo cells by nickel sulphate and benzo(a)pyrene. *Cancer Lett* 1980;8:203-208.

180. Roberts RS, Julian JA, Muir DCF, Shannon HS. A study of mortality in workers engaged in the mining, smelting and refining of nickel II: Mortality from cancer of the respiratory tract and kidney. *Toxicol Ind Health* 1989;5:975-993.

181. Roberts RS, Julian JA, Sweezey D, Muir DCF, Shannon HS, Mastromatteo E. A study of mortality in workers engaged in the mining, smelting and refining of nickel I: Methodology and mortality by major cause groups. *Toxicol Ind Health* 1989;5:957-974.

182. Roels H, Van de Voorde R, Vargas VMM, Lauwerys R. Relationship between atmospheric and urinary nickel in workers manufacturing electrical resistances using nickel oxide: the role of bioavailability of nickel. *Occup Med* 1993;43:95-104.

183. Rossetto FE, Turnbull JD, Nieboer E. Characterization of nickel-induced mutations. *Sci Total Environ* 1994;148:201-206.

184. Sahu RK, Katsifis SP, Kinney PL, Christie NT. Ni(II) induced changes in cell cycle duration and sister-chromatid exchanges in cultured human lymphocytes. *Mutat Res Fund Mol Mech* 1995;327:217-225.

185. Sandström AIM, Wall SGI, Taube A. Cancer incidence and mortality amon Swedish smelter workers. *Br J Ind Med* 1989;46:82-89.

186. Sanford WE, Nieboer E. Renal toxicity of nickel in humans. In: Nieboer E, Nriagu JO, eds. *Nickel and Human Health. Current Perspectives*. New York: John Wiley & Sons, Inc, 1992:123-134.

187. Santucci B, Manna F, Cannistraci C, Cristaudo A, Capparella R, Bolasco A, Picardo M. Serum and urine concentrations in nickel-sensitive patients after prolonged oral administration. *Contact Dermatitis* 1994;30:97-101.

188. Santucci B, Manna F, Cristaudo A, Cannistraci C, Capparella MR, Picardo M. Serum concentrations in nickel-sensitive patients after prolonged oral administration. *Contact Dermatitis* 1990;22:253-256.

189. Scholz RC, Holcomb ML. Feasibility study for reduction of workers exposure to nickel and chromium alloy foundries. *Report submitted to OSHA Docket H-110 by the Foundry nickel committee*. Wadhington DC: US Occupational Health and Safety Administration, 1980.

190. Seidenari S, Danese P, Di-Nardo A, Manzini BM, Motolese A. Contact sensitization among ceramics workers. *Contact Dermatitis* 1990;22:45-49.

191. Shannon HS, Julian JA, Muir DCF, Roberts RS, Cecutti AC. A mortality study of Falconbridge workers. In: Sunderman FW Jr, Aitio A, Berlin A, et al., eds. *Nickel in the Human Environment*. Lyon: International Agency for Research on Cancer, 1984:117-124. (IARC Scientific Publications; 53).

192. Shannon HS, Walsh C, Jadon N, Julian JA, Weglo JK, Thornhill PG, Cecutti AG. Mortality of 11,500 nickel workers--extended follow up and relationship to environmental conditions. *Toxicol Ind Health* 1991;7:277-294.

193. Shirakawa T, Kusaka Y, Fujimura N, Kato M, Heki S, Morimoto K. Hard metal asthma: cross immunological and respiratory reactivity between cobalt and nickel? *Thorax* 1990;45:267-271.

194. Simonato L, Fletcher AC, Andersen A, Anderson K, Becker N, Chang-Claude J, et al. A historical prospective study of European stainless steel, mild steeel, and shipyard welders. *Br J Ind Med* 1991;48:145-154.

195. Smialowicz RJ, Rogers RR, Riddle MM, Garner RJ, Rowe DG, Luebke RW. Immunological effects of nickel. II. Suppression of natural killer cell activity. *Environ Res* 1985;36:56-66.

196. Smialowicz RJ, Rogers RR, Rowe DG, Riddle MM, Luebke RW. The effects of nickel on immune fucntion in the rat. *Toxicology* 1987;44:271-281.

197. Smith MK, George EL, Stober JA, Feng HA, Kimmel GL. Perinatal toxicity associated with nickel chloride exposure. *Environ Res* 1993;61:200-211.

198. Snow ET, Xu LS, Kinney PL. Effects of nickel ions on polymerase activity and fidelity during DNA replication in vitro. *Chem Biol Interact* 1993;88:155-173.

199. Snyder RD, Davis GF, Lachmann PJ. Inhibition by metals of X-ray and ultraviolet-induced DNA repair in human cells. *Biol Trace Elem Res* 1989;21:389-398.

200. Socialstyrelsen. Socialstyrelsens allmänna råd om hållagning i öronen; den 29 November 1989. *Socialstyrelsens författningssamling* 1990;40:1-7 (in Swedish).

201. Stridsklev IC, Hemmingsen B, Karlsen JT, Schaller KH, Raithel HJ, Langård S. Biologic monitoring of chromium and nickel among stainless steel welders using the manual metal arc method. *Int Arch Occup Environ Health* 1993;65:209-219.

202. Sunderman FW Jr, Aitio A, Berlin A, et al., eds. *Nickel in the Human Environment*. Lyon, France: International Agency for Research on Cancer, 1984 (IARC Scientific Publications; 53).

203. Sunderman FW, Sunderman FW Jr. Nickel poisoning VIII. Dithiocarb: A new therapeutic agent for persons exposed to nickel carbonyl. *Am J Med Sci* 1958;236:26-31.

204. Sunderman FW Jr. Biological monitoring of nickel in humans. *Scand J Work Environ Health* 1993;19 Suppl 1:34-38.

205. Sunderman FW Jr, Aitio A, Morgan LG, Norseth T. Biological monitoring of nickel. *Toxicol Ind Health* 1986;2:17-78.

206. Sunderman FW Jr, Dingle B, Hopfer SM, Swift T. Acute nickel toxicity in electroplating workers who accidentally ingested a solution of nickel sulphate and nickel chloride. *Am J Ind Med* 1988;14:257-266.

207. Sunderman FW Jr, Hopfer SM, Plowman MC, Knight JA. Carcinogenesis bioassays of nickel oxides and nickel-copper oxides by intramuscular administration to Fischer-344 rats. *Res Commun Chem Pathol Pharmacol* 1990;70:103-113.

208. Sunderman FW Jr, Horak E. Biochemical indices of nephrotoxicity, exemplified by studies on nickel nephropathy. In: Brown SS, Davies DS, eds. *Organ-directed toxicity. Chemical indices and mechanisms*. Oxford: Pergamon Press, 1981:55-67.

209. Takamura K, Hayashi K, Ishinishi N, Yamada T, Sugioka Y. Evaluation of carcinogenicity and chronic toxicity associated with orthopedic implants in mice. *J Biomed Mater Res* 1994;28:583-589.

210. Tandon SK, Mathur AK, Gaur JS. Urinary excretion of chromium and nickel among electroplaters and pigment industry workers. *Int Arch Occup Environ Health* 1977;40:71-76.

211. Templeton DM, Sunderman FW Jr, Herber RF. Tentative reference values for nickel concentrations in human serum, plasma, blood, and urine: evaluation according to the TRACY protocol. *Sci Total Environ* 1994;148:243-251.

212. Teraki Y, Uchiumi A. Experimental studies on metal carcinogenesis: A comparative assessment of nickel and lead. In: Nieboer E, Nriagu JO, eds. *Nickel and Human Health.* Current perspectives. New York: John Wiley & Sons, Inc, 1992:527-535.

213. The Council of the European Union. European Parliament and Council directive 94/27/EC amending for the 12th time Directive 76/769/EEC on the approximation of the laws, regulations and administrative provisions of the Member States relating to restrictions on the marketing and use of certain dangerous substances and prepartions. *Offic J Eur Commun* 1994 July 22;L188:1-2.

214. Thielke SA. Personal communication, AMAX nickel refining company, Greenwich, Connecticut, U.S.A. 1982. Quoted in: Nieboer E, Yassi A, Jusys AA, Muir DCF. *The Technical Feasibility and Usefulness of Biological Monitoring in the Nickel Producing Industry.* Hamilton, Ontario: McMaster University, 1984.

215. Tkeshelashvili LK, Reid TM, McBride TJ, Loeb LA. Nickel induces a signature mutation for oxygen free radical damage. *Cancer Res* 1993;53:4172-4174.

216. Tola S, Kilpiö J, Virtamo M. Urinary and plasma concentrations of nickel as indicators of exposure to nickel in an electroplating shop. *J Occup Med* 1979;21:184-188.

217. Tomokuni K, Ichiba M, Hirai Y. Urinary N-acetyl-ß-D-glucosaminidase and ß-aminoisobutyric acid in workers occupationally exposed to metals such as chromium, nickel, and iron. *Int Arch Occup Environ Health* 1993;65:19-21.

218. Torjussen W, Andersen I. Nickel concentrations in nasal mucosa, plasma, and urine in active and retired nickel workers. *Ann Clin Lab Sci* 1979;9:281-287.

219. Torreilles J, Guerin M-C, Slaoui-Hasnaoui A. Nickel(II) complexes of histidyl-peptides as Fenton-reaction catalysts. *Free Radicals Res Commun* 1990;11:159-166.

220. Tossavainen A, Nurminen M, Mutanen P, Tola S. Application of mathemathical modelling for assessing the biological half-times of chromium and nickel in field studies. *Br J Ind Med* 1980;37:285-291.

221. Toyoshima M, Sato A, Taniguchi M, Imokawa S, Nakazawa K, Hayakawa H, Chida K. A case of eosinophilic pneumonia caused by inhalation of nickel dusts. *Nippon Kyobu Shikkan Gakkai Zasshi* 1994;32:480-484 (Medline English abstract).

222. Triebig G, Zschiesche W, Schaller KH, Weltle D, Valentin H. Studies on the nephrotoxicity of heavy metals in iron and steel industries. In: Foá V, Emmett EA, Maroni M, Colombi A, eds. *Occupational and Environmental Chemical Hazards. Cellular and Biochemical Indices for Monitoring Toxicity.* Chichester: Ellis Horwood Limited, 1987:334-338.

223. Tveito G, Hansteen I-L, Dalen H, Haugen A. Immortalization of normal human kidney epithelial cells by nickel(II). *Cancer Res* 1989;49:1829-1835.

224. Työministeriö. N:o 838 Työministeriön päätös syöpäsairauden vaaraa aiheuttavista tekijöistä. Annettu Helsingissä 16 päivänä syyskuuta 1993. *Suomen Säädöskok* 1993;112:2293-2308 (in Finnish).

225. Työministeriö. Kemian työsuojeluneuvottelukunta. *HTP-arvot* 1993. *Turvallisuustiedote 25.* Tampere: Työministeriö, 1993 (in Finnish).

226. Ulrich L, Sulcová M, Spacek L, Neumanová E, Vladar A. Investigation of professional nickel exposure in nickel refinery workers. *Sci Total Environ* 1991;101:91-96.

227. U.S. Department of Health & Human Services. *Draft toxicological profile for nickel.* Atlanta, Georgia: Agency for Toxic Substances and Disease Registry, 1991.

228. U.S. Department of Health & Human Services. *Toxicological profile for nickel* (Update). Atlanta: Agency for Toxic Substances and Disease Registry, 1993.

229. Veien NK, Hattel T, Justesen O, Nÿrholm A. Dietary treatment of nickel dermatitis. *Acta Derm Venereol* 1985;65:138-142.

230. Veien NK, Hattel T, Laurberg G. Low nickel diet: an open, prospective trial. *J Am Acad Dermatol* 1993;29:1002-1007.

231. Verma DK, Julian JA, Roberts RS, Muir DC, Jadon N, Shaw DS. Polycyclic aromatic hydrocarbons (PAHs): a possible cause of lung cancer mortality among nickel/copper smelter and refinery workers. *Am Ind Hyg Assoc J* 1992;53:317-324.

232. Vyskocil A, Senft V, Viau C, Cìzkov· M, Kohout J. Biochemical renal changes in workers exposed to soluble nickel compounds. *Human Exp Toxicol* 1994;13:257-261.

233. Vyskocil A, Smejkalova J, Tejral J, et al. Lack of renal changes in stainless steel welders exposed to chromium and nickel. *Scand J Work Environ Health* 1992;18:252-256.

234. Vyskocil A, Viau C, Cizkova M. Chronic nephrotoxicity of soluble nickel in rats. *Human Exp Toxicol* 1994;13:689-693.

235. Wahlberg JE, Boman AS. Cross-reactivity to palladium and nickel studied in the guinea pig. *Acta Derm Venereol* 1992;72:95-97.

236. van der Wal JF. Exposure of welders to fumes Cr, Ni, Cu and gases in Dutch industries. *Ann Occup Hyg* 1985;29:377-389.

237. van der Wal JF. Further studies on the exposure of welders to fumes, chromium, nickel and gases in Dutch industries: plasma welding and cutting of stainless steel. *Ann Occup Hyg* 1986;30:153-161.

238. Wall LM, Calnan CD. Occupational nickel dermatitis in the electroforming industry. *Contact Dermatitis* 1980;6:414-420.

239. Warner JS. Occupational exposure to airbourne nickel in producing and using primary nickel products. In: Sunderman FW Jr, Aitio A, Berlin A, et al., eds. *Nickel in the Human Environment.* Lyon: IARC, 1984:419-437. (IARC scientific publications No 53).

240. Webster JD, Parker TF, Alfrey AC, Smythe WR, Kubo H, Neal G, Hull AR. Acute nickel poisoning by dialysis. *Ann Intern Med* 1980;92:631-633.

241. White MA, Boran AM. Urinary excretion of nickel in nickel-chromium electroplaters. In: Nieboer E, Nriagu JO, eds. *Nickel and Human Health. Current Perspectives.* New York: John Wiley & Sons, 1992:89-96.

242. Wilkinson DS, Wilkinson JD. Nickel allergy and hand eczema. In: Maibach J, Menné T, eds. *Nickel and the Skin: Immunology and Toxicology.* Boca Raton, FL: CRC Press, 1989:133-165.

243. Yang Z, Gang B, Sun S. Urinary and hair nickel as exposure indices. In: Nieboer E, Nriagu JO, eds. *Nickel and Human Health. Current Perspectives.* New York: John Wiley & Sons, 1992:97-101.

244. Zeromski J, Jezewska E. Functional alterations of human blood monocytes after exposure to various nickel compounds in vitro: An effect on the production of hydrogen peroxide. *Immunol Lett* 1995;45:117-121.

245. Zeromski J, Jezewska E, Sikora J, Kasprzak KS. The effect of nickel compounds on immunophenotype and natural killer cell function of normal human lymphocytes. *Toxicology* 1995;97:39-48.

246. Zober A, Schaller K-H, Weltle D. *Untersuchungen zur Kinetik fon Chrom und Nickel im biologischen Material während einwöchigen Lichtbogenschweissens mit Chrom-Nickel-haltigen Zusatzwerkstoffen.* Düsseldorf: Deutscher Verlag für Schweisstechnik, 1985 (DVS Berichte; 95).

247. Zober A, Weltle D. Cross-sectional study of respiratory effects of arc welding. *J Soc Occup Med* 1985;35:79-84.

248. Zober A, Weltle D, Schaller K-H. Untersuchungen zur Kinetik von Chrom und Nickel im biologischen Material währendeinwöchigen Lichtbogenschweissens mit Chrom-Nickel-haltigen Zusatzwerkstoffen. *Schweissen Schneiden* 1984;36:461-464.

249. Zschiesche W, Emmerling G, Schaller KH, Weltle D. Investigation on renal impairments of high alloy steel welders. In: Foá V, Emmett EA, Maroni M, Colombi A, eds. *Occupational and Environmental Chemical Hazards. Cellular and Biochemical Indices for Monitoring Toxicity*. Chichester: Ellis Horwood, 1987:339-343.

250. Zwennis WCM, Franssen AG. Exposition to insoluble nickel compounds in a plant for nickel catalysts. Relation between concentrations of nickel in urine and plasma (Abstract). In: *Proceedings of the second international conference on clinical chemistry and clinical toxicology of metals*. Montreal:, 1983:128.

Submitted for publication, 23rd January, 1996.

Appendix

Permitted or recommended maximum levels of Nickel, metal and insoluble compounds, in air

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark	-	0.05	Ni-metal	1994	1
	-	1	insoluble compounds		
Finland	-	1		1993	2
Germany	-	0.5	TRK; C	1995	3
Iceland	-	0.5	S	1989	4
Netherlands	-	1		1995	5
Norway	-	0.1	C	1995	6
Sweden	-	0.5	S	1993	7
USA (ACGIH)	-	1		1995-96	8
	-	0.05	C; intended change		
(NIOSH)	-	0.015	C	1994	9
(OSHA)	-	1		1994	9

C = carcinogenic
S = sensitizing
TRK = technical guideline

Permitted or recommended maximum levels of Nickel compounds (oxide, carbonate and soluble compounds) in air

Country	ppm	mg/m3	Comments	Year	Ref.
Denmark	-	0.1		1994	1
Finland	-	0.1		1993	2
Germany	-	0.5	C; TRK	1995	3
Iceland	- -	0.1 0.01	C; S subsulfide; C; S	1989	4
Netherlands	-	0.1		1995	5
Norway	-	-		1995	6
Sweden	- -	0.1 0.01	C; S subsulfide; C; S	1993	7
USA (ACGIH)	- -	0.1 0.05	C; intended change	1995-96	8
(NIOSH)	-	0.015	C	1994	9
(OSHA)	-	1		1994	9

C = carcinogenic
S = sensitizing
TRK = technical guideline

Permitted or recommended maximum levels of Nickel carbonyl in air

Country	ppm	mg/m3	Comments	Year	Ref.
Denmark	0.001	0.007	H	1994	1
Finland	0.001 0.003	0.007 0.021	 15 min exposure	1993	2
Germany	-	-	C; H	1995	3
Iceland	0.001	0.007	C	1989	4
Netherlands	0.05	0.35		1995	5
Norway	0.001	0.007		1995	6
Sweden	0.001	0.007	C; R	1993	7
USA (ACGIH)	0.05 -	0.12 0.05	 C; intended change	1995-96	8
(NIOSH)	0.001	0.007	C	1994	9
(OSHA)	0.001	0.007	C	1994	9

C = carcinogenic
H = skin uptake
R = reproduction disturbances

References

1. *Grænsværdier for stoffer og materialer*. Køpenhavn: Arbejdstilsynet,1994 (At-anvisning Nr.3.1.0.2) .
2. *HTP-värden 1993*. Tammerfors: Arbetsministeriet, 1993 (Säkerhetsmeddelande 25). ISBN 951-47-8343-3.
3. *MAK- und BAT-Werte-Liste 1995*. Weinheim: VCH Verlagsgesellschaft, 1995.
4. *Mengunarmörk og adgerdir til ad draga úr mengun*. Skrá yfir mengunarmörk. Reykjavik: Vinnueftirlit Rikisins,1989.
5. *De Nationale MAC-lijst 1995*. Den Haag: 1995 (Publikatiebladen/1-SZW; P 145). ISBN 90-399-0819-2.
6. *Administrative normer for forurensninger i arbeidsatmosfaere*. Veiledning til arbeidsmiljøloven. Oslo: Direktoratet for arbeidstilsynet, 1995 (Bestillingsnr. 361).
7. *Hygieniska gränsvärden*.. Stockholm: Arbetarskyddsstyrelsen, 1993 (AFS 1993:9). ISBN 91-7930-046-4.
8. *Threshold Limit Values and biological exposure indices for 1995-96*. Cincinnati, Ohio: American Conference of Governmental Industrial Hygienists,1995. ISBN 1-882417-11-9.
9. *NIOSH Pocket Guide to Chemical Hazards*. Washington: U.S. Department of Health and Human Services, 1994.