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Criteria Document for Swedish Occupational Standards

Cobalt and Cobalt Compounds

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Preface

The Swedish Criteria Group for Occupational Standards (SCG) of the Swedish National Institute for Working Life (NIWL) has engaged Dr Nicole Palmen at Encare Arbozorg, Maastricht, Netherlands, to write this criteria document concerning Cobalt and Cobalt Compounds. Based on this document the Criteria Group has presented a report to be used as the scientific background material by the Swedish Work Environment Authority in their proposal for an occupational exposure limit.

Johan Högberg
Chairman
Criteria Group

Johan Montelius
Secretary
Criteria Group

Abbreviations

AAS	Atomic absorption spectrometry
BAL	Bronchoalveolar lavage
B-CO	Cobalt concentration in blood
bw	Body weight
CI	Confidence interval
Co-air	Cobalt concentration in the air
Co-HSA	Cobalt-conjugated human serum albumin
DL_{CO}	Diffusing capacity of CO
ECG	Electrocardiogram
FEV_1	Forced expiratory volume in 1 second
FSH	Follicle-stimulating hormone
FVC	Forced vital capacity
ICP-MS	Inductively coupled plasma mass spectrophotometry
ILD	Interstitial lung disease
Hard metal	Mixture between cobalt and tungsten carbide
LH	Luteinizing hormone
MMF	Maximum midexpiratory flow
OEL	Occupational exposure limit
OR	Odds ratio
PAS	Personal air sampling
PEF	Peak expiratory flow
RAST	Radioallergosorbent test
ROS	Reactive oxygen species
SD	Standard deviation
SMR	Standardized mortality ratio
SS	Stationary sampling
SSB	Single strand breaks
U-CO	Cobalt concentration in urine
V_{50}	Forced expiratory flow at 50% vital capacity
VC	Vital capacity
WC	Tungsten carbide
WC-Co	Mixture of tungsten carbide and cobalt

Contents

1. Introduction

In this document metallic cobalt, cobalt alloys and cobalt compounds will be included. The aim of this review is a description and evaluation of studies that are relevant for setting occupational exposure limits. For this reason human studies will be described in detail. Only animal studies that use inhalatory exposure or studies that contribute to the understanding of a different toxicity for Co and different Co compounds, will be discussed. Last literature search was performed in October 2004.

Important previously published criteria documents and toxicity reviews of cobalt and cobalt compounds are those of the Nordic Expert Group for Criteria Documentation (Midtgård & Binderup 1994), the UK Health and Safety Executive (Evans et al 1991), the IARC document (IARC 1991), Elinder and Friberg (Elinder & Friberg 1986) and Lison (Lison 1996, Lison et al 2001).

2. Physical and Chemical Properties of Metallic cobalt, cobalt compounds, cobalt alloys and mixtures

Cobalt has one naturally occurring isotope ^{59}Co (atomic weight 58.93) and has magnetic properties. It can form alloys, is not corroded by air or water at ordinary temperature and is resistant to alkalis but soluble in acids. Synonyms are Cobalt-59, Super cobalt, Aquacat, C.I. 77320, NCI-C60311. The melting point is about 1500 °C and the boiling point is about 3000 °C (IARC 1991, Jensen & Tuchsen 1990, Kipling 1980, Midtgård & Binderup 1994, Suvorov & Cekunova 1983, Windholz 1976). The main oxidation states of cobalt are +II and +III. Most commercially used cobalt compounds are water soluble bivalent salts (see Table 1). Alloys which are important regarding occupational exposure are stellite (which is an alloy mainly composed of Co (48-58%), chromium, nickel and tungsten) and vitallium (mainly composed of cobalt (56-68%), chromium and molybdenum) (IARC 1991). Hard metal is a mixture between cobalt and tungsten carbide (Lasfargues et al 1994), see below.

3. Occurrence, production and use

The average concentration of cobalt in the earth's crust is 20 μg/g but higher concentrations are found in nickel and copper ore deposits from which about 25,000 tons of cobalt metal are produced annually (Lison 1996). Cobalt is extracted from ore and concentrated by pyrometallurgical, hydrometallurgical and electrolytic processes alone or in combination. Cobalt metal is available for industrial use as 'broken' or 'cut' cathodes (purity >99.5%) or electrolytic coarse powder (mean particle size 4-10 μm) (IARC 1991).

Table 1. Identity and solubility of various cobalt compounds, alloys and mixtures.

Compound name	Formula	M.W.	CAS no.	Solubility in water[1)]	Solubility in blood serum
Cobalt	Co	58.94	7440-48-4	i	200 mg/l (37°C)
Cobalt(II) oxide	CoO	74.94	1307-96-6	3.13 mg/l	273 mg/l (37°C)
Cobalt(II,III) oxide	Co_3O_4	240.80	1308-06-1	i	
Cobalt(III) oxide	Co_2O_3	165.86	1308-04-9	i	
Cobalt(III) oxide hydrate	Co_2O_3, H_2O	183.88	-	0.84 mg/l (37°C)	53,9 mg/l (37°C)
Cobalt(II) sulphide	CoS	90.99	1317-42-6	i	
Cobalt(II) chloride	$CoCl_2$	129.84	7646-79-9	529 g/l (20°C)	
Cobalt(II) chloride hexahydrate	$CoCl_2$, $6H_2O$	237.93	7791-13-1	767 g/l (0°C)	
Cobalt(II) sulphate	$CoSO_4$	154.99	10124-43-3	393 g/l (25°C)	362 g/l (20°C)
Cobalt(II) sulphate heptahydrate	$CoSO_4$,$7H_2O$	281.10	10026-24-1	604 g/l (3°C)	
Cobalt(II) nitrate hexahydrate	$CoNO_3$,$6H_2O$	291.03	10026-22-9	1338 g/l (0°C)	
Cobalt(II) carbonate	$CoCO_3$	118.94	513-79-1	1.1 g/l (15°C)	
Cobalt(II) acetate tetrahydrate	$(CH_3COO)_2Co$,$4H_2O$	249.08	71-48-7	s	
Cobalt(II) naphthenate	-	-	61789-51-3	s	
Cobalt(II) potassium nitrite	$K_3(Co(NO_2)_6)$	452.56	13782-01-9	9 g/l (17°C)	
Cobalt aluminate blue	CoO,Al_2O_3		1333-88-6	i	
Stellite[2]	Co(48-58%), Cr,Ni,W alloy		12638-07-2		
Vitallium[2]	Co(56-68%), Cr,Mo alloy		12629-02-6		
Hard metal	Co(10-25%), WC mixture				

[1]s = soluble, i = insoluble,
[2]Trade mark

Cobalt salts and cobalt oxides are used as catalysts in organic reactions or as drying agents in paints, lacquers, varnishes and printing inks. Cobalt oxides, cobalt zinc silicate and spinels (mixed metal oxides with a special crystal structure, based on magnesium and aluminium oxides) are used as pigments in glass, enamels, ceramic and porcelain products (Donaldson 1986).

The most important use of metallic cobalt is in alloys with other metals (e.g, chromium, nickel, copper, aluminium, beryllium and molybdenum). Cobalt is also applied in the production of super alloys (high temperature alloys), high strength steels, magnetic alloys, electrodeposited alloys, dental and surgical implants. Hard-metals (cemented carbides) are the most important application of cobalt (Donaldson 1986, Lison 1996). Hard-metals are produced using a powder metallurgy process (sintering) in which tungsten carbide particles and cobalt metal (10-25%) are mixed, heated in hydrogen atmosphere, pressed, shaped, sintered and grinded (see figure 1). Cobalt acts as a binder for tungsten carbide (Lasfargues et al 1994). Cobalt has also been used in certain polishing disks of microdiamonds cemented into ultrafine cobalt metal powder (Co amount of the disk: 80-90%) (Demedts et al 1984, Lison 1996, van den Oever et al 1990).

The human body contains 1000 to 2000 μg of Co; most of it is found in liver (vitamin B12), kidney, heart and spleen, and low concentrations in serum, brain and pancreas (Elinder & Friberg 1986, Lison 1996, Midtgård & Friberg 1994).

4. Exposure

4.1. Working population

The main route of occupational exposure is the respiratory tract (dusts, fumes or mists containing cobalt although skin contact is important (IARC 1991, Linnainmaa & Kiilunen 1997, Scansetti et al 1994). Occupational exposures mainly occur in hard-metal production, processing and use, during the production of cobalt powder, in the use of cobalt-containing pigments and driers and during regeneration of spent catalysts (IARC 1991). In the following overview of Co exposures, only studies using personal air sampling will be taken into account. Airborne Co exposures are highly dependent on the type of industry, the stage of the production process, the physical/chemical state of the cobalt compound and the availability of local and/or general exhaust ventilation (see Table 2).

In hard metal industry highest airborne exposures were measured for powder and press handlers and lowest for grinders and sinter workers (see Table 2). Within these groups, the geometric standard deviations indicating within-worker variation and between-worker variation were 1.88-2.77 and 1.00-2.31, respectively, which is rather high compared to other industries (1.60 and 1.73, respectively) (Kumagai et al 1996). During powder handling and mixing of cobalt and tungsten carbide powders mean inhalable cobalt concentrations in air (Co-air) between 45 and 460 μg Co/m^3 have been reported (Alexandersson & Bergman 1978, Ichikawa et al 1985, Kumagai et al 1996, Meyer-Bisch et al 1989, Scansetti et al 1994).

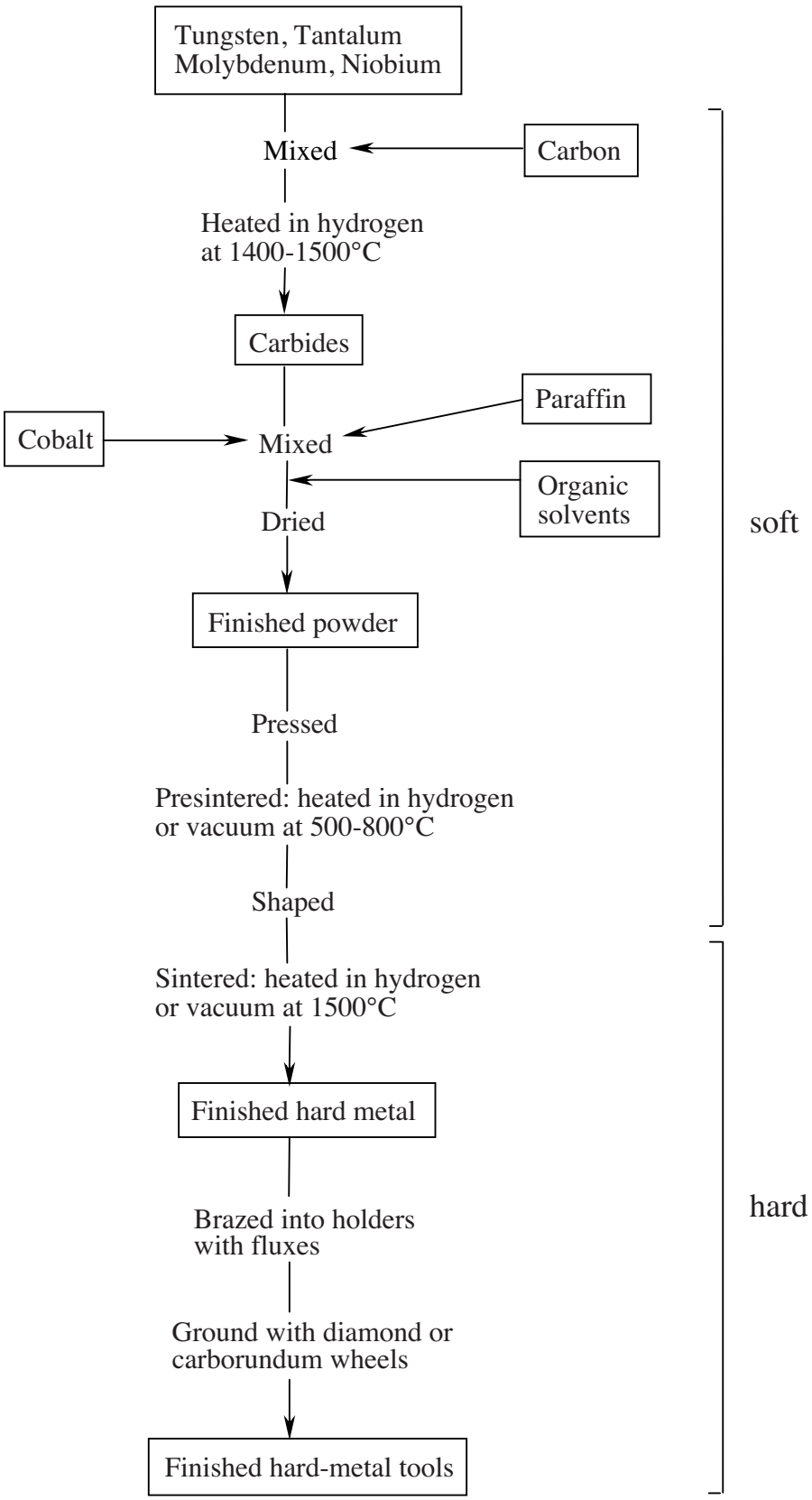

Figure 1. Steps in the manufacture of hard-metal tools (Kusaka, et al 1986a).

Table 2. Occupational exposure to cobalt (μg Co/m^3) in various types of industries and at different production stages.

Type of industry	n	Process	Mean	Lowest	Highest	Ref.
hard metal	3	mixing	227	200	250	(Scansetti et al 1994)
	3	pressing	147	130	170	
	3	grinding	97	90	100	
hard metal	4	wet+dry grinding	54-87	50	194	(Stebbins et al 1992)
hard metal	2	mixing	186	110	262	(Ichikawa et al 1985)
	6	pressing	367	92	859	
	27	wet grinding	44-92	3	291	
hard metal		mixing	60-150	50	950	(Alexandersson &
		pressing	<10-250	<10	250	Bergman 1978)
		dry grinding	3-8			
		wet grinding	3-77	3	90	
hard metal		mixing	327-32 470	20	438 000	(Sprince et al 1984)
		pressing	326-755	13	7 359	
		wet+dry grinding	17-118	3	307	
hard metal		mixing	45-272			(Meyer-Bisch et al 1989)
		pressing	30-220			
hard metal		pressing	>100 (10%) 50-100 (20%) 10-50 (38%) <10 (32%)			(Scansetti et al 1985)
hard metal		mixing	459	7	6 390	(Kumagai et al 1996)
		pressing	339	48	2 910	
		grinding	45	1	482	
cobalt refinery	82	no distinction	570*	2	7 700	(Swennen et al 1993)
diamond/cobalt	16	mixing room		9	2 860	(Gennart &
saw production	7	oven room		6	51	Lauwerys 1990)
diamond polishing		polishing	5.3-15.1	0.2	42.8	(Nemery et al 1992)
dental prostheses	3	melting bay	4			(Leghissa et al 1994)
production	3	refinishing bay	10	3	50	
dental prostheses production	79		>10 (2.5%) 25-100 (13.9%) <25 (83.6%)			(Kempf & Pfeiffer 1987)
dental technicians	8	not described		<detection	1.6	(Selden et al 1995)
pottery painting	19	plate painting	33.4	21.9	79.9	(Christensen & Poulsen 1994)
pottery painting	19	plate painting	>50 (20%)**	68	8 610	(Tuchsen et al 1996, Raffn et al 1988)
magnet production	100	not described	33* >50 (18%)	1	466	(Deng et al 1991)
welding stellite	5	oxy acetylene	5.2*			(Ferri et al 1994)
	7	MAG welding	175*			

*calculated arithmetic mean with assumption of normal distribution
**Co-air concentration was 50 μg Co/m^3 after improving the ventilation system
n = The number of samples taken

However, mean inhalable Co-air concentrations up to 32 000 μg Co/m^3 have also been reported (Sprince et al 1984). During pressing mean inhalable Co-air concentrations between <10 and 370 μg Co/m^3 were reported (Alexandersson & Bergman 1978, Ichikawa et al 1985, Kumagai et al 1996, Meyer-Bisch et al 1989, Scansetti et al 1994, Scansetti et al 1985). Higher mean inhalable values (760 μg Co/m^3) were again reported by Sprince (Sprince et al 1984). Inhalable Co-air concentrations during grinding varied between 17 and 120 μg Co/m^3 (Kumagai et al 1996, Scansetti et al 1994, Sprince et al 1984, Stebbins et al 1992). Alexandersson reported 3-8 μg Co/m^3 during dry grinding and 3-77 μg Co/m^3 during wet grinding (Alexandersson & Bergman 1978). The higher exposure during wet grinding is caused by cobalt containing aerosols (Einarsson et al 1979, Linnainmaa et al 1996, Sjögren et al 1980, Stebbins et al 1992, Teschke et al 1995). Regarding tungsten carbide grinding machines, cobalt concentrations in coolants show large variations (mean 696 mg/l, SD 868, range 1.2-5100 mg/l). Maximally 12% are solid particles. Cobalt is easily dissolved in the coolants especially during the first weeks of use. Coolants that were especially developed for hard metal grinding had the lowest cobalt concentrations (Linnainmaa 1995). Cobalt concentrations in coolants from stellite grinding machines were much lower compared to tungsten carbide grinding machines despite the higher concentration of cobalt in stellite (Teschke et al 1995). The presence of local dust ventilation reduces Co-air values both in dry and wet grinding (Imbrogno & Alborghetti 1994). In a recent study respirable Co-air concentrations between 8-64 μg Co/m^3 during powder processing, 0.9-116 μg Co/m^3 during pressing and 0.5 and 0.2 μg Co/m^3 during dry and wet grinding, respectively (Kraus et al 2001).

The Co exposure in a Swedish hard metal plant was recently reported in an abstract (Seldén et al 2000). The air samples showed total dust and tungsten levels well below Swedish national standards but the Co concentration was sometimes high (extreme value 1100 μg/m^3). Urine specimen collected at the end of the working week revealed U-Co levels of ≥15 μg/l in 29% of the workers (n=17) at the milling and mixing department.

In a Belgian cobalt refinery (production of cobalt powder) the mean inhalable Co-air concentration was 570 μg Co/m^3 (estimated Co concentration with assumption of normal distribution). About 70% of the workers were exposed to Co-air concentrations higher than 50 μg/m^3; 25% was exposed to Co-air values higher than 500 μg/m^3 (Swennen et al 1993). Co-air exposures during the production of diamond-cobalt circular saws and during polishing of diamonds with this type of saw are presented in Table 2. Interestingly, the mean inhalable Co-air concentrations reported by Nemery et al (5.3-15.1 μg Co/m^3) was lower than the mean respirable Co-air concentration reported by van den Oever et al (23 μg Co/m^3, not shown in the Table) (van den Oever et al 1990).

Inhalable Co-air concentrations during dental technicians work, the production of dental prostheses, pottery painting, magnet production and welding of stellite are given in Table 2.

To summarize, the highest exposure levels are found in the hard metal industry during handling of powders and pressing (Kumagai et al 1996). Cobalt in air

concentrations during wet grinding may be higher than in dry grinding because of exposure to Co containing aerosols of cutting/cooling fluids (Einarsson et al 1979, Linnainmaa et al 1996, Sjögren et al 1980, Teschke et al 1995). High airborne Co concentrations were also found in Co refineries and during the production of Co containing diamond saws (Gennart & Lauwerys 1990, Swennen et al 1993).

4.2. General population

Environmental airborne Co concentrations are usually around 1 ng/m^3 but in heavily industrialised cities concentrations up to 10 ng/m^3 have been reported. Cobalt concentrations in drinking water vary between 0.1-5 μg/l. Tobacco contains <0.01-2.3 μg Co/kg dry weight (0.5% of the cobalt content being transferred into smoke) and is thus an insignificant Co source. (IARC 1991).

The daily cobalt intake for the general population ranges between 1.7-100 μg; the diet being the main source (IARC 1991). The cobalt containing hydroxy-cobalamin (vitamin B12) is an essential nutrient to humans: the minimum recommended daily intake of an adult is 3 μg, corresponding to 0.012 μg of cobalt. Vitamin B12 deficiency leads to the development of pernicious anaemia (Lison 1996).

5. Measurements and analysis of workplace exposure

Environmental measurements for compliance with OEL values have to be set up according to international standards (SS-EN 481, SS-EN 482, SS-EN 689) (Levin 2000), which state that only properly taken personal air samples are valid indicators of exposure. Stationary samples can only give an insight into sources of contamination and background concentrations. Atomic absorption spectrometry (AAS) or X-ray fluorescence are advised for cobalt analysis in environmental samples (Levin 2000). Inductively coupled plasma (ICP) is as sensitive as AAS (0,1 μg/filter).

Blood Co (B-Co) and urine Co (U-Co) concentrations should be analysed with graphite furnace AAS with Zeeman background correction, which is a very sensitive method (Bouman et al 1986, Stebbins et al 1992). More recently, inductively coupled plasma mass spectrophotometry (ICP-MS) was found to be a sensitive method for evaluation of environmental samples and U-Co. However, overestimation of U-Co was found at low concentrations (non-exposed persons). A high correlation between the formerly used AAS and the more recent ICP-MS methods suggest that both methods are reliable (White 1999). Inductively coupled plasma emission spectrometry and X-ray fluorescence appear to be too insensitive for determination of cobalt in biological matrices (IARC 1991).

6. Toxicokinetics

6.1. Human studies

6.1.1. Uptake

The respiratory tract (dusts, fumes, aerosols or gases) and the digestive tract are the main routes of absorption (IARC 1991). Absorption rates of cobalt or cobalt compounds are dependent on their solubility in biological media, which may also be influenced by the concomitant presence of other substances (Lison 1996). For humans almost no quantitative data are available but from measurements of cobalt in blood and urine samples obtained from exposed workers it is evident that inhaled soluble cobalt is taken up from the lungs to a great extent (see section 7. Biological monitoring). The lung retention in 2 human volunteers after inhalation of cobalt(II,III) oxide particles varied between 64% and 75% after 90 days for particles with a diameter of 0.8 μm and 1.7 μm, respectively (Bailey et al 1989). Mineralogical analysis of lung tissues or bronchoalveolar lavage fluid taken from hard metal workers with lung disease show tungsten- and/or tantalum- and titanium-containing particles but no or insignificant cobalt accumulation, which might be explained by its high solubility in liquids with high protein content (Ferioli et al 1987, Lison 1996). Nevertheless, Hartung found a cobalt concentration of 1010 μg/kg wet weight in a lung biopsy of a grinder with marked fibrosis exposed to sintered hard metal (normal cobalt lung concentration 3.0-33.0 μg/kg wet weight (n=21)) (IARC 1991, Lison 1996). These authors state that studies, in which low cobalt concentrations were found in lungs of patients with hard metal lung disease, were performed with unreliable methods. Diamond polishers (n=2) having intersitial lung disease had high cobalt concentrations in lung and bronchoalveolar lavage fluid, which tended to decrease after cessation or reduction of exposure to cobalt (Demedts et al 1984, van den Oever et al 1990).

Gastrointestinal absorption of orally supplied cobalt chloride is reported to vary between 1 and 50% and is influenced by the amount of cobalt given (Midtgård & Binderup 1994). Christensen and co-workers performed a blind controlled study (n= 23) on gastrointestinal uptake of cobalt chloride and cobalt(II,III) oxide in men and women by measuring U-Co and B-Co concentrations. They found that uptake of cobalt chloride was significantly higher than uptake of cobalt(II,III) oxide in both men and women. U-Co concentrations in females were significantly higher compared to males after ingestion of cobalt chloride, which suggests that gastrointestinal uptake of cobalt is higher for females than males (Christensen et al 1993). Absorption is reduced when cobalt is administered after a meal and higher in patients with iron deficiency (Midtgård & Binderup 1994, Sorbie et al 1971). Cobalt may also compete with other metal ions for absorption from the gastrointestinal tract, thereby producing deficiency of essential elements (Midtgård & Binderup 1994). Increased urine, blood and synovial fluid cobalt concentrations have been reported among patients having a cobalt-chromium containing surgical implant (e.g. knee or hip replacement) (IARC 1991).

Dermal uptake of hard metal powder (5-15% Co) can be calculated from U-Co concentrations measured up to 48 hours after exposure of one hand (420 cm^2) to the powder during 90 minutes. The amount of cobalt excreted was not mentioned by the authors but the area under the curve was calculated from a figure presenting U-Co concentrations up to 24 hours after the exposure. The estimated amount of Co excreted was 21 µg (highest excretion of 4 persons, volume of urine 3 l in 48 h) and the calculated dermal penetration rate is 0,033 μg Co/cm^2/h (Scansetti et al 1994). Applying the ECETOC criteria (ECETOC 1998) for skin notation (exposed area 2000 cm^2, exposure time 1 hr), the calculated uptake is 66.7 µg. This is 18% of the amount absorbed during 8-h exposure to 50 μg Co/m^3 (current Swedish OEL). The inhalatory uptake was calculated assuming a ventilation of 10 m^3 in 8 hours and a Co retention of 75%. From Linnainmaa and Kiilunen (Linnainmaa & Kiilunen 1997) it can be calculated that the increase in the amount of Co excreted in urine in 24 h, after exposure of both hands (840 cm^2) to coolant solution (1600 mg Co/l) for 1 hour, was 20.4 nmol (1.2 µg). The calculated dermal penetration rate is 0.0014 μg Co/cm^2/h. The uptake of Co applying the ECETOC criteria for skin notation is 2.9 µg. This is 0.8% of the amount absorbed during 8-h exposure to the current Swedish OEL (Linnainmaa & Kiilunen 1997). In both calculations, an assumption is made in which Co absorbed through the skin is excreted in urine within 48 and 24 hours after the exposure, respectively. Wahlberg found an absorption rate of 38 nmol cm^{-2} hr^{-1} (2.2 μg Co/cm^2/h) after application of 0.085 M Co chloride to *in vitro* human abdominal skin (autopsy material, washed with soap and water and frozen before use) during the first 4 hours of exposure (Wahlberg 1965). Applying the ECETOC criteria (ECETOC 1998) for skin notation the absorbed dose is 4.48 mg Co. This is 12 times the amount absorbed during 8-h exposure to the current Swedish OEL. From these calculations it can be concluded that dermal exposure to hard metal powder or cobalt chloride may result in significant systemic uptake.

It has been shown that metallic cobalt is oxidized to cobaltous ions by sweat before permeating the skin (Filon et al 2004).

6.1.2. Distribution

The human body contains about 1 to 2 mg of cobalt; most of it is found in liver (0.01-0.07 mg Co/kg wet weight mainly as vitamin B12), kidney, heart and spleen, whereas low concentrations were found in serum, brain and pancreas. (Elinder & Friberg 1986, Lison 1996, Midtgård & Binderup 1994). Intravenous injection of radioactive cobalt chloride in humans (n=8) was mainly distributed to the liver, as liver cobalt concentration was estimated to be 8 times higher than the mean cobalt concentration of other tissues three hours after administration (Smith, et al 1972). Cobalt concentrations in breast milk may increase significantly in cobalt exposed mothers (Byczkowski et al 1994).

Post mortem analysis of the hart of patients with cardiomyopathy caused by consumption of beer containing cobalt salts, revealed that cobalt concentrations were 10 times higher than in normal cardiac muscle (Seghizzi et al 1994). A

patient that was treated with cobalt chloride (up to 50 mg/day for 3 months) had a higher myocardial cobalt concentration (1.65 mg Co/kg wet weight) compared to controls (0.01-0.06 mg Co/kg wet weight) (IARC 1991).

There is an equal distribution of cobalt between plasma and red blood cells *in vivo* (IARC 1991). *In vitro* experiments and animal studies have shown that cobalt binds to serum proteins (mainly albumin) (Merritt et al 1984, Midtgård & Binderup 1994).

6.1.3. Excretion

Intravenous administration of ^{60}Co (1 μCi ^{60}Co, specific activity 100 μCi /μg) was mainly excreted via urine (28-56%) and faeces (2-12%). The average fraction of faecal and urine ^{60}Co was about 0.2:1. The urinary excretion is characterised by a rapid phase of a few days duration (half-times of 9 and 17 hours (n=2)) followed by 2 intermediate components (half-times of 3-8 and 40-80 days) and a long-term component (half-time of about 800 days). Between 9-16% of the administered dose had a very long biological half-time (half-time of about 800 days) (Smith et al 1972). The kinetics of urinary excretion after inhalatory exposure to cobalt dust of workers in diamond wheel industry was also multiphase (half-times 1st phase 43.9 h; 2nd phase 10 days, 3rd phase in the order of years in subjects with higher exposure). In controls, excretion was much faster during the 1st phase (half-time 20 h). This may be related to the different body burden or to different kinetics induced by continuous exposure to cobalt (Mosconi et al 1994). In a case study (oral uptake of radioactive cobalt chloride; dose unknown) biological half lives of whole body clearance were 0.47, 2.7, and 59 days for the fast, intermediate and slow component, respectively (IARC 1991). Mean urinary excretion of orally administered cobalt chloride (1.18 mg) was estimated to be 18% (range 9-23%) of the dose within 24 hours (Sorbie et al 1971). Urinary excretions of 5.7 and 8.3% were reported one week after oral administration of 50 mg cobalt chloride in two healthy persons. Elimination was considerably slower in uraemic patients. A small proportion of inhaled cobalt metal or cobalt oxide was found to be eliminated with a biological half-time of several years also (IARC 1991).

U-Co concentrations in hard metal workers decreased rapidly during the first 24 hours after relatively high exposures (4 powder workers, Co-air not given) which indicates rapid excretion. This was followed by a phase with slower excretion. U-Co values were relatively constant at lower exposures (Alexandersson & Lidums 1979). U-Co levels returned to normal rather slowly after interruption of hard metal exposure (about 100 $\mu g/m^3$), reaching values comparable to those of control subjects after about 4 weeks. At the end of the first working week after the holidays, U-Co had increased four fold, but decreased to the control values the next Monday before work. Thereafter, the weekend was no longer sufficient to reduce U-Co levels to normal (Scansetti et al 1985).

Six weeks after cessation of plate painting (n=46, exposure to 70-8610 $\mu g/m^3$ soluble cobalt salts (not further specified)), U-Co and blood cobalt (B-Co) concentrations were still 5-7 and 2 times higher than control values, respectively. Only slight decreases in both values were seen even two years after improvement of the workplace (exposure 50 $\mu g/m^3$) (Christensen & Mikkelsen 1985).

6.2. Animal studies

Pulmonary absorption is dependent on particle size and solubility of the cobalt compound. Lung clearance of Co_3O_4 is slower in larger animals than in smaller rodents and decreases with increasing age (Bailey et al 1989, Collier et al 1991, Kreyling et al 1991). Lung clearance in rats exposed to ultrafine cobalt particles (20 nm, 2000 $\mu g/m^3$, 5 h/day for 4 d) was high (biological half lives 52.8 and 156 hours for the fast and slow component, respectively) and 75% of the cobalt was eliminated within 3 days (Kyono et al 1992). In hamsters absorption of inhaled cobalt(II) oxide (0.8 mg, particle size 1.0-2.5 μm) was high since 25% was recovered in the carcass, lung and liver, 24 hours after inhalation. Essentially all cobalt(II) oxide was eliminated 6 days after exposure (IARC 1991). Whole body clearance in beagle dogs after inhalatory exposure to cobalt(II) oxide was much higher than after exposure to cobalt(II,III) oxide. Both compounds were eliminated following a fast and slow kinetics (Barnes et al 1976). Slow clearance from rat lung was reported after inhalatory administration of abrasive dust of dental laboratories containing chromium and cobalt, but exposures were very high (10 000-50 000 $\mu g/m^3$, 8 hours a day during 107 days) (Brune et al 1980).

Gastrointestinal absorption of cobalt chloride in rats was found to vary between 11 and 34%; decreasing with increasing dose (0.01-1000 μg/rat) (IARC 1991). An absorption half-time of 0.9 hours was reported in rats (oral dose of cobalt chloride 33.3 mg Co/kg). The cobalt absorption across the gastrointestinal tract was found to be incomplete at this dose (Ayala-Fierro et al 1999). Cobalt absorption is increased in iron-deficient humans and animals (Schade et al 1970).

The *in vivo* dermal absorption rate in guinea pigs was in the same range as the *in vitro* dermal absorption rate reported for humans (51-86 and 38 nmol cm^{-2} h^{-1}, respectively; application of 0.085 M cobalt chloride) (Wahlberg 1965).

Cobalt is distributed mainly to the liver, with lower concentrations in kidney, pancreas and spleen after oral administration of cobalt chloride. Relatively high concentrations were also found in myocardium, cartilage and bone (IARC 1991). After application of cobalt salts to the skin of hamsters, cobalt was retained for an exended period of time (Lacy et al 1996). The amount of cobalt found in the CNS was very small after intravenous administration of cobalt (Midtgård & Binderup 1994). In rats it has been shown that cobalt (applied in the nose as $CoCl_2$ dissolved in saline) can be taken up into the brain from the nasal mucosa via the olfactory pathways (Persson et al 2003).

Following single intravenous administration of cobalt chloride in rats (4.16 mg/kg), 10% of the dose was excreted in feaces indicating biliary excretion; 75%

of the dose was excreted in urine 36 hours after administration. The U-Co-time curve displayed 3 segments; the first which occurred during the first 4 hours had a half-time of 1.3 hours; the second phase from 4 to 12 hours had a half-time of 4.3 hours and the final phase from 12 to 36 hours had a half-time of 19 hours (Ayala-Fierro et al 1999). U-Co excretion in dogs after parenteral administration of cobalt sulphate was 40-70% of the administered dose in 7-13 hours (IARC 1991).

Oral administration of cobalt sulphate heptahydrate (25, 50, 100 mg/kg bw) to pregnant rats has shown that Co can cross the placenta. Both maternal and fetal blood concentrations were higher after oral cobalt sulphate heptahydrate treatment compared to cobalt chloride hexahydrate (Szakmary et al 2001). High Co concentrations in the fetal skeleton (and cartilaginous structures of the mother) were found after parenteral $CoCl_2$ administration to pregnant mice (IARC 1991).

7. Biological monitoring

Urine, serum and whole blood cobalt concentrations of persons not occupationally exposed to cobalt are between 0.1-2 μg/l (IARC 1991). U-Co concentrations obtained with less sensitive colorimetric methods were between 1.5 and 7 μg/l (Ferioli et al 1987). Greatly increased urinary levels have been reported in persons taking multivitamin pills containing cobalt (IARC 1991). No increase in U-Co was found however, in non-smoking women after taking 0.6 mg and 0.9 mg vitamin B_{12} (2 consecutive days) when U-Co was measured during the 2 following days (Linnainmaa & Kiilunen 1997). Non-occupationally exposed smokers (U-Co 0.59 μg/l) had higher U-Co concentrations than non-smokers (U-Co 0.30 μg/l). No differences in B-Co were found between smokers and non-smokers (Alexandersson 1988).

There is a good correlation between exposure to soluble Co compounds (metal, salts and hard metal) and U-Co or B-Co levels when Co exposure is assessed by personal air sampling. These data can be used for assessing exposure on a group basis (Lison et al 1994). U-Co is preferred above B-Co since increases in airborne Co can be detected at lower levels (Ferioli et al 1987, IARC 1991). According to Scansetti et al, Monday end of shift U-Co gives an estimate of the exposure to hard metal on that day, while Friday end of shift samples are related to the cumulative exposure of the week (Scansetti et al 1985). Some studies did not find a good correlation between cobalt exposure and U-Co (Meyer-Bisch et al 1989, Scansetti et al 1994), which could be attributed to the time that the samples were taken during the workweek (Scansetti et al 1985) or by significant dermal uptake (Linnainmaa & Kiilunen 1997, Scansetti et al 1994). Poor correlations between Co in air concentrations and U-Co or B-Co were reported in Co oxide processing (Lison et al 1994).

In hard metal industry a relationship between Co-air (x) and U-Co (y) of $y=0.67 x + 0.9$ ($r=0.99$, $p<0.001$) was found at cobalt exposures between 28-367 $\mu g/m^3$ and sampling at the end of shift on Wednesday or Thursday. U-Co was analysed

with AAS (Ichikawa et al 1985). Since cobalt is eliminated following a multi phase kinetics and the slow phase has a half-time of a few years, U-Co concentrations increase during the workweek (Ferioli et al 1987). This phenomenon was investigated by Scansetti who took urine samples of hard metal workers both on Monday and on Friday at the end of shift (exposures between 2-100 μg /m^3). The relationships between Co-air (x) and U-Co (y) were y=0.287x+0.828 (r=0.831, p<0.01) and y=0.704x+0.804 (r=0.805, p<0.01) during Monday and Friday, respectively. Monday end of shift samples give an impression of daily exposure while Friday end of shift samples are related to cumulative exposures of that week at cobalt exposures around 100 μg/m^3. Moreover, these authors found that the mean cobalt exposure levels during the preceding weeks are well reflected by the difference between U-Co taken at the end of shift on Friday and U-Co taken before the shift on Monday. Cobalt was analysed using AAS with graphite oven (Scansetti et al 1985). The relation between Co-air (x) and B-Co (y) can be described as y=0.0044x+0.23 (r=0.96, p<0.001), using the mean values of the two parameters in 10 groups of workers. The correlation between Co-air and U-Co (both analysed with AAS) was better than that of Co-air and B-Co (analysed by AAS with Zeeman background corrector) at cobalt exposures lower than 100 μg/m^3 (Ichikawa et al 1985).

U-Co concentrations were also correlated with dust exposure from cobalt containing abrasive wheels (cobalt concentrations below 50 μg/m^3) used in diamond polishing (r=0.85-0.88, Co analysis by AAS) (Nemery et al 1992). The time of sampling is very important since U-Co concentrations increased during the first 3 h after the end of Co exposure (Mosconi et al 1994).

The importance of the chemical nature of the exposure was pointed out by Christensen en Mikkelsen who found increased B-Co (0.2 to 24 μg/l) and U-Co (0.4-848 μg/l) concentrations after exposure to a soluble cobalt pigment used in pottery painting in contrast to slightly increased values after exposure to an insoluble cobalt pigment (0.05-0.6 μg/l and 0.05-7.7 μg/l, respectively, analysed by AAS with Zeeman background correction) (Christensen & Mikkelsen 1985).

8. Mechanisms of toxicity and interactions

Cobalt can bind to thiol groups, inhibits heme synthesis in the liver, induces heme oxygenase with the combined effect of rapidly decreasing cytochrome P450 concentrations and it can mimic or replace Mg^{2+} and Ca^{2+} (Bucher et al 1999, Dingle et al 1962, Leonard & Lauwerys 1990, Maines & Kappas 1976, Jennette 1981).

Interstitial lung disease (ILD), see section 9.1.2. Exposure to hard metal, has been reported in workers with combined exposure of dusts containing cobalt and tungsten carbide (WC) or cobalt and diamond. Although there are many more workers exposed to cobalt alone (metal, salts or oxides) than to hard metal (about

30 times more in the U.S.), only rare cases, if any, of ILD have been reported in this group of workers (Lison 1996).

An interaction between Co and tungsten carbide has been shown in animal experiments. The acute toxic effect in rats after intratracheal instillation of WC particles, a mixture of tungstencarbide and cobalt particles (WC-Co) or an equivalent dose of cobalt metal particles (Co), were compared with a control group. Acute lung toxicity of WC-Co metal powder was found to be much higher than that of each of the individual components of the mixture. U-Co excretion was about 4 times higher in rats treated with WC-Co compared to Co, which means that the bioavailability is higher at combined exposure (Lasfargues et al 1992). Subacute and chronic studies after a single dose of the same particles in rats revealed that WC-Co induced an immediate toxic response in BAL, followed by a subacute response that persisted after 28 days but was not detected 4 months after the exposure. The effect of equivalent doses of cobalt or WC were modest. Repeated exposure of the different kinds of particles (4 administrations at 1 month interval) showed that no effect on parenchymal architecture could be found in the groups treated with WC or Co; in contrast, clear fibrotic lesions were observed in the group instilled with WC-Co particles. These findings indicate that the long-term response to WC-Co is different from that of each of the compounds. Additional experiments showed that the mechanism of WC-Co toxicity seems to be different from that of crystalline silica, which persists in the lung and induces a progressive inflammatory reaction (Lasfargues et al 1995), producing TNF-α and IL-1. In contrast, WC-Co in lung toxic concentrations does not induce TNF-α and IL-1 production (Lison 1996). The high biological activity of WC-Co compared to pure Co or WC, which was not toxic at all, was evidenced in a macrophage culture model. Both Co and WC had to be present at the same time to produce the toxic effect, so the *in vitro* findings were consistent with the *in vivo* experiments (Lison & Lauwerys 1990). A similar interaction between Co and WC was also found for other carbides with specific surface area and chemical nature (NbC, Cr_2C_3, TaC and TiC) *in vitro* (Lison 1996). Cobalt solubilisation from a toxic dose of WC-Co was insufficient to affect macrophage viability *in vitro*. This is in agreement with the absence of toxic effects after incubation of cobalt chloride (mM) with macrophages (Lison & Lauwerys 1992). Cellular uptake of Co or WC-Co particles could not clarify the difference in cytotoxicity between the different particles (Lison & Lauwerys 1994).

Electron spin resonance studies and electrochemical techniques have shown that WC-Co particles produce large amounts of reactive oxygen species (ROS) and presumably hydroxyl radicals (Lison et al 1995, Mao et al 1996). Typical products of hydroxyl radical attack in DNA have been found in rat lung after administration of cobalt acetate (Kasprzak et al 1994). Cobalt is able to reduce oxygen at a low reaction rate but when WC is present, electrons provided by cobalt metal are easily transferred to the surface of carbide particles where reduction of oxygen can occur at a rate greatly increased. In this reaction Co^{2+} of the WC-Co particle is solubilised (Lison et al 1995). This provides an explanation for the higher

solubilisation and bioavailability of cobalt when associated with a carbide. It may also explain the specific type of toxicity induced by hard metal (Lison et al 1996).

Four different possible mechanisms of cobalt toxicity on the cardiovascular system were reported by (Seghizzi et al 1994):

- inhibition of the cellular respiration due to inhibition of the mitochondial dehydrogenase (Co binds to the –SH group of lipoic acid);
- damage of the electromechanical matching of myocardiac tissues, probably connected with a decreased concentration of Ca^{2+} ions in the cell, due to damage of the transmembrane transport system induced by Co;
- inhibition of the sympathetic tone. The ß-adrenergic system was changed during the induction of Co cardiomyopathy in dogs;
- an 'allergic mechanism'.

9. Observations in humans

In workers exposed to cobalt containing dust, the two main target organs are the respiratory tract and the skin. In addition, cobalt affects the cardiovascular system, induces erythropoiesis, has a goitrogenic effect, can lead to progressive hearing loss and atrophy of the optic nerve. Co may also lead to allergic reactions and inflammation caused by orthopedic or dental prostheses.

9.1. The respiratory system

9.1.1. Exposure to metallic cobalt, cobalt oxides or cobalt salts

A cross sectional study among 82 workers of a Co refinery and 82 controls that were not exposed to lung irritants and were matched for age and sex, was performed. The workers were exposed to Co metal, oxides and salts at concentrations between 2-7 700 μg Co/m^3 (geometric mean 125 μg Co/m^3, 164 exposure measurements) and had a mean exposure duration of 8 years. The exposed workers complained significantly more often of dyspnoea and wheezing, especially the smokers. In addition, there was a significant positive relationship between current concentrations of Co in air or U-Co and dyspnoea during exercise. A significant relation was also found in the exposed group between the intensity of current exposure to Co (Co in air and U-Co) and the reduction of FEV_1/FVC (Swennen et al 1993).

In a longitudinal study a total of 122 male workers of a cobalt plant were assessed for FEV_1 and FVC at least four times (median 6). The interval between two successive lung function tests ranged from 1-4 years and the duration to follow-up ranged from 6-13 years (median 12 years). FEV_1 decreased with increasing U-Co, only in smokers (Verougstraete et al 2004).

A case-referent study (Roto 1980) with 21 cases (workers with asthma) and 55 referents (workers without asthma randomly selected from the whole company) was carried out in a company, with complex exposure, that consisted of a cobalt,

a zinc, and a sulfur plant. The asthma risk was increased for subjects exposed to Co (age adjusted OR=4.8, 95%CI=2.0-11.7), i.e. for those working in the cobalt plant with exposure to cobalt sulphate or cobalt metal dust. Smoking was not associated with asthma. The levels ranged from less than 10 to 100 μg Co/m^3 in the cobalt plant (stationary sampling) and from 10 to 50 μg Co/m^3 in the cobalt roasting area (personal sampling). Five of 15 asthmatics regularly exposed to Co had a positive reaction to $CoCl_2$ in a provocation test and one had a positive reaction to dust from the Co roasting building. Pre-employment examination forms did not indicate that any of the cobalt workers had asthma before their current employment. The median average exposure time before onset of asthmatic symptoms was 11 month (range 2-36 month) for the 6 workers with positive provocation test. In 12 of the asthmatic cobalt workers, the asthma disappeared after removal from exposure. Two were later accidentally re-exposed to Co (water-soluble Co dust and metallic Co, respectively) and experienced typical clinical symptoms of asthma and had a positive provocation test to $CoCl_2$ (Roto 1980). In a later study in the same plant, an additional case of occupational asthma with positive reaction to Co in a provocation test has been reported (Linna et al 2003).

In a cross sectional study by the same authors, 224 cobalt plant workers, 234 zinc workers, 158 sulfur workers and 161 'non-exposed' controls (laboratory, office and power plant workers) were examined. Selection criteria were applied to the exposed groups: males who worked more than one year in the cobalt plant, workers without heterogenous exposures, and those who were free of asthma. No exposure-related differences in lung function between exposed and controls were found. More chronic phlegm production and wheezing was found in the exposed groups, although in the 'cobalt' group this could be attributed to smoking. No relationship between cobalt exposures less than 100 $\mu g/m^3$ during 6-8 years and chronic bronchitis were found in non-smokers. Chronic bronchitis was defined as production of phlegm and chronic cough, together for at least 3 months a year during the 2 years preceding the examination, with no other local of specific pulmonary disease present (Roto 1980).

In an other cross sectional study, Morgan found no changes in lung function (FEV_1 and VC) and X-rays in workers (n=49) exposed to Co-metal and oxides for a mean exposure duration of 10.7 (SD 6.4) years compared with a matched control group (n=46). The authors conclude that there is no evidence of lung fibrosis in workers exposed to cobalt and oxides. Mean exposure was 520 $\mu g/m^3$ (std=0.7) and median exposure was 200 $\mu g/m^3$ (n=49) (Morgan 1983).

In a Belgian cobalt plant 120 workers were examined (exposure time more than 8 years, no cobalt concentrations available). None of the employees had lung fibrosis. Some people developed chronic bronchitis (no diagnose criteria mentioned) after several years that progressed towards complete remission after removal from the contaminated atmosphere in several cases. On admission, only workers without respiratory problems and without atopy were accepted (Verhamme 1973).

No interstitial lung disease (see below, section 9.1.2. Exposure to hard metal) was reported in these studies of workers exposed to Co metal, oxides or salts (Linna et al 2003, Morgan 1983, Swennen et al 1993, Verhamme 1973).

Based on these studies it can be concluded that Co metal, oxides and salts may induce asthma (Linna et al 2003, Roto 1980), see further (Shirakawa et al 1989) in section 9.1.2. Exposure to hard metal. A positive dose-effect relationship between Co exposure, originating from Co metal, oxides and salts, and obstructive lung function impairment was reported in one study (Swennen et al 1993). Two other studies did not find a relationship (Morgan 1983, Roto 1980).

9.1.2. Exposure to hard metal

Interstitial lung diseases are a group of diseases that are characterised by inflammatory changes in the lung interstitium. These diseases are often characterised by fibrosis and examples are allergic alveolitis, sarcoidosis, asbestosis, silicosis and hard metal disease. The signs and symptoms associated with these diseases include cough, phlegm, restrictive alterations, and decreased diffusion capacity. In severe cases of hard metal disease the lung function is severely impaired and death has been reported.

Coates et al reported progressive diffuse interstitial pneumonia in 12 persons working in the hard metal industry (exposure to Co, tungsten, carbon, tungsten-carbide). In the early stage cough with scanty sputum and dyspnoea on exertion were reported followed by weight loss, reduction in vital capacity with normal FEV_1, arterial hypoxemia, low carbon monoxide diffusing capacity and abnormal chest X-ray. Lung tissues of seven patients showed (1) interstitial cellular infiltrate with fibrous tissue reaction, (2) areas of cystic air spaces lined by cells that show metaplasia to a cuboidal epithelium and (3) desquamation into the alveoli of large vacuolated, mononuclear cells. In some instances multinucleated giant cells were present. In addition, 5 hard metal workers with normal chest X-rays developed attacks of wheezy cough related to exposure to hard metal exposure (clinical picture: asthmatic bronchitis). Past cobalt concentrations exceeded 100 $\mu g/m^3$ (way of sampling not given) and the mean duration of exposure was 12.6 yrs (1 month-28 yrs) (Coates & Watson 1971).

In a case study, 3 hard metal workers with interstitial pneumonia and fibrosis were described. Multinuclear giant cells were present in these cases. Giant cells comprised both type II alveolar epithelial cells and alveolar macrophages. In one patient a severe restrictive effect developed only after 25 months work with hard metal. No exposure measurements are available (Davison et al 1983).

Four wet grinders of hard metal were exposed to coolants in which cobalt-ions were dissolved. Three patients had symptoms of allergic alveolitis that disappeared after absence of work, and the fourth patient had occupational asthma. All four had contact eczema and a positive patch test to cobalt. Latency periods were 2-4 years. The author suggested that ionised cobalt can react with proteins, act as a hapten and induce lung and skin disease (Sjögren et al 1980). Reported cobalt concentrations in air were 2-4 $\mu g/m^3$, but sampling method is not described.

A fatal case of a 24-year old hard metal tool wet grinder (exposure to Co aerosols, Co concentration not available) was reported who died of hard metal disease after 4.5 years of exposure (Ruokonen et al 1996).

A medical and environmental survey was carried out on hard metal workers who had the highest exposure to airborne Co and the longest duration of exposure (21-35 years; n=290 which was 19.2% of the total work force, no control group). Eleven subjects had interstitial infiltrates. A lung biopsy in one of them showed interstitial fibrosis. Two of nine subjects with interstitial infiltrates showed reduced total lung capacity. All subjects with interstitial infiltrates were exposed to airborne peak cobalt concentrations >500 $\mu g/m^3$ at the time of the study. Four workers had an occupational history in coal mines or foundries. Because there was no control group together with the low frequency of interstitial fibrosis among the workers in this study, the authors decided that it was not possible to be definite about a causal relationship between hard metal exposure and interstitial lung disease. Obstructive lung disease was found in 3 of 61 non-smokers (Sprince et al 1984).

Sprince et al later performed a cross sectional study among 1039 hard metal production workers (Sprince et al 1988). Work-related wheeze occurred in 113 participants. The prevalence of work-related wheeze by present exposure category were ≤50 $\mu g/m^3$, 9.2%; >50 $\mu g/m^3$ to ≤100 $\mu g/m^3$, 18.1%; >100 $\mu g/m^3$, 15.4%. The odds ratio for work-related wheeze was 2.1 times (X^2=9.5, p<0.002) for present cobalt exposure exceeding 50 Co $\mu g/m^3$ compared with exposures ≤50 Co $\mu g/m^3$ after adjusting for current smoking, age, gender and race (no relative risk estimate could be calculated from the data given in the study). Abnormal chest radiographs was defined as showing profusion of small opacities ≥1/0 (ILO-classification) and occurred in 26 workers. The odds ratio for profusion ≥1/0 was 5.1 times (X^2=4.8, p<0.029) for average lifetime cobalt exposures exceeding 100 Co $\mu g/m^3$ compared with exposures ≤100 Co $\mu g/m^3$ in those with latency exceeding 10 years after adjusting for pack-years and age. Average lifetime exposure was defined as cumulative Co exposure divided by total duration of exposure. Interstitial lung disease was defined as profusion ≥1/1, FVC or DL_{CO} ≤70% and FEV_1/FVC% ≥75% and occurred in 7 workers (no control group). In two of the subjects with ILD, lung biopsies were made that showed interstitial fibrosis. Grinders of hard metal had a lower diffusion capacity for carbon monoxide compared to non-grinders, even though they were exposed to lower airborne Co concentrations (Sprince et al 1988). This phenomenon was also reported by Sjögren et al and Kennedy et al who found a higher prevalence of lung disease and restrictive lung function impairment among wet grinders (Kennedy et al 1995, Sjögren et al 1980). Since wet grinders use coolants that often contain high Co concentrations, additional exposure via skin and/or gastro-intestinal tract may be responsible for the increased toxic effects in grinders.

A cross sectional study was performed among 3 hard metal factories (425 exposed workers [351 men and 74 women] and 88 controls [69 men and 19 women]). The exposed group was divided into subgroups: 'soft' (presintered), 'hard' (sintered) and 'maintenance', see figure 1. The subgroups were matched

for age, height, weight and duration of employment. There were some differences regarding smoking habits between exposed and non-exposed but additional subdivision into smokers and non-smokers was performed. Cough, sputum and dyspnoea were more frequent in men engaged in 'soft' work (Co exposures 30-272 $\mu g/m^3$), especially among non-smokers. Cough and sputum were more frequent in women in 'hard' work (Co exposures 30-210 $\mu g/m^3$). A significant increase in obstructive or restrictive syndromes were found among women working in 'hard' work; in men changes in lung function were more related to smoking habits. Diffusing capacity of carbon monoxide was lower in exposed groups (Co exposures 30-272 $\mu g/m^3$), especially among women both in smokers and non-smokers. Slight abnormalities of chest radiographs (according to ILO classification) were more frequent in exposed men than in controls (12.8% and 1.9%, respectively; Co exposures 30-272 $\mu g/m^3$); 24% of the powder workers (Co exposures 45-272 $\mu g/m^3$) and 19.5% of workers in the press department (Co exposures 30-220 $\mu g/m^3$) had abnormal chest X-rays. The differences could not be explained by smoking. Subjects with abnormal chest radiographs had lower FVC, FEV_1 and carbon monoxide-diffusion capacity compared to those with normal chest radiographs (Meyer-Bisch et al 1989).

In a cross sectional study, hard metal workers from four major Swedish hard metal industries were divided in six different exposure groups according to job category (Alexandersson & Bergman 1978, Alexandersson 1979). The mean cobalt exposure duration was 7-11 years, except for dry grinders who had a mean duration of 4 years. Office workers in the same industries were used as controls; these were matched pairwise to each exposure group by sex, age, length, and smoking habits. Exposure levels were based on personal monitoring data (breathing zone) from the same work places. Several symptoms were more common in the cobalt exposed workers (Table 3). According to an interview survey, prevalence of irritation of eyes, nose or throat was significantly elevated in all relevant exposure groups (given mean exposure levels: 3-60 $\mu g/m^3$), but with no clear dose-response (Table 3). Cough with phlegm was also significantly increased in the lowest exposure group, but with an inconsistent dose-response pattern. Chronic bronchitis was significantly more frequent in the highest (60 μg Co/m^3), but not in lower exposure groups (Table 3). These chronic symptoms were more common among smokers. Details about the interview survey are not reported. Lung function tests of the workers in the highest exposure group (60 μg Co/m^3) revealed significant impairment in FEV_1, FEV%, and MMF (maximum midexpiratory flow) compared to paired controls and in FVC, FEV_1, and MMF over the working week. In dry grinders exposed to 12 μg Co/m^3, tendencies to impairment in FVC compared to controls was seen and in wet grinders, exposed to 8 μg Co/m^3, in FEV_1 and MMF over the working week. No significant impairment of lung function parameters was found in the other exposure groups.

Table 3. Symptom frequency (% exposed/% control) in different groups occupationally exposed to cobalt in four hard metal plants in Sweden. Adapted from Alexandersson 1979[1].

Job type (exposure group)	Office work (control)	Quality inspection[2]	Surface grinding	Powder handling	Wet grinding	Dry grinding	Powder handling
Mean exposure[3] (μg Co/m^3)	0.8 – 0.9	2	3	5-10	8	12	60
Irritation of eyes, nose or throat	-	**18/0**	**35/7**	**27/0**	**35/4**	**32/0**	**40/2**
Breathlessness or feeling of heavy in breathing during work	-	9/0	3/0	10/0	**16/0**	16/0	**24/0**
Cough without phlegm	-	14/4	14/17	20/3	**23/7**	8/8	8/10
Cough with phlegm	**-**	**21/0**	**28/3**	10/0	**23/5**	4/4	**35/6**
Chronic bronchitis[4]	-	4/0	0/0	0/0	5/0	0/0	**11/0**
Chest tightness	-	34/18	24/21	33/17	**46/18**	32/16	27/18
Number of subjects[5]	-	44	29	30	57	27	63

[1]Bold figures indicate significant difference between exposed group and control group ($p \leq 0.05$).
[2]According to authors, symptoms in this group is probably due to selection and not related to cobalt exposure.
[3]Previous exposures were reported to have been higher.
[4]Diagnosed by physician.
[5]Exposed and controls were pair wise matched, considering sex, age, height, and smoking habit. Asthmatics were excluded.

It should be noted that the controls were also slightly exposed and that exposure measurements were the most recent ones, performed within a couple of years (no further details given). Exposures were markedly higher in the past (Alexandersson & Bergman 1978). Thus, the chronic symptoms may have been caused by earlier, higher exposures.

A 5-year follow-up of 27 workers showed additional FEV_1 impairment in smokers. The mean exposure of these workers decreased from 80 to 30 μg Co/m^3 during this period (Alexandersson et al 1986). A dose-effect relationship was demonstrated between U-Co and FEV_1 and between B-Co and FEV_1 only in smokers (Alexandersson et al 1979).

In eight lumber mills that voluntarily participated in a cross sectional study, (118 saw filers, 90% participation) were compared with an external population of bus mechanics (number of bus mechanics not given). The saw filers were divided in 7 groups that performed different tasks, including wet grinding and dry grinding. Wet grinding was defined as grinding of tungsten carbide at least

10% of the time, for which at least 50% of the grinding was performed with a coolant; dry grinding was similarly defined, but required at least 50% of the grinding without a coolant. The full shift air Co concentration was determined in every filer between 1 and 4 times. Cobalt was detected (detection limit 0.64 $\mu g/m^3$) in 62 of 278 samples (mean 9, max. 106, SD 20 $\mu g/m^3$). The within subject variability was very high; therefore exposure was estimated at group levels. Mean Co concentrations in used coolants from tungsten carbide grinding machines was 0.7 g/l (n=29). About three times the rate of cough, phlegm and wheeze related to work was reported by the filers compared to the bus mechanics. The wet grinders had significantly lower FEV_1 and FVC values compared to the other saw filers and the bus mechanics, whereas no differences were seen between other saw filers and bus mechanics. The effects on the wet grinders could not be explained by smoking habits. The estimated mean Co exposure for dry grinding was 5.4 μg Co/m^3 and for wet grinding was 5.6 μg Co/m^3. Both Co exposure during wet grinding of tungsten carbide and duration of work were significantly associated with reductions in FEV_1 and FVC in the wet grinders. The airborne Co exposures were comparable for wet grinders and dry grinders and the authors speculate that dermal absorption of Co in the wet grinders might have contributed to systemic uptake. Other speculations to explain the different effects seen in dry and wet grinders were that the coolant might have an adjuvant effect or might change the state of Co. Wet grinders of other metals, eg. stellite and mild steel, using the same coolant, did not show reductions in lung function (Kennedy et al 1995, Teschke et al 1995).

Shirakawa et al reported mean Co exposures between 7-227 $\mu g/m^3$ in 8 patients who developed occupational asthma and were exposed to hard metal. Four of these eight patients were atopic and seven showed bronchial hyperresponsiveness to methacholine. All patients had positive reactions to 1% $CoCl_2$ in the provocation test while the control subjects, including 6 asthmatic patients with high responsiveness to methacholine, showed no reaction. Tungsten was incapable of provoking asthma in challenge tests. Four patients had specific IgE antibodies to cobalt conjugated human serum albumin based on comparison of serum samples from 60 asthmatic patients and 25 asymptomatic workers in the same plant (Shirakawa et al 1989).

During a 3 years observation period, 319 hard metal workers were medically examined and their exposure to cobalt was measured. Mean cobalt exposures varied depending on the manufacturing step (range 3-1292 $\mu g/m^3$). Eighteen employees had occupational asthma related to exposure to hard metal, a prevalence of 5.6%. Nine had a positive bronchial provocation test to cobalt chloride (1%) of the immediate, late or dual type; the other patients refused to take the test. The mean cobalt concentration to which four cases were exposed was 18, 24, >31 and >1 203 $\mu g/m^3$. No exposure measurements could be made for the other 5 cases since they already had been transferred to other works. Only 2 of the nine workers with occupational asthma had a positive patch test to cobalt. Chest radioghraphs of 3 workers showed diffuse shadows of category 1 or over, but

in two of the patients this may be caused by exposure to silica and dust generated by carborundum wheels. No cases of interstitial lung disease were found (Kusaka et al 1986a).

Kusaka et al exposed 15 healthy men to hard metal dust (mean 38 μg Co/m^3, range 14-76 μg Co/m^3 during 6 hours) and ventilatory function was measured before and after exposure. These men were normally not exposed to hard metal dust and 53% were smokers. All complained of coughing, expectoration or a sore throat. A drop in FVC was found which was attributed to an irritative effect. There was no dose response relationship (Kusaka et al 1986b). In the same study 42 shaping workers (3 of them had occupational asthma related to hard metal) were exposed to hard metal dust (mean 85 μg Co/m^3, range 17-610 μg Co/m^3; mean exposure time was 10 yrs, range 2-20 yrs) and ventilatory function was measured before and after 7 hours of exposure. They showed no effect on ventilatory function and no cases of interstitial pneumonitis were found. No control group was in this part of the study and a healthy worker effect may have taken place. The same 42 shapers were compared with controls (n=84) that were matched for sex, age, height and smoking. Mean cobalt exposures were 126 μg/m^3 (range 6-610 μg Co/m^3). All ventilatory functions were lower in the shapers than in the controls and significant for FEV_1% (defined as FEV_1/FVC). The authors concluded that exposure to hard metal dust at a mean Co concentration of 126 μg/m^3 caused chronic obstruction of the bronchi (Kusaka et al 1986b).

In a nine year prospective study, the prevalence of hard metal asthma was 5.6% (n=700). Hard metal asthma was defined as a time relation between attacks of asthma and exposure to hard metal; involvement of fibrosis was ruled out by making X-rays, chest computed tomography or BAL. The workers developed asthma at a cobalt concentrations less than 50 μg/m^3, and had a latency period less than 1 year (Kusaka et al 1991).

Eight asthmatic patients with hard metal asthma due to cobalt underwent a bronchial provocation test with nickel sulphate. Nickel concentrations between 4.2-25.5 μg Ni/m^3 were measured in the breathing zone of hard metal workers. Seven patients developed a fall in FEV_1 of 20% or more, inhaling 1 or 2% nickel sulphate (4 immediate, 3 late response). Eight controls (including 6 asthmatics) with no hard metal exposure, showed no reaction in the test. Specific IgE antibodies against cobalt and nickel conjugated albumin were found in 4 patients; no specific antibodies were seen in 60 non-exposed asthmatic and 25 symptomless exposed workers. The results suggest that nickel as well as cobalt sensitivity plays a role in hard metal asthma (Shirakawa et al 1990).

In a cross sectional survey among hard metal workers (n=706) a significant increase in Co-HSA RAST indices was found among Co exposed men (Co-HSA RAST [exposed] 1.37, SD 0.13, and Co-HSA RAST [non-exposed] 1.16, SD 0.13). Subjects with a Co-HSA RAST index of the mean plus three times SD (n=9) had all been diagnosed with occupational asthma from hard metal exposure. No difference was found among females, which could not be explained by differences in age or dust-exposure doses. Exposure to Co was the same as in Kusaka et al (Kusaka, et al 1986a). The Co-HSA RAST indices were strongly

associated with the intensity of cobalt exposure ($p<0.001$) and to the logarithm of the total exposure doses ($p<0.001$). Smoking had no effect on Co-HSA RAST values (Shirakawa & Morimoto 1997).

Cobalt-sensitised lymphocytes play a role in some hard metal asthmatics. In 4 patients who had been reported to have IgE antibody specific to Co, the lymphocytes of 2 of them proliferated with metal (one to free Co and the other to free Co and Co-HSA). Slight proliferation of lymphocytes to these antigens was also found in the other patients (Kusaka et al 1989).

To elucidate factors contributing to hard metal asthma, the entire workforce of a hard metal plant in Japan (n=703) was examined in a cross sectional study. Asthma was defined as attacks of reversible dyspnoea with wheeze and was examined by a trained health staff using a questionnaire. The prevalence of self reported asthma using this definition was 13.1%, which is about twice the reported prevalence of clinically established asthma in Japan. Univariate analysis showed that the prevalence of the asthmatic symptoms was significantly higher in formerly and currently exposed male workers than in non-exposed male workers. Hard metal workers with current Co exposures of 50 $\mu g/m^3$ or lower, had a significantly higher prevalence of asthmatic symptoms than the non-exposed subjects. This was not found in the higher exposed group (Co-air >50 $\mu g/m^3$). There was no dose response relationship. Positive IgE antibody reaction against cobalt was found in 2% of the workers that all had asthmatic symptoms. A significant correlation between asthmatic symptoms and atopy, positive IgE antibody against Co, and age of 40 or older was found. Multilogistic analysis clearly showed that age, atopy and exposure to hard metal were risk factors associated with asthmatic symptoms. Exposure to mists of coolants containing ionic cobalt was not associated with any increase of the frequency of asthmatic symptoms in comparison with exposure to hard metal dust (Kusaka et al 1996a)

Individual effects on pulmonary function of exposure to hard metal were studied in all of the workers of a hard metal industry (583 men and 120 women). Astma was defined in the same manner as in the study of Kusaka (Kusaka et al 1996b). All workers were examined for smoking, respiratory symptoms, ventilatory function, history of exposure to hard metal and present exposure to airborne cobalt. Two way analysis of variance showed that an interaction of hard metal exposure and smoking decreased $\%V_{50}$ (forced expiratory flow at 50% vital capacity as a percentage of the predicted value) for men and women. Among men currently exposed to hard metal, all indices of ventilatory function except %FVC (forced vital capacity as a percentage of the predicted value) were significantly lower in astmatics compared to non-asthmatics. The ventilatory dysfunction did not differ between exposed and non-exposed workers with asthmatic symptoms. When men with astmatic symptoms were excluded, the interaction of hard metal exposure and smoking still affected %PEF (peak expiratory flow as a percentage of the predicted value) and $\%V_{50}$. Neither FEV_1 nor $FEV_1\%$ (FEV_1/FVC) were affected. Asthmatic symptoms and smoking had significant effects on indices of ventilatory function and the decrease in $\%V_{25}$ was associated with hard metal exposure. In addition, duration of exposure had significant decreasing effects

on %FVC, %MMF (mid-maximal flow as a percentage of the predicted value) and $\%V_{25}$. $\%V_{25}$ tended to decrease with increasing Co-air and was significant at Co concentrations higher than 100 $\mu g/m^3$. %FVC remained stable at all concentrations (Kusaka et al 1996b).

In a cross sectional study, self-reported respiratory symptoms of grinders and brazers working with hard metal or stellite (cobalt exposure 2-240 $\mu g/m^3$) were compared with the symptoms of referents. Co-exposed workers who were not exposed to wood dust (n=108) were compared with referents (n=106, no Co, no wood dust). Cobalt-exposed workers who were also exposed to wood dust (n=116) were compared with referents who were exposed to wood dust but not to Co (n=103). Cobalt exposed non-smokers reported more work related cough, dyspnoea, fever or chills. In addition, combined exposure of wood dust and cobalt was associated with these symptoms, especially among non-smokers (Linnainmaa et al 1997).

A group of 20 patients with interstitial lung disease having multinucleated giant cells, lymphocytes and polymorphonuclear granulocytes in BAL, were compared with 35 exposed unaffected hard metal workers regarding HLA class II genes. Hard metal disease was strongly associated with residue Glu-69 of the HLA-DP beta chain (Potolicchio et al 1997). *In vitro* experiments showed that HLA-DP Glu-β69 binds cobalt and that the Glu-β69 residue is in a position relevant in determining peptide specificity (Potolicchio et al 1999).

In summary, irritative effects (eyes, nose and throat) from hard metal exposure has been reported at a mean exposure level of 3 $\mu g/m^3$ (Alexandersson R 1979). ILD from hard metal exposure has been reported (Coates et al 1971, Meyer-Bisch et al 1989, Sjögren et al 1980, Sprince et al 1988). No epidemiological data are available on ILD caused by tungsten(carbide) without Co. Restrictive lung impairment was found among wet grinders exposed to mean Co concentrations of 5.6 $\mu g/m^3$ (Kennedy et al 1995). Several studies reported increased lung toxicity for wet grinders compared to dry grinders, that may be a result of additional dermal Co exposure from Co containing coolants (Kennedy et al 1995, Sjögren et al 1980, Sprince et al 1988). Hard metal can also induce asthma (Kusaka et al 1991, Kusaka et al 1986a, Shirakawa et al 1989).

9.1.3. Exposure to cobalt in diamond industry

Demedts et al reported 5 cases of interstitial lung disease among diamond polishers using Co containing abrasive disks. Mineralogic analysis of lung tissue, lavage fluid, filtered air and exhaust dust in the work environment revealed cobalt as the only toxic agent. No exposure measurements were available (Demedts et al 1984).

Bronchial asthma among diamond polishers was described in 3 cases. The patients had worked with Co containing abrasive disks. All three patients were positive in a cobalt inhalation challenge test (Gheysens et al 1985).

A cross sectional study among 48 workers producing diamond-cobalt circular saws and 23 controls that were not exposed to known pneumotoxic chemicals,

showed that exposure to cobalt containing dust leads to significant differences in prevalence of cough, sputum and dyspnoea. Both smoking and non-smoking workers (exposure time >5 years) had spirometric disturbances which are compatible with moderate restrictive syndrome (decrease of FVC and FEV_1, but not FEV_1/FVC). A tendency for an obstructive effect was found among non-smokers who were exposed more than 5 years. Average Co concentrations in the mixing and oven room were 9.4-2 875 μg Co/m^3 and 6.2-51.2 μg Co/m^3, respectively (Gennart & Lauwerys 1990).

Dust generated by diamond disks and gathered at the workers breathing zone contained mainly cobalt, iron and small amounts of diamond and silica. Cobalt concentrations in total dust up to 45 μg/m^3 were measured. The fraction of Co in total dust (between 2-7%) is comparable to the hard metal industry. Cobalt concentrations in lung tissue of diamond polishers (n=2) and hard metal workers contained comparable amounts of Co that were much higher than lung tissue of non-exposed subjects (van den Oever et al 1990).

In a cross-sectional study among 194 diamond polishers working with Co-containing disks and 59 controls who worked with disks without Co, three dose groups were formed. The Co exposure of the controls varied between 0.08 and 1.5 μg/m^3. The mean Co exposure in the low and high exposure group was 5.3 μg Co/m^3 and 15 μg Co/m^3, respectively. Mean U-Co concentrations for the three dose groups were 2, 7 and 21 μg/g creatinine respectively. FVC and FEV_1, but not FEV_1/FVC, were significantly lower in the high exposure group compared to the low exposure group. This was also found when the high exposure group was compared with the pooled low Co and control group. The effects were more pronounced in women. The differences were not due to differences in smoking habits. Both exposure and health measurements were cross sectional, thus a healthy worker effect may have underestimated the effect of Co exposure on lung function (Nemery et al 1992).

A total of 19 cases of fibrosing alveolitis were diagnosed in diamond polishers, 6 documented by open lung biopsy and 9 by bronchoalveolar lavage fluid analysis which displayed giant cells. Circulating immune complexes were transiently evidenced in two cases and a positive lymphocyte transformation test with cobalt has been documented in one patient with a large excess of lymphocytes in bronchoalveolar lavage fluid (90%). Increased Co levels were found in urine (up to 60 μg/g creatinine), bronchoalveolar lavage fluid and lung tissue. Improvement of symptoms were seen with reduction of the exposure to Co. In one case a rapid fatal outcome in a 52 year old diamond polisher was reported who received supplemental oxygen. The authors speculated that the oxygen treatment in combination with a high pulmonary concentration of cobalt could have contributed to the rapid deterioration by increasing the formation of reactive oxygen species (Lison 1996).

No effects on lung function or chest X-rays were found among 40 workers in powder sintering industry making stone cutting diamond wheels (cobalt exposures 20-1100 μg/m^3) (Ferdenzi et al 1994).

It can be concluded that combined exposure to Co and diamond particles leads to interstitial lung disease and induces asthma. Restrictive lung impairment was reported among workers exposed to both diamond particles and a mean Co concentration of 15 μg Co/m^3.

9.1.4. Exposure to vitallium

Exposure to vitallium dust, an alloy of Co (56-68%), chromium and molybdenium, has been associated with the development of pneumoconiosis in dental technicians (Nayebzadeh et al 1999, Selden et al 1996, Selden et al 1995).

In a cross-sectional study 37 dental technicians with at least 5 years (range 5-36 years) exposure to vitallium showed a restrictive lung function impairment compared with historical reference material. A dose-response relation between exposure to vitallium dust in hours per week and reductions in both FVC and FEV_1 was found. The reduction was more pronounced in smokers than in non-smokers and ex-smokers. Six (16%) of the 37 dental technicians showed radiological evidence of pneumoconiosis. Dust measurements were carried out for those technicians (10 subjects) who had a minimum weekly working time with vitallium of 20 hours. Cobalt concentrations in the air between 25 and 1600 μg Co/m^3 were measured when no local exhaust was available. When local exhaust ventilation was available the Co concentrations were lower than 25 μg Co/m^3 (Selden et al 1995). Dental technicians are exposed to a complex mixture of dust particles and it is not possible to make a distinction between asbestos or silicon carbide fibres or other elements such as aluminium silicate, quartz, corundum, or vitallium as a single causative agent (Selden et al 1995).

Lison (Lison 2000) has described the differences seen between the mixed dust pneumoconiosis associated with vitallium exposure and the interstitial lung disease caused by hard metal dust. Vitallium is a homogenous alloy and hard metal is not and Co in vitallium is remarkably stable in biological fluid, whereas Co in hard metal is rapidly solubilized and cannot be found in lung or broncho-alveolar lavage fluid of patients. No giant cells or desquamative alveolitis have been seen in the dental technicians with vitallium induced pneumoconiosis.

9.1.5. Exposure to Co-Zn silicate

Lung functions of 46 plate painters who were exposed to Co-Zn silicate for 11 years (2-25 y) were compared with 51 controls (painters without Co exposure) in a cross sectional study. Technical adjustments to the fume cupboards were made during the study (mean Co exposure before the study =80 μg Co/m^3; range 68-8610 μg/m^3; Co exposure one month after the study =around 50 μg Co/m^3). B-Co and U-Co of plate painters compared to controls were 9 and 85-90 times higher, respectively. Even after a workfree period (median 41 days) B-Co and U-Co were 2 and 5 times higher in plate painters, respectively. Irritation of mucous membranes (mouth and throat), cough and expectoration was more common in Co exposed women. A decreased forced expiratory flow rate at 25% and 50% of the vital capacity were found during working periods. No improvements were

observed during holidays. The lung function changes were not related to B-Co or U-Co (Raffn et al 1988). The number of plate painters with chronic impaired lung functions was significantly higher than in the referents. The authors remarked that 'cigarette smoking may have been a confounder since the number of smokers in the plate painter group was higher than in the control group' (Christensen & Poulsen 1994).

9.2. The skin

Skin exposure to cobalt and cobalt compounds may occur in the industries already mentioned in Table 2, and also in concrete construction work since cement contains Co. Cobalt is one of the major contact allergens, and 4% of patch-tested dermatitis patients are patch-test positive to $CoCl_2$ (Kanerva et al 2000). Knowledge about sources of sensitisation and elicitation is however limited. Solitary Co allergy, without simultaneous contact allergy to nickel or chromate, is seen mainly among hard-metal workers and in glass and pottery industry. Five percent of 853 hard-metal workers in a plant were allergic to cobalt (Fischer & Rystedt 1983). Although Co sensitivity generally occurs simultaneously with allergy to other metals (nickel and/or chromium), this is not believed to be due to a cross reactivity phenomenon but rather to combined exposure (Hostynek et al 1993, Lidén et al 2001). $CoCl_2$ was classified as a grade 3 allergen in a human maximisation test (highest: 5) (Lidén et al 2001). Single cases of photocontact dermatitis due to cobalt have been described (Romaguera et al 1982).

9.3. Thyroid gland

Cobalt therapy of patients with anaemia caused thyroid hyperplasia associated with thyroid hypofunction (dose 3-4 mg/kg/day, length of exposure 3-7.5 month) (Kriss & Carnes 1955).

A cross sectional study was carried out among 82 exposed workers and 82 age matched controls workers in a Belgian cobalt refinery. A slight interference with thyroid metabolism (decreased T3, T4 and increased TSH) was found in cobalt exposed workers (cobalt metal, oxides and salts). Mean exposure time of the exposed workers was 8 years and inhalable dust concentrations between 2-7700 μg Co/m^3 were measured (about 70% and 25% of the workers were exposed to concentrations higher than 50 μg/m^3 and 500 μg/m^3, respectively). No clinical case of hypothyroidism was found but the findings are in agreement with findings in patients treated with Co (Swennen et al 1993).

In a cross sectional study, female plate painters who were exposed to Co-Zn silicates (semi soluble compound, n=25) or Co aluminate (insoluble compound, n=36) were compared to unexposed controls (n=48). Only the painters exposed to Co-Zn silicates had an increased T4 level (p=0.0001), marginally reduced T3 and unaltered TSH. These effects are in contrast with the findings in patients treated

with Co. Mean U-Co in the Co-Zn group was 1.17 µg/mmol creatinine (SD 1.18) compared to 0.13 μg/mmol creatinine (SD 0.12) in the controls. No significant changes in gland function, gland volume or TSH were found. Co-air measurements of about 50 μg/m^3 were reported, but no description was given of the measurement strategy and the analysis of the samples (Prescott et al 1992).

Overall, the data on toxic effects on the thyroid gland from occupational exposure to Co are inconclusive.

9.4. Cardiovascular system and blood and blood-forming organs

Cardiomyopathy was found in heavy beer drinkers after cobalt (chloride or sulphate) was added to beer to improve the stability of the foam (estimated daily intake 6-8 mg). They had cardiocirculatory insufficiency with dyspnoea, hypotension, tachycardia, cyanosis, enlarged heart with reduced cardiac output and, in many cases, a large pericardial effusion. The heart cobalt concentration in these patients was about 10 times of the normal value. These heavy beer drinkers swallowed less cobalt compared to patients that were treated with cobalt chloride (up to 100 mg/day) and who did not develop cardiomyopathy. Alcohol intake and bad nutritional status (low protein) may have contributed to the cardiomyopathy in the beer drinkers. Microscopic examination showed myocellular degeneration, vacuolisation, focal myocytolisis and fibrosis without clear signs of inflammation. Inhibition of the cellular respiration due to inhibition of the mitochondrial dehydrogenase is the most likely pathogenetic mechanism (Lison 1996, Seghizzi et al 1994)

Cardiomyopathy was also described in 2 workers exposed to dust from cobalt-containing ores (cobalt concentration case 1, <6 000-84 000 μg/m^3 during 26 months; case 2, 64 000-103 000 μg/m^3 during 2 months) (Jarvis et al 1992), in a 'metal worker' who was exposed to cobalt for 4 years (Barborik & Dusek 1972) and in a "hard metal worker" who was exposed to Co and WC dust for 4 years (Kennedy et al 1981). In the two latter cases, there were no exposure data available.

In a cross sectional study among 30 hard metal workers (mean exposure 9.9 years, SD 5.3) rest and exercise biventricular function was normal. There was a weak inverse correlation between duration of exposure and resting left ventricular function ($p<0.03$). Nine workers had abnormal X-rays. They had a lower right ventricular ejection fraction during exercise ($p<0.02$). This was probably due to fibrotic pulmonary disease and early cor pulmonale (Horowitz et al 1988, Seghizzi et al 1994).

Alexandersson and Atterhög compared dry grinders (n=42, 3-30 μg Co/m^3, mean 10 μg Co/m^3), wet grinders (n=43, 2-34 μg Co/m^3, mean 10 μg Co/m^3) and powder handlers (n=61, 10-150 μg Co/m^3, mean 60 μg Co/m^3) who were exposed to hard metal, with controls (n=126, no exposure to hard metal). They found ST- and T-depressions in the ECG and an overfrequency of ectopic beats in the wet grinders while no pulmonary dysfunction was found in this group. In the other

groups no effects on the heart function were found. The authors believe that the effects are not due to cobalt but probably to cutting oil (Alexandersson & Atterhög 1980). The small ECG changes in the wet grinders had disappeared after 4 weeks holiday (Alexandersson & Atterhög 1983).

No excess mortality from diseases of the circulatory system were found in a cohort study among Co production workers born in France (SMR=0.88, CI(95%) 0.36-1.51 (Moulin et al 1993) and in a cohort study among hard metal workers (n=7459, SMR=0.88, CI(95%) 0.75-1.03) (Moulin et al 1998). This is in contrast to a Swedish cohort study in which increased mortality from ischemic heart disease was found in hard metal workers in the highest exposure group (up to 11 mg Co/m^3) with more than 10 years employment who had died more than 20 years after the beginning of exposure (16 cases vs 9.4 expected, SMR=1.69, CI(95%) 0.96-2.75 (Hogstedt & Alexandersson 1990). It is important to notice that the calculated SMRs are based on national rates. Health effects may by underestimated when SMRs are calculated since the general population is less healthy than the working population.

In the past Co was used as a therapy to increase red blood cell number, hemoglobin, and hematocrit (oral doses 6.2-12.4 mg Co/day during 12-30 weeks) (Elinder & Friberg 1986). No effect on hematocrit was found in workers exposed to cobalt blue dyes (Raffn et al 1988). In a cross sectional study among Co refinery workers (82 workers, 82 age matched controls), a reduction in hematocrit and hemoglobin was reported, which could not be explained by the authors (Swennen et al 1993). Cobalt increases erythropoietin concentrations by simulating hypoxia (Alippi et al 1992, Goldwasser et al 1958, Lison 1996).

9.5. Optic atrophy and deafness

Bilateral deafness and visual failure were reported in a case study of a 48-year-old employee exposed to Co powder for 20 months, working 50 hours a week (no exposure measurements available). Complaints disappeared after he stopped working. Optic atrophy was found in a patient who received a total dose of 73 g $CoCl_2$ in 3 years. Bilateral deafness due to nerve damage was found in a patient who received a daily dose of 100 mg $CoCl_2$ for 6 months. Four out of 16 patients who were treated with $CoCl_2$ complained of tinnitus after 4-16 weeks of therapy. The effect disappeared after stopping the therapy (Meecham & Humphrey 1991).

10. Effects in animals

10.1. Skin sensitisation

$CoCl_2$ was classified as a grade 5 allergen (highest: 5) in a guinea pig maximisation test. The animals did not react to nickel sulfate or chromate which is in agreement with the theory of multiple sensitisation rather that cross reactivity (Lidén et al 1994, Wahlberg et al 1978, Wahlberg et al 2000).

10.2. Acute and subchronic studies

Acute lung toxicity in female rats was studied 24 hours after intratracheal instillation of pure cobalt particles, pure tungsten carbide particles, a mixture of tungsten carbide and cobalt powder (Co 6.3%, W 84%, C 5.4%). WC alone (156 700 μg/kg bw) was inert and Co alone (10 000 μg Co/kg bw) caused a moderate inflammatory response. Severe alveolitis and fatal pulmonary edema were seen after exposure to a mixture of WC and Co (166 700 μg/kg bw, corresponding to 10 000 μg Co/kg bw). U-Co concentrations were significantly higher when animals are exposed to the mixture of tungsten carbide and cobalt powder as compared to an equivalent amount of pure Co, suggesting an increased availability of Co when combined with WC (Lasfargues et al 1992).

Inhalation exposure of rats to Co sulfate heptahydrate during 13 weeks affected the lungs. Inflammation (histiocytic infiltrates) of the lung was found at concentrations equal or higher than 400 μg Co/m^3 and more severe inflammation was found at a concentration equal or higher than 1100 μg Co/m^3. Bronchiolar regeneration, peribronchiolar and septal fibrosis were seen at concentrations equal or higher than 11 000 μg Co/m (Bucher et al 1990, NTP 1991).

Decreased lung compliance and microscopic evidence of interstitial fibrosis by an increase of septal collagen were found in miniature swine after inhalation exposure to 100 μg/m^3 Co powder during 3 months. In addition ECG changes were reported (loss of QRS voltage indicating a decrease in ventricular contraction, T-wave changes indicating repolarisation abnormalities) (Kerfoot et al 1975).

Hyperplasia of alveolar type II cells in rabbits was reported after exposure to cobalt chloride (400-600 μg cobalt/m^3) during 4 to 6 weeks (Johansson et al 1984).

Rats, pigs and guinea pigs developed cardiomyopathy after oral administration of cobalt salts (3 000-100 000 μg Co/kg/day for 3 days to 20 weeks). The results also suggest that poor diet (thiamine or protein deficiency) may exacerbate this condition (Evans et al 1991).

10.3. Chronic studies

Hamsters exposed to Co(II) oxide aerosols (8000 μg Co/m^3) up to 22 months developed pneumoconiosis from early on. This was characterised by interstitial pneumonitis, diffuse granulomatous pneumonia and fibrosis of alveolar septa (Wehner et al 1977).

Rats who were exposed to Co sulfate heptahydrate aerosols during 2 years developed alveolar inflammation and interstitial fibrosis at 100 μg Co/m^3. Mice were less sensitive in this study (Bucher et al 1999, NTP 1998).

The same animal model as in Lasfargues (Lasfargues et al 1992) was used to test the delayed lung response. A single intratracheal instillation of a mixture of Co and tungsten carbide particles in saline (10 000 μg/kg bw, corresponding to

600 μg Co/kg bw), showed acute alveolitis for at least 1 month. No fibrosis was seen after 4 months. Exposure to either cobalt (600 μg Co/kg bw) or tungsten carbide (10 000 μg/kg bw) resulted in very modest effects. Extension of the treatments to 4 administrations at 1 month interval resulted in interstitial fibrosis after exposure to the mixture of Co and tungsten carbide. No effects were seen after exposure to Co or tungsten carbide alone (Lasfargues et al 1995).

Rabbits were exposed to 400 or 2000 µg Co/m^3 as Co chloride aerosols for 14 to 16 weeks. At the higher Co chloride concentration an increased number of macrophages in bronchoalveolar lavage fluid was found. Lysozyme activity and oxidative metabolic activity of macrophages were increased in both exposed groups (Johansson et al 1986).

Male B6C3F1 mice were exposed to cobalt sulfate heptahydrate particles (mass median aerodynamic diameter 1.5-1.8 μm) by inhalation of 3000 μg/m^3 (corresponding to 630 μg Co/m^3) for 2 years. Arteritis was detected in heart and kidney (Moyer et al 2002).

11. Mutagenicity and carcinogenicity

The carcinogenic potential of cobalt and its compounds was evaluated by IARC in 1991 (IARC 1991). The overal evaluation was that cobalt and its compounds are possibly carcinogenic to humans (group 2B).
This evaluation was based on:

- *inadequate evidence* for the carcinogenicity of cobalt and cobalt compounds in *humans;*
- *sufficient evidence* for the carcinogenicity of cobalt metal powder and cobalt(II) oxide in *experimental animals*;
- *limited evidence* for the carcinogenicity of metal alloys containing cobalt-chromium-molybdenum, cobalt(II) sulfide, cobalt(II) chloride in *experimental animals;*
- *inadequate evidence* for the carcinogenicity of cobalt-aluminium-chromium spinel, cobalt(II,III) oxide, cobalt naphthenate and cobalt(III) acetate in *experimental animals*.

A recent review about genotoxicity and carcinogenicity of Lison et al describes the studies published since the IARC assessment of 1991 (Lison et al 2001). Lison stresses the importance of a clear distinction between the different compounds of the element, and the need to take into account the different mechanisms involved.

11.1. Cobalt ions

Cobalt ions may originate from soluble cobalt compounds and from cobalt metal or hard metal particles which are readily solubilised in biological media but may be precipitated in the presence of phosphates and bind to proteins *in vivo*. It has been shown that cobalt ions (µM) plus hydrogen peroxide probably can generate hydroxyl radicals that cause chemical damage to DNA bases in human lymphocytes and isolated DNA *in vitro* (Kawanishi et al 1994, Lloyd et al 1997, Mao

et al 1996, Nackerdien et al 1991). Cobalt ions can also affect the repair of DNA damage induced by other agents in mammalian cells by competing with essential magnesium ions, binding to zinc finger domains in repair proteins and modulating the DNA binding capacity and function of the p53 protein *in vitro* (Asmuß et al 2000, Hartwig et al 1991, Kasten et al 1997, Lee et al 2001, Meplan et al 2000, Palecek et al 1999). Intratracheal instillation of cobalt chloride to hamsters caused thiol oxidation in lung tissue indicating oxidant stress (Nemery et al 1994). Intraperitoneal administration of Co(II) ions to rats (0.05 or 0.1 mmol cobalt acetate/kg) produced oxidative DNA damage caused by hydroxyl radicals in renal, hepatic and pulmonary chromatin (Kasprzak et al 1994). Chromosomal aberrations were also found in mice after oral administration of cobalt chloride (20-80 mg/kg) (Palit et al 1991). DNA breakage was shown in human lymphocytes exposed to non-cytotoxic cobalt chloride concentrations (De Boeck et al 1998).

Rats who were exposed to Co sulfate heptahydrate aerosols during 2 years developed alveolar epithelial metaplasia at 100 μg Co/m^3. The incidences of alveolar/bronchiolar neoplasms were increased in male at 1100 μg Co/m^3 and in female at 400 μg Co/m^3. In mice, alveolar/bronchiolar neoplasms were found at 1100 μg Co/m^3 both in males and females (Bucher et al 1999, NTP 1998).

Lison et al conclude that the genotoxic potential of cobalt(II) compounds is demonstrated *in vitro* and that there is evidence that cobalt(II) exerts genotoxic as well as carcinogenic effects in animals. No evidence about genotoxicity or carcinogenicity is available in humans. The European Union has classified cobalt chloride and sulphate as Category 2 carcinogens (R49, may cause cancer in humans by inhalation) (Lison et al 2001).

11.2. Cobalt metal and cobalt oxides

In recent studies it was questioned whether the biological activity of cobalt metal particles was mediated by the ionic form. Physicochemical studies have shown that cobalt metal, and not cobalt(II), is thermodynamically able to reduce oxygen into reactive oxygen species at a very low rate. In this system, soluble cobalt ions are produced during, but do not drive, the critical reaction; so reactive oxygen species are not produced by a Fenton-like reaction as described with cobalt ions in the presence of hydrogen peroxide (Lison et al 1995, Lison & Lauwerys 1992). Cobalt metal was shown to be genotoxic *in vitro* (induction of alkali labile sites or DNA strand breaks in isolated DNA and human lymphocytes) in a dose and time dependent way by producing reactive oxygen species (a process independent of the cobalt(II) species) (Anard et al 1997, De Boeck et al 1998, Van Goethem et al 1997). In addition, cobalt metal is able to inhibit the base excision repair system (De Boeck et al 1998). No increase in genotoxicity biomarkers in lymphocytes was found in 35 workers form cobalt refineries (average concentration 20 μg Co/m^3) compared with matched controls (De Boeck et al 2000). Two successive cohort studies among workers in an electrochemical plant producing cobalt and sodium were performed. The first study (1950-1980) found a significant excess of

lung cancer among workers in the production of cobalt (SMR 4.66; CI(95%) 1.46-10.64), but the number of cases was few (n=4). The authors suggested that a complementary study should be undertaken because they could not take into account the consumption of tobacco. Simultaneous exposure to nickel and arsenic might have occurred (Mur et al 1987). Extension of the follow up (1981-1988) by the same authors did not confirm the hypothesis of a relation between lung cancer and cobalt exposure (SMR 0.85; CI(95%) 0.18-2.50). Explanations that were mentioned by the authors for the apparent discrepancy between the results were, (a) no further deaths from lung cancer during the follow up, (b) revaluation of the 4 cases in the first study in which general practitioners' records were used to set the number of lung cancers showed that there was no death certificate for one of the 4 cases. This means that there were only 3 cases of lung cancer in the latter study (Moulin et al 1993).

It may be concluded that genotoxic effects of cobalt metal particles have been demonstrated *in vitro* in human lymphocytes. Epidemiological studies are insufficient to evaluate the carcinogenic potential for Co metal alone. In addition, no significant increase of genotoxic effects was detected in workers exposed to cobalt dust at a mean cobalt concentration of 20 $\mu g/m^3$.

No study examining the genotoxic or carcinogenic activity of cobalt oxides was found in literature published since the 1991 IARC evaluation.

11.3. Hard metal

The association of cobalt metal and carbide particles represents a specific toxic entity, producing larger amounts of reactive oxygen species than cobalt metal alone. The mechanism of this interaction involves the oxidation of cobalt metal catalysed at the surface of carbide particles, reduction of dissolved oxygen into reactive oxygen species, and production of soluble cobalt cations (Lison et al 1995). *In vitro* WC–Co particles have shown to be more potent in causing genotoxic effects than cobalt alone (Anard et al 1997, Van Goethem et al 1997). Dose and time dependency of DNA breakage or alkali labile sites were shown for WC-Co *in vitro* (De Boeck et al 1998). Intra-tracheal treatment of rats with a bolus of 16,6 mg WC-Co/kg bw showed increased DNA damage of type II pneumocytes (De Boeck et al 2003). No increased genotoxic effect in lymphocytes was found in hard metal workers (mean cobalt concentration 20 $\mu g/m^3$, n=29) compared to controls. A multivariate analysis showed however that being a worker who smoked and was specifically exposed to hard metal dust (not cobalt alone) was a significant and positive determinant of urinary 8-OHdG and micronuclei in lymphocytes (De Boeck et al 2000). Transmission electron microscopy on lung tissues and BAL from patients with severe restrictive ventilatory defect after they started work in hard metal industry, showed hyperplasia of type II alveolar epithelial lining cells (Anttila et al 1986, Davison et al 1983). A retrospective cohort (1951-1982) of 3163 hard metal workers showed an excess mortality from lung cancer only in workers with more than 10 years employment who had died more than 20 years after the beginning of exposure

(seven cases observed versus 2.5 expected; SMR 2.78, CI (95%) 1.11-5.72). A dose-response relationship was not found. No firm conclusion could be drawn since the contribution of smoking could not be assessed individually (Hogstedt & Alexandersson 1990). An increased mortality from lung cancer was found in a French follow up from 1956-1989 among hard metal workers (n=709, 10 cases observed, SMR 2.13, CI (95%) 1.02-3.93). This excess was highest among workers employed in the areas with cobalt exposures higher than 50 $\mu g/m^3$ (6 cases observed, SMR 5.03, CI (95%) 1.85-10.95). Lung cancer mortality could not be explained by smoking alone (Lasfargues et al 1994). Extension of this study to a cohort of 7459 workers from all hard metal plants in France (from 1968-1991) showed again that mortality from lung cancer in this cohort was significantly increased (63 cases observed, SMR 1.30, CI (95%) 1.00-1.66) and increased slightly with time since first employment. A nested case control study (61 cases and 180 controls) showed a twofold lung cancer risk among workers simultaneously exposed to cobalt and tungsten carbide when the exposures during the last 10 years were ignored (OR=1.93, CI (95%) 1.03-3.62). The Odds ratio increased with cumulative exposure and duration of exposure. Smoking could not explain the excess of lung cancer (Moulin et al 1998). A historic cohort study was set up in one of the sites already included in the study of Moulin et al. Full job histories were available in contrast to the study of Moulin et al that relied on job exposure matrices. The results of the study were in agreement with the results of Moulin et al (Wild et al 2000)

Lison et al (Lison et al 2001) concluded that although *in vivo* evidence of the genotoxic activity of WC-Co particles is lacking, evaluation of *in vitro* studies and human mortality studies strongly indicates evidence of genotoxicity and carcinogenicity of hard metal particles.

11.4. Unspecified and other cobalt compounds

In a retrospective cohort among women occupationally exposed to poorly soluble cobalt-aluminate spinel (n=874) and 520 women not exposed to cobalt, showed that the standardised incidence of lung cancer was higher than expected from national rates in both the control and the exposed group. The exposed group had a non-significantly increased relative risk ratio of 1.2 (CI (95%) 0.4-3.8) compared with the control group. No relationship with duration of exposure was found and 3 of the 8 cases had been exposed to cobalt spinel for less than 3 months. Smoking could not be taken into account in this study (Christensen & Poulsen 1994, Tuchsen et al 1996). Lison et al (Lison et al 2001) concluded that this study does not provide a solid evidence of an increased risk for lung cancer caused by cobalt spinel.

In a population (n= 78) of workers selected for Cd exposure, but also exposed to Co (mean air level: 2.0 μg Co/m^3, state of Co not defined) and Pb, levels of DNA-SSB (single strand breaks) in mononuclear blood cells correlated strongly to Co levels in air (personal sampler) and in blood. Increased levels of SSB was recorded at Co levels of between 4-10 $\mu g/m^3$. An inhibition of repair activity of

DNA adducts (8-oxoguanine) in blood from these workers was also reported, but referred to as unpublished data. The authors conclude that Co was the strongest determinant, but that interactions with Cd and/or Pb seem likely (Hengstler et al 2003).

12. Reproductive and developmental effects

No information about reproductive effects of Co is available in humans.

Inhalation exposure of male mice to Co sulfate heptahydrate during 13 weeks affected sperm motility at 1100 μg Co/m^3. Increased numbers of abnormal sperm and decreased testis and epididymal weights occurred at 11 000 μg Co/m^3. In female mice, the length of the oestrous cycle was increased at 11 000 μg Co/m^3 (Bucher et al 1990). Rats exposed in the same way showed no effects on the reproductive system (Bucher et al 1990).

Orally administered Co salts to male rodents showed reproductive toxicity. Mice administered 100, 200 and 400 ppm cobalt chloride in the drinking water (corresponding to 23, 42 and 72 mg Co/kg bw per day) for 12 weeks showed a dose dependent decrease in testicular weight and epididymal sperm concentration (significant at all three doses compared to control). At the highest dose the mobility of the sperm was affected and the fertility (measure as percentages of fertilized and unfertilised ova after mating) was decreased. After 20 weeks of recovery testicular weight, sperm concentration, percent motile sperm and fertility remained significantly depressed. Serum testosterone levels were increased, 5 to 7 times, in Co treated animals, while FSH and LH serum levels were normal (Pedigo et al 1988). Cobalt chloride was administrated to male mice (Co concentration in drinking water 400 ppm, corresponding to a daily dose of 50 to 70 mg Co/kg bw) for up to 13 weeks. The treatment resulted in a sequential pattern of seminiferous tubule degeneration and decreased testicular weight; initial changes involved vacuolation of Sertoli cells and formation of abnormal spermatid nuclei (Andersen et al 1992). Similar changes were found in rats administered 20 mg Co/kg bw per day, for 14 weeks, in the diet (Corrier et al 1985). Oral administration of cobalt chloride to male mice (400 ppm in drinking water, 10 weeks of treatment before mating with untreated females) resulted in preimplantation losses (Pedigo & Vernon 1993).

The effects on fetal development of cobalt sulphate administrated by gavage to pregnant mice (0 and 50 mg/kg bw, day, day 6-15 of gestation), rats (0, 25, 50 and 100 mg/kg bw, day, day 1-20 of gestation) and rabbits (20, 100 and 200 mg/kg bw, day, day 6-20 of gestation) was studied by Szakmáry et al (Szakmáry et al 2001). In mice and rats the treatment significantly increased the frequency of fetuses with retarded body weight and produced skeletal retardation (in rats in a dose dependent manner). A few anomalies in the urogenital system were observed in the treated groups. Also skeletal malformations, cranium (mice) and vertebra (mice and rats) were reported. In rabbits the two higher doses caused death of the mothers or total resorption of fetuses. The lowest dose (20 mg/kg) caused

maternal toxicity (decreased weight gain) and caused inhibition of fetal skeletal development but no malformations (Szakmáry et al 2001). No firm conclusions about the teratogenic effects of cobalt sulphate in experimental animals can be drawn from this study since it contains several inconsistencies regarding, e.g. data presentation, maternal toxicity and dose-response relationships.

Paternain et al reported no embryotoxic or teratogenic effects in rats after oral administration of $CoCl_2$ to pregnant rats at concentrations up to 100 mg/kg/day on day 6-15 of gestation (Paternain et al 1988). A single injection in the tail vein of pregnant mice of $CoCl_2$ (dose: 1.2 mg Co/kg bw on day 8 of pregnancy) showed an interference of the metal with the fetal skeletal ossification (Wide 1984).

Lowered birth weight after oral administration of cobalt sulphate to pregnant rats (25 mg Co/kg bw per day, day 1-21 of gestation) compared to controls has been reported (Szakmáry et al 2001). Also a reduction of the number of litters 5 days after birth and lowered ability in a swimming test (day 18 to 22 after birth) was found. Domingo et al also found a lowered birth weight and reduction of the number of litters and a dose-dependent delay in the growth of living pups after oral administration of cobalt chloride to pregnant rats (12, 24, 48 mg/kg bw per day, from day 14 of gestation through day 21 of lactation) (Domingo et al 1985).

13. Dose-response/dose-effect relationships

In Table 4 and 5, human data on inhalation exposure are presented. Table 4 summarizes the effects of exposure to Co metal, salts and oxides; Table 5 gives an overview of effects from exposure to hard metal dust, vitallium and diamond polishing dust. Animal data is summarized in Table 6 (inhalation exposure) and Table 7 (intratracheal instillation).

Irritative effects have been shown after exposure to Co containing dust. Workers in the hard metal industry complained of irritation of eyes, nose and throat at a mean exposure of 3 μg Co/m^3 and diamond polishers at a mean exposure of 15 μg Co/m^3 (Table 5).

Induction of asthma has been reported after mixed exposure to water soluble Co and Co metal as well as to hard metal at an exposure level of 10-50 μg Co/m^3 (Table 4 and Table 5), but no conclusions about dose-response relationships can be made.

ILD has been reported from hard metal exposure and restrictive lung impairment was found among wet grinders exposed to mean Co concentrations of 5.6 $\mu g/m^3$ (Table 5). In this case the state of absorbed Co might have been altered by the coolant, or skin absorption might have been involved.

Another study reports reduction of FEV_1 and MMF among (hard metal) grinders at 8 $\mu g/m^3$, but no reduction among grinders at 3 $\mu g/m^3$ (Table 5). Both groups were exposed to cutting fluids.

A reduction of FEV_1 and FVC has been reported among diamond polishers exposed to 15 μg/m^3 when compared with polishers exposed to 5.3 μg/m^3 (Table 5).

An increased risk of abnormal chest radiographs (profusion ≥1/0) has been reported in hard metal workers at an average life time exposure of >100 μg Co/m^3 compared to hard metal workers with an average life time exposure of ≤100 μg Co/m^3 (Table 5).

No epidemiological data are available on ILD caused by tungsten(carbide) without Co. Animal studies, however, support an interaction between tungsten carbide and Co in the development of ILD (Table 7).

Increased levels of DNA damages (SSB) have been reported in workers exposed to 4-10 μg Co/m^3, but interactions with Cd and Pb seem likely.

Animal inhalation studies indicate alveolar inflammation, interstitial fibrosis and ECG changes at a level of 100 μg Co/m^3 and testicular toxicity (decreased sperm motility) at 1100 μg Co/m^3 (Table 6).

14. Conclusions

The critical effect of occupational exposure to Co and Co compounds is irritation of eyes, nose and throat. This was found at a mean Co exposure of 3 μg Co/m^3. Other effects on the respiratory system appear at slightly higher levels. Impairment of lung function was seen among hard metal grinders at 5.6 but not at 3 μg Co/m^3. Co and Co compounds can induce occupational asthma, but no conclusions about dose-response relationships can be made. Pneumoconiosis has been associated with exposure to hard metal dust, vitallium dust and combined diamond and cobalt dust. Several studies report a positive interaction between the effects of Co exposure and smoking (chronic bronchitis and impaired FEV_1).

Cobalt is genotoxic presumably via an indirect mechanism involving reactive oxygen species. Genotoxic potential *in vitro* has been shown for Co ions and Co metal particles.

There is evidence that Co ions and Co oxides are carcinogenic in animals. One study indicates that inhalation of hard metal dust is carcinogenic in humans.

Cobalt and Co compounds are skin sensitisers. Dermal exposure to hard metal and cobalt chloride may result in significant systemic uptake of cobalt.

Table 4. Effects in humans exposed to Co metal, oxide or salt.

Concentration* (μg Co/m^3)	Exposure/duration	Effects	Ref.
case 1: <6 000-84 000 case 2: 64 000-103 000	dust from cobalt-containing ores, case 1: 26 months case 2: 2 months	Cardiomyopathy in 2 workers	(Jarvis et al 1992)
AM: 520 median: 200 SD 700 range 100-3000	Co metal and Co oxide, 10.7 yrs (SD 6.4)	No X-ray changes, no lung fibrosis No significant changes in lung function (FEV_1 and VC) (49 workers, 46 matched referents)	(Morgan 1983)
10-50	Co roasting, leaching, packing, water soluble Co, Co metal, minimum duration: 6 months, 2-4 h/day plus maintenance operations for all factories	Case-referent study Age adjusted odds ratio for asthma: 4.8 (95%CI: 2.0-11.7) 21 cases with asthma, 55 randomly selected workers without asthma. 6 of 15 Co workers with asthma were positive in a challenge test with $CoCl_2$ or dust of Co roasting	(Roto 1980)
2–7700 GM: 125 70% >50 25% >500	Co metal, oxides, salts, mean exposure duration was 8 yrs (0.3-39.4 yrs)	Significant relationship between the level of current exposure to Co (Co-air and U-Co) and reduction in FEV_1/FVC ratio No signs of pulmonary fibrosis Decreased T3 and T4, increased TSH in plasma (82 workers, 82 age matched controls)	(Swennen et al 1993)
4–10	pigment prod., battery work, recycling electronics, Cd and Pb exposure	DNA damage (SSB)	(Hengstler et al 2003)

Arithmetic mean (AM), Geometric mean (GM), Standard deviation (SD)
* Personal air sampling

Table 5. Effects in humans exposed to hard metal dust, vitallium or diamond polishing dust.

Concentration* (μg Co/m^3)	Exposure/ duration	Effects	Ref.
6.2-2875	Co metal and diamond dust, 0.1-32 yrs	More cough, sputum and dyspnoea Restrictive effect when >5 yrs exposure Tendence for obstructive effect among non-smokers when >5 yrs exposure (48 workers, 23 non-exposed controls)	(Gennart & Lauwerys 1990)
up to 1600	Vitallium, 5 yrs or more	Reduction FVC and FEV_1 (37 workers, no control group)	(Selden et al 1995)
20-1100	Co metal and diamond dust, mean exposure time 2.4 yrs	No lung function impairment No changes in X-rays (n=40, no control group)	(Ferdenzi et al 1994)
peak exposures up to 1000, but declining over time	Co production, mean exposure time not given	Decline of FEV_1 over time only for smokers Follow up of 122 male workers: at least 4 lung function tests; duration of follow up 6 to 13 yrs; median 12 yrs)	(Verougstraete et al 2004)
peak exposures: >500	hard metal, 21-35 yrs	Interstitial lung disease Obstructive lung disease (n=290, no control group)	(Sprince et al 1984)
45-272 (powder) 30-220 (presses)	hard metal, 13-14 yrs	Slight abnormalities in chest radiographs Lower FVC, FEV_1, carbon monoxide diffusion capacity (425 workers, 88 controls from mechanical workshops, warehouses and shipping departments)	(Meyer-Bisch et al 1989)
>100 (way of sampling not given)	hard metal, mean 12.6 yrs 1 month-28 yrs	Interstitial lung disease Asthmatic bronchitis (12 cases)	(Coates & Watson 1971)
>100	hard metal, duration of exposure is not given	Decreased $\%V_{25}$ but stable %FVC (n=583 men, 120 women, no control)	(Kusaka et al 1996b)
6-610 AM: 126 SD 191	hard metal, mean 10 yrs (2-20 yrs)	Significant decrease in FEV_1/FVC (42 workers, 84 controls)	(Kusaka et al 1986b)
≥100 “average lifetime exposures”**	hard metal, latency >10 yrs	Relative odds of abnormal chest radiographs (profusion ≥1/0) was 5.1, compared with average lifetime exposures ≤100 μg Co/m^3	(Sprince et al 1988)

Table 5. Cont.

Concentration* (μg Co/m^3)	Exposure/ duration	Effects	Ref.
AM: 60	hard metal, 7-11 yrs	Reduction of FEV_1, FEV% and MMF compared to paired controls (63 workers, 63 controls). Reduction of FVC, FEV_1, and MMF over the working week (73 workers)	(Alexandersson 1979)
50	tungsten carbide production, 7 yrs (SD 6)	Work related wheezing: Odds ratio=2.1 (p=0.002) when Co-air >50 was compared to Co-air less or equal to 50 μg Co/m^3 (n=1039, no control group)	(Sprince et al 1988)
<50	hard metal, latency period: <1 yr in more than 50% of the cases	Prevalence of occupational asthma: 5.6% (n=700, no control group)	(Kusaka et al 1991)
mean Co conc. in 4 cases of asthma 18, 24, >31, >1203	hard metal, latency period: 3 months to 10 yrs	Occupational asthma in 18 workers (319 workers, no control group)	(Kusaka et al 1986b)
7–227	hard metal, latency period: 2 months to 20 yrs	Occupational asthma, positive in provocation test with $CoCl_2$; 4/8 had IgE against Co-HSA (8 asthmatics, 8 controls)	(Shirakawa et al 1989)
14-76 AM: 38 SD 22	hard metal, 6 hours	Decrease in FVC Irritation of the large bronchi (cough, expectoration, sore throat) (15 subjects normally not exposed to hard metal)	(Kusaka et al 1986b)
2-24 GM: 17	hard metal and stellite, exposure time not given	Increase in self reported work-related cough, dyspnoea, or fever or chills among Co exposed non-smokers and workers exposed to Co and wood dust (n=108 Co exposed vs n=106 not Co exposed; n=116 Co+wood exposed vs n=103 wood but no Co)	(Linnainmaa et al 1997)
0.7-43 AM: 15	diamond polishing dust of Co-containing abrasive disks, duration not given	Irritation of eye, nose and throat Reduction of FEV_1, FVC (unchanged ratio) compared to a lower exposed group (92 workers)	(Nemery et al 1992)

Table 5. Cont.

Concentration* (μg Co/m^3)	Exposure/ duration	Effects	Ref.
2-34 AM: 10	hard metal, wet grinders, 7-10 yrs	ST- and T-depressions in ECG and overfrequency of ectopic beats	(Alexandersson & Atterhög 1980)
AM: 8	hard metal, 7-11 yrs	Decreased FEV_1 and MMF between Monday morning and Friday afternoon Cough with/without phlegm, chest tightness, breathlessness (67 workers)	(Alexandersson 1979)
5.6 estimated exposure during wet-grinding	hard metal, mean duration: 6.9 yrs (0.5-22 yrs)	Cough, phlegm and wheeze Reduction of FEV_1 and FVC (118 workers, number of controls [bus mechanics] is not given)	(Kennedy et al 1995)
AM 3	hard metal 7-11 yrs	No effect on FEV_1 and MMF between Monday morning and Friday afternoon (32 workers)	(Alexandersson 1979)
AM 3	hard metal 7-11 yrs	Irritation of eyes, nose and throat (44 workers and 44 controls [office workers])	(Alexandersson 1979)

Arithmetic mean (AM), Geometric mean (GM), Standard deviation (SD)
* Personal air sampling
**"Average lifetime exposure": fraction of cumulative Co exposure and total exposure duration.

Table 6. Effects in animals from inhalation studies.

Concentration (μg Co/m^3)	Exposure/ duration	Species	Effects	Ref.
400	Co chloride 6 hr/day, 5 days/week, 4-6 weeks	rabbits (male)	Hyperplasia of alveolar type II cells	(Johansson et al 1984)
400 or 2000	Co chloride 6 hr/day, 5 days/week, 14-16 weeks	rabbits (male)	Increased number of macrophages in the high dose group Increased lysozyme activity and oxidative metabolism in macrophages in both dose groups	(Johansson et al 1986)
8000	Co(II) oxide 7 hr/day, 5 days/week, from age 2 months until natural death up to 22 months	hamster	Interstitial pneumonitis, diffuse granulomatous pneumonia, fibrosis of alveolar septa	(Wehner et al 1977)
11 000	Co sulfate 6 hr/day, 5 days/week, 13 weeks	mice	Decrease of testis and epididymal weight Increase of abnormal sperm Increase of oestrous cycle	(Bucher et al 1990)
11 000	Co sulfate 6 hr/day, 5 days/week, 13 weeks	rat	Bronchiolar regeneration Peribronchiolar and septal fibrosis	(Bucher et al 1990)
1100	Co sulfate 6 hr/day, 5 days/week, 13 weeks	mice	Decrease of sperm motility	(Bucher et al 1990)
1100	Co sulfate 6 hr/day, 5 days/week, 13 weeks	rat	Inflammation of the lungs	(Bucher et al 1990)
630	Co sulfate 24 month	mice (male)	Arteritis in heart and kidney	(Moyer et al 2002)
400	Co sulfate 6 hr/day, 5 days/week, 13 weeks	rat	Histiocytic infiltration	(Bucher et al 1990)
100	Co metal particles, 6hr/day, 5 days/week, 3 month	miniature swine	ECG changes	(Kerfoot et al 1975)
100	Co sulfate 6 hr/day, 5 days/week, 104 weeks	rat	Alveolar inflammation, Interstitial fibrosis	(Bucher et al 1999, NTP 1998)

Table 7. Effects in animals from intratracheal instillation of Co, WC and Co-WC.

Metal/dose (mg/kg,bw)	Exposure (intratracheal instillation)	Species	Effects	Ref.
Co 10	single	female rat	Moderate inflammatory response comparable to control group	(Lasfargues et al 1992)
WC 156.7	single	female rat	Mild accumulation of alveolar macrophages in alveolar duct walls	(Lasfargues et al 1992)
Co-WC 166.7 (10 mg Co/kg bw)	single	female rat	Severe alveolitis and fatal pulmonary edema	(Lasfargues et al 1992)
Co-WC 16.6	single	male rat	Mutagenic potential of hard metal dust (increase in tail DNA and in micronuclei)	De Boeck et al 2003)
Co 0.6	single	female rat	No cellular and biochemical changes in BAL	(Lasfargues et al 1992)
WC 10	single	female rat	No cellular and biochemical changes in BAL	(Lasfargues et al 1992)
Co-WC 10 (0.6 mg Co/kg bw)	single	female rat	Significant increase in macrophage and neutrofil numbers, LDH activity, total protein and albumin concentration.	(Lasfargues et al 1992)
Co-WC 10 (0.6 mg Co/kg bw)	single	female rat	Acute alveolitis for at least 1 month; after 4 months there was no fibrosis	(Lasfargues et al 1995)
Co-WC 10 (0.6 mg Co/kg bw)	4 times with 1 month intervals	female rat	Increased hydroxyproline interstitial fibrosis	(Lasfargues et al 1995)

15. Summary

Nicole Palmen. *Criteria Document for Swedish Occupational Standards. Cobalt and Cobalt Compounds*. Arbete och Hälsa, 2005;12:1-54. National Institute for Working Life, Stockholm.

Cobalt (Co) is a metal with one naturally occurring isotope (^{59}Co). Cobalt has magnetic properties, can form alloys, is not corroded by air or water at ordinary temperature, and is resistant to alkalis but soluble in acids. Cobalt is used in the production of alloys, magnets, dental and surgical implants, and in hard metal. Cobalt salts and oxides are used as catalysts in organic reactions or as drying agents in paints, lacquers, varnishes and printing inks. Cobalt compounds are also used as pigments in glass, enamels, ceramic and porcelain products.

Cobalt and Co compounds are absorbed via inhalation as well as via dermal penetration. The amount of cobalt absorbed after inhalation is dependent on the solubility of the compound in biological media and the diameter of the particles. Dermal exposure to hard metal and cobalt chloride may result in significant systemic uptake of cobalt.

Occupational exposure to Co and Co compounds has been shown to be irritating to eyes, nose and throat at a mean Co exposure of 3 μg Co/m^3. Other effects on the respiratory system have been reported after occupational exposure to cobalt or cobalt containing compounds. Cough, phlegm, wheeze and changes in lung function (FEV_1 and FVC) were reported among hard metal grinders at 5.6 μg Co/m^3, but not at 3 μg Co/m^3. Co and Co compounds can induce occupational asthma, but no conclusions about dose-response relationships can be made. Pneumoconiosis has been associated with exposure to hard metal dust, vitallium dust and combined diamond and cobalt dust.

Cobalt is genotoxic presumably via an indirect mechanism involving reactive oxygen species. Genotoxic potential *in vitro* has been shown for Co ions and Co metal particles. There is evidence that Co ions and Co oxides are carcinogenic in animals. One study indicates that inhalation of hard metal dust is carcinogenic in humans.

Cobalt and cobalt compounds are skin sensitisers.

Keywords: Cobalt, cobalt alloys, cobalt compounds, cobalt oxide, cobalt salts, hard metal, irritation, lung function, OEL, occupational exposure, pneumoconiosis, Stellit, toxicity, Vitallium.

16. Summary in Swedish

Nicole Palmen. *Criteria Document for Swedish Occupational Standards. Cobalt and Cobalt Compounds*. Arbete och Hälsa, 2005;12:1-54. Arbetslivsinstitutet, Stockholm.

Kobolt (Co) är en metall med en naturligt förekommande isotop (^{59}Co). Kobolt har magnetiska egenskaper, kan blida legeringar, korroderar inte i luft eller vatten vid normala temperaturer, och är resistent mot alkali men löser sig i syror. Kobolt används i tillverkningen av hårdmetall, legeringar, magneter, tandinplantat och kirurgiska inplantat. Koboltoxider och -salter används som katalysatorer i organiska reaktioner eller som torkmedel i färger, lacker, fernissor och trycksvärtor. Koboltföreningar används även som pigment i glas, emalj, keramik och porslin.

Kobolt och koboltföreningar kan absorberas via upptag i andningsvägarna och via hudupptag. Den mängd som absorberas vid inhalation är beroende av koboltföreningens partikeldiameter och löslighet i biologiska medier. Hudexponering för hårdmetall och koboltklorid kan resultera i ett signifikant systemiskt upptag av kobolt.

Yrkesmässig exponering för kobolt och koboltföreningar har visats vara irriterande i ögon, näsa och hals vid en medelexponering av 3 μg Co/m^3. Andra effekter på andningsvägarna har rapporterats vid yrkesmässig exponering för kobolt och koboltföreningar. Hosta, slem, pipande andning och försämring av lungfunktionen (FEV_1 och FVC) har rapporterats bland hårdmetallslipare vid 5,6 μg Co / m^3, men inte vid 3 μg Co/m^3. Exponering för kobolt och koboltföreningar kan framkalla yrkesrelaterad astma, men inga slutsatser om dos-responssamband kan göras. Pneumokonios har associerats till exponering för hårdmetalldamm, vitalliumdamm och kombinerad exponering för diamant och koboltdamm.

Co är genotoxiskt, förmodligen genom en indirekt mekanism som involverar reaktiva syreradikaler. En genotoxisk potential *in vitro* har konstaterats för Co-joner och partiklar av metalliskt Co. Det finns belägg för att koboltoxid och -joner är carcinogena på djur. En studie indikerar att inhalation av hårdmetall kan vara carcinogent på människa.

Co och Co-föreningar är hudsensibiliserare.

Nyckelord: Hygieniska gränsvärden, hårdmetall, irritation, kobolt, koboltföreningar, koboltlegeringar, koboltoxid, koboltsalter, lungfunktion, Stellit, toxiska effekter, Vitallium, yrkesmässig exponering.

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