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

114. Cobalt and cobalt compounds

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ARBETS MILJÖ INSTITUTET
NATIONAL INSTITUTE OF OCCUPATIONAL HEALTH

A Center for Research on Occupational Health

Sweden's National Institute of Occupational Health employs over 300 scientists in research on the work environment. The research is led by 30 professors. The Institute does mostly applied research, but some questions also require focused basic research.

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Preface

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

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

Helgi Gudbergsson	Municipal Institute of Public Health, Iceland
Petter Kristensen	National Institute of Occupational Health, Norway
Per Lundberg (chairman)	National Institute of Occupational Health, Sweden
Vesa Riihimäki	Institute of Occupational Health, Finland
Adolf Schaich Fries	National Institute of Occupational Health, Denmark

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

An editorial work is performed by the Group's Scientific Secretary, Brita Beije, at the National Institute of Occupational Health in Sweden.

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

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

The evaluation of the literature and the drafting of this document on Cobalt was made by Dr. Uffe Midtgård, National Institute of Occupational Health, Lersø Parkallé 105, DK- 2100 Copenhagen OE,Denmark and Dr. Mona Lise Binderup, Institute of Toxicology, National Food Agency, DK-2610 Søborg, Denmark. The final version was accepted by the Nordic Expert Group, October 21, 1994, as its document.

Brita Beije
Scientific Secretary

Per Lundberg
Chairman

Contents

1. Substance Identification

CAS No: 7440-48-4

RTECS No: GF8750000

Chemical name: Cobalt

Synonyms: Cobalt-59, Super cobalt, Aquacat, C.I. 77320, NCI-C60311

Formula: Co

2. Physical and Chemical Properties

Cobalt is a steel-grey, hard metal located between iron and nickel in the periodic table and with somewhat similar properties. It is not corroded by air or water, and it is resistant to alkalis but soluble in acids. Cobalt has magnetic properties, it can form alloys and is an essential trace element in the formation of vitamin B_{12}.

Some constants for cobalt are given in Table 1.

The main oxidation states of cobalt are +2 and +3. Most cobalt compounds used commercially are bivalent salts, since the trivalent form is relatively unstable (163, 304).

Table 1. Some physical and chemical data for cobalt (189, 324).

Atomic weight	58.93
Atomic number	27
Density	8.92 g/cm^3
Melting point	1493°C
Boiling point	3100°C
Solubility in water	Insoluble
Solubility in blood serum	200 mg/l (37°C)
Valences	2, 3; rarely 4 and 5

Table 2. Identity and solubility of various cobalt compounds. Data from (137).

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	Co_2O_3,H_2O	183.88	-	0.84 mg/l (37°C)	53.9 mg/l hydrate (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	

1) i = insoluble, s = soluble

Cobalt(II) salts tend to be pink in colour in the cationic state and blue in the anionic state.

The hydrated salts of cobalt are red and the soluble cobalt salts form red solutions which become blue on adding concentrated HCl. Data concerning the solubility of cobalt and cobalt compounds that are relevant for the later discussion of health effects are given in Table 2. Cobalt salts are generally very soluble in water, while cobalt, cobalt oxides, cobalt sulphide and cobalt aluminate blue are insoluble or only very sparingly soluble in water.

3. Production, Occurrence and Use

3. 1. Production

Most cobalt is obtained as a by-product during the processing of other metals, mainly copper, nickel and lead. The extraction of cobalt from the parent ores is by chemical and electrolytic techniques involving many stages, and the methods employed depend on the nature of the original ore. The annual mine production and metal production of cobalt in 1980-1989 were in the range of 24,567-48,903 tonnes and 18,084-36,720 tonnes, respectively. The main producers of cobalt are Zaire, the USSR, Zambia, Canada, and Norway (listed in decreasing order). The consumption of cobalt in the western world accounted for about 85% of the world's total consumption in the years from 1983 to 1988, and the largest amount was used by the USA (133).

Cobalt metal is available for industrial use in various forms such as "broken" or "cut" cathodes, briquets, rondelles, strips, powder, wire, and foil. The powders are referred to as being coarse, fine, or ultrafine depending on the particle size (133). The grain size of the powders used in production of hard-metals is usually in the range of 50 to 150 µm, but fine (1-10 µm) and ultrafine powders (1-100 nm) are also used (210).

3. 2. Occurrence

Cobalt is a relatively rare metal composing about 0.002% of the earth's crust. Cobalt minerals occur in nature as a small percentage of other metal deposits, particularly copper, nickel and lead, generally as sulphides, arsenides and oxides. There is only one naturally occurring isotope; ^{59}Co (163, 304, 324).

The level of cobalt in the air depends on the extent to which soil particles are whirled up by the wind. The air concentration is around 1 ng/m^3, but in heavily industrilized cities values exceeding 10 ng/m^3 have been reported (133).

The daily diet of a 70-kg reference man contains 0.01-0.02 mg Co/kg fresh weight and most of the ingested cobalt is in the inorganic form. The concentration of cobalt in the drinking water is usually between 0.1-5 µg/l. Green vegetables

and cereals contain 0.2-0.6 µg/g dry weight, while dairy products contain 0.01-0.03 µg/g dry weight (133)

Cobalt is an essential element as it is part of vitamin B_{12} (cyanocobalamin) which is required for hemoglobin synthesis. Vitamin B_{12} is present only in food of animal origin and the recommended daily dose for adults is 3 µg corresponding to 0.012 µg cobalt (82).

3. 3. Use

Cobalt compounds have been used as blue colouring agents in ceramic and glass for thousands of years and cobalt has many important uses in industry to day. The most important use of metallic cobalt is in alloys with other metals like chromium, nickel, copper, aluminium, beryllium and molybdenum. For example, cobalt occurs in high temperature alloys (superalloys) used primarily for gas turbine blades and jet engine parts. Cobalt is also an important constituent of hard-metal alloys (cemented carbides), where it acts as a binder for tungsten carbide and other metal carbides. Hard-metals are particularly used as cutting and drilling tools for metals, rocks, and other hard materials (76,163). Alloyed with nickel and aluminium, cobalt is used in the manufacture of permanent magnets, and together with chromium and molybdenum cobalt forms an alloy that is used for dental and surgical implants due to its resistance to body fluids (76).

Cobalt compounds (salts and oxides) are used as catalysts for many organic reactions in the chemical industry and for oil refining. An important use of cobalt, primarily as cobalt naphthenate, is as a drying agent in paints, lacquers, varnishes and printing inks.

Cobalt oxides, cobalt zinc silicate, and spinels (mixed metal oxides with a special crystal structure) like cobalt-aluminium-oxide and cobalt-magnesium-aluminium spinels are used as pigments in glass, enamels, ceramic and porcelain products (34, 76, 258).

4. Occupational Exposure Data

The major route of exposure to cobalt in the work environment is through the respiratory organs, although dermal contact also is important in some types of occupations.

Most of the available information on occupational inhalation exposure concern the hard-metal industry and cobalt refinery industry. In addition, there are some data available for diamond polishers, dental technicians and ceramic plate decorators. Data from some of the more recent studies have been summarized in Table 3 and 4. As other authors also have noted, exposure data may not be directly comparable due to differences in workplace ventilation, sampling technique, etc. However, the tables reflect the general exposure level with the industrial hygiene standards that currently prevails in industrialized countries in the western world.

Table 3. Workplace concentrations of cobalt in various types of industries.

Industry	Process, work operation	Concentration [1] (mg Co/m^3)	Ref
Hard-metal [2]	Powder mixing	0.045-1.240	(9,134,167,
	Pressing	0.010-0.250	208,274,297)
	Dry grinding	0.003-0.210	
	Wet grinding	0.003-0.092	
Cobalt refinery	Roasting	0.030-0.070	(268)
	Leaching/reduction	0.004-0.025	
	Packing area	0.010-0.100	
Cobalt refinery	-	0.120 (0.001-7.800)	(307)
Cobalt foundry	Reduction	0.049	(17)
	Electrolysis	0.239	
	Grinding	1.05	
Production plant (cobalt-diamond circular saws)	Mixing room	0.135 (0.009-2.800)	(97)
	Oven room	0.015 (0.006-0.051)	
Production plant (sintered permanent magnets)	Various	0.018 (0.001-0.466)	(73)
Jewel	Diamond polishing	0.006-0.045	(315)
Porcelain	Plate decoration		(258)
	initial	0.800 (0.068-8.61)	
	after improving ventilation	<0.050	
Dental laboratory	Room concentration	0.005-0.010	(153)
	Polishing Co-Cr-alloys	<0.025-0.19	
Dental laboratory	Melting/refinishing	0.003-0.050	(185)
Welding (with stellite)	oxy-acetylene	0.004	(86)
	MAG-welding	0.161	

1) Figures are average values and range (in parentheses).
2) See Table 4 for details on individual studies

Exposure to airborne dust containing cobalt is well-characterized for several work operations in the hard-metal industry. Generally, it appears that exposure is highest for powder handlers and lowest for wet grinders and sinter workers (Table 4) (see also 23). The composition of the dust varies from process to process, but the fraction of cobalt usually ranges from 1.5 to 15% of the total dust (208). Isolated cobalt particles are found only in dust from the mixing room (167). The individual grains of the presintered cobalt powder are very porous and appear to be an agglomerate of smaller particles less than 1 or 2 µm in diameter (167, 210).

Table 4. Selected examples showing workplace concentrations of cobalt in relation to work processes in various hard-metal industries.

Industry, location Year of publication	Process	Concentration (mg Co/m^3)	Ref.
Hard-metal Sweden (1968-76) [1]	Mixing	0.06-1.24	(9)
	Pressing	<0.01-0.25	
	Dry grinding	0.003-0.034	
	Wet grinding	0.003-0.08	
Hard-metal Finland (1982)	Mixing	0.290 (0.12-0.43)	(167)
	Pressing	0.012 (0.008-0.015)	
	Forming	0.070 (0.05-0.10)	
	Grinding	0.150 (0.105-0.210)	
Hard-metal Japan (1985)	Mixing	0.186 (0.11-0.262)	(134)
	Automatic pressing	0.056 (0.009-0.210)	
	Forming	0.050 (0.008-0.144)	
	Wet grinding	0.056 (0.004-0.291)	
Hard-metal France (1989)	Mixing	0.045-0.272	(208)
	Pressing	0.030-0.220	
	Forming	0.060-0.160	
	Finishing	0.030-0.210	
Hard-metal USA (1992)	Grinding	0.017-0.120	(297)
Hard-metal Italy (1994)	Mixing/shaping	0.130-0.140	(274)
	Pressing	0.230	
	Grinding	< 0.050	

1) Figures are average values and range (in parentheses)
2) Year of study

Alexandersson and Bergman (9) reported on exposure levels in Swedish hard-metal industries and noted an improvement during the years from 1968 to 1976. Koponen et al (167) found that total dust levels in a hard-metal manufacturing plant in Finland ranged from 1.2 to 2.9 mg/m^3 and the cobalt content accounted for less than 1% to 10% of the dust. Average air cobalt concentrations in mixing, pressing, and grinding departments were 0.29, 0.012, and 0.15 mg/m^3, respectively. Exposure levels in the same range have been reported in a Japanese study of hard metal workers (134). In a more recent study from Japan (175), it was reported that 12% of the hard-metal workers were exposed to more than 0.05 mg Co/m^3 and 6.8% were exposed to more than 0.100 mg Co/m^3. The peak concentrations (short-term exposure levels) may be considerably higher than these values, as reported in a study from two American tungsten carbide producing plants (296). The average peak concentrations in one of the plants were as high as 32.5 mg Co/m^3 (range 0.044-438 mg/m^3, n=18) during weighing and mixing of

powder, and 16 and 32% of all air samples in the two plants exceeded 0.5 mg Co/m^3. With respect to wet grinding, it should be noted that cobalt is dissolved and accumulates in the coolants and workers may therefore also be exposed to cobalt in the ionized form both by dermal contact and by inhalation of aerosols (81, 288, 297).

Roto (268) monitored total airborne dust in a cobalt plant in Finland by using stationary samplers and analyzed the metallic content. In the roasting building (pyrometallurgical stage), cobalt concentration ranged from 0.03 to 0.07 mg/m^3 and in the leaching and reduction buildings (hydrometallurgical stage) the concentration ranged from 0.004 to 0.025 mg/m^3. In the packing area, cobalt in the air ranged from 0.01 to 0.1 mg/m^3. More recently, the exposure level has been assessed with personal samplers in a cobalt refinery in Belgium where cobalt salts, cobalt oxides and metallic cobalt powder is produced from scrap by using milling and hydrometallurgical purification (307). The average air concentration was 0.125 mg Co/m^3 (range 0.001-7.8 mg/m^3, n=82) and 25% of the values were higher than 0.5 mg/m^3. In a cobalt foundry in Germany, the average air concentration of cobalt ranged from 0.05 to about 1 mg/m^3 (17).

Exposure levels have also been recorded in a plant producing cobalt-diamond circular saws (97). The work operations included weighing and mixing of powder, cold pressing, heating and hot pressing. Airborne cobalt concentrations in mixing room and oven room were 0.135 mg/m^3 (range 0.009-2.8 mg/m^3, n=16) and 0.015 mg/m^3 (range 0.006-0.051 mg/m^3, n=7), respectively. In a plant producing sintered magnets, average breathing zone concentrations for various job processes was 0.018 mg Co/m^3 (range 0.001-0.466 mg/m^3, n=100), and 18% of the samples exceeded the OSHA permissible exposure level for cobalt (0.050 mg/m^3) (73).

Analysis of dust in small workshops where diamonds are polished with small abrasive disks made from micro-diamonds embedded in a cobalt matrix show air cobalt concentrations ranging from 0.006 to 0.045 mg/m^3 (n=7). This was about 100 times the values found when cobalt-containing disks were not used (315).

Ferri et al (86) measured cobalt exposure in welders using stellite. Air samples was taken in the breathing zone over the whole workshift. Average exposure levels during oxy-acetylene welding and gas-shielded arc welding were 0.004 mg Co/m^3 (n=5) and 0.161 mg/m^3 (n=7), respectively.

Raffn et al (258) reported on workplace concentrations of cobalt in Danish porcelain factories where cobalt blue dyes (cobalt aluminate or cobalt-zinc silicate) are used. The plate decorators were exposed to an average of 0.8 mg Co/m^3 (range 0.068-8.61 mg/m^3) and the OEL (0.05 mg/m^3) was exceeded between 10 and 50-fold in 9 out of 19 personal samples. After improving the exhaust ventilation the average concentration was below 0.05 mg Co/m^3 (see also 211). Surveillance of the cobalt concentration in the following years (1983-1991) showed average cobalt concentrations in the range of 0.022-0.035 mg Co/m^3 (372-593 nmol/m^3) (52).

Kempf and Peiffer (153) measured cobalt air concentrations in 40 dental laboratories in Germany. Stationary sampling in over one week in two

laboratories showed air concentrations ranging from 0.005 to 0.010 mg Co/m^3 with highest values in the middle of the week. During polishing of artificial dental crowns (cobalt-chromium alloys), 66 out of 79 personal samples had cobalt concentrations below 0.025 mg/m^3, 11 ranged from 0.025 to 0.1 mg/m^3, and two samples showed values higher than 0.1 mg/m^3. In a study from Italy, cobalt exposure in dental laboratories was in the range from 0.003 to 0.05 mg/m^3 (185).

5. Measurements and Analysis of Workplace Exposure

Determination of airborne particulate cobalt involves the use of stationary or personal air samplers equipped with appropriate collecting filters (cellulose ester membrane filters, polycarbonate membrane filters, cellulose fibre filters, or polystyrene filters) (230). For quantitative analysis of cobalt, atomic absorption spectrophotometry (AAS) appears to be the most popular and widespread method, although colorimetry, emission spectrometric methods, neutron activation analysis, and x-ray fluorescence also are used (82, 230). More recently, inductively coupled plasma atomic emission spectroscopy (ICP-AES) has been introduced (e.g. 73).

AAS has been used for analyzing cobalt in air samples as well as in biological samples (e.g. 6, 134, 176, 257). The method is sufficiently sensitive to determine the concentrations usually encountered in the working environment. A detection limit of 0.6 µg per sample has been reported (231), which corresponds to about 1 µg/m^3 using a flow rate of 2 l/min and a sampling time of 4 h. The detection limit for cobalt in urine analyzed by graphite furnace AAS with Zeeman background correction has been reported to be 0.001 µg/ml (297) or lower (36). With neutron activation analysis, a detection limit of 5 ng cobalt has been reported for 5 ml biological samples (181). (For details on air sampling and analysis of cobalt, see NIOSH Manual of Analytical Methods (231)).

In an interlaboratory study on the precision and accuracy of AAS, it was found that the mean air cobalt concentration was about 12% below a reference value, indicating that some of the sample is lost. Furthermore, the coefficient of variation was 45.5% for all 17 laboratories and 2-10% for replicate analyses within single laboratories (230). This variation should be kept in mind when comparing reported exposure levels.

6. Toxicokinetics

6.1. Uptake

The major route of absorption of cobalt in occupationally exposed humans is via the lungs. The fact that the concentration of cobalt in urine of hard-metal workers increases during the day and workweek, as well as the finding of a strong

correlation between cobalt in the breathing zone and in blood or urine, indicate that inhaled cobalt is rapidly absorbed from the lungs (4, 11, 307).

Animal studies have demonstrated that the dissolution and absorption of cobalt and cobalt compounds in the lungs depends on the physicochemical properties of the particles (particle size, porosity, solubility). In experiments where dogs were exposed to aerosols of cobalt nitrate and cobalt oxides (CoO, Co_3O_4) it was found that the amount absorbed decreased in the order cobalt nitrate, CoO and Co_3O_4, which is in accordance with differences in solubility of the compounds (25, 169). Furthermore, it was shown that the dissolution rate and absorption was inversely proportional to particle size (169). Similarly, ultrafine cobalt particles (20 nm) are 4-6 times more soluble in artificial lung fluid than "normal" sized particles (11 µm) and cobalt accumulated in the lungs of rats is rapidly transferred to the blood (177). In Syrian golden hamsters, it was found that the majority of inhaled CoO was absorbed within 3-4 days after inhalation exposure (319).

Gastrointestinal absorption has been studied in humans given oral doses of cobalt chloride. The amount of cobalt absorbed varies considerably: values ranging from 1% to almost 50% have been reported (291, 314). Absorption is reduced when cobalt is administered after a meal or if cobalt chloride has been equilibrated with serum albumin before administration (243). In contrast, absorption of cobalt is significantly increased in patients with iron deficiency (314). The gastrointestinal absorption of cobalt chloride and cobalto-cobaltic oxide has recently been studied in human volunteers (53). The uptake of the soluble cobalt chloride was considerably higher than the insoluble cobalt oxide and the absorption was significantly higher in females compared to males.

Animal experiments have shown that cobalt crosses the intestinal mucosa rapidly and that absorption mainly takes place in the proximal part of the small intestine (46, 277). In experiments with rats, it was found that the absorbed dose was 28.9% and 33.5% for cobalt(II) chloride and cobalt(III) chloride, respectively, and the amount absorbed decreased when cobalt was administered together with histidine, lysine, or EDTA (309). In contrast, absorption was increased when cobalt was administered in milk. As in humans, iron deficiency significantly increases cobalt absorption (277). Cobalt nitrate is also absorbed to a great extent in the gastrointestinal tract, whereas only a small fraction (0.5-5%) of orally administered cobalt oxides is absorbed (169, 319).

Absorption of metallic cobalt through the skin has been demonstrated in an experiment where four subjects were exposed by putting their right hand into a box filled with hard-metal powder (5-15% cobalt) or waste powder for a period of 90 min (274). The concentration of cobalt in urine samples taken after the exposure was up to 10-fold that in pre-exposure samples. In experiments with guinea pigs, it was found that absorption of cobalt from an aqueous solution of cobalt chloride (2 ml, 0.24 M) applied to the skin was sufficiently large to cause death in about half of the animals within 11 days (316). (For information on the permeability coefficient, the reader is referred to the recent review by Hostynek et al (130)).

6. 2. Distribution

The overall picture from *in vitro* experiments and animal studies is that cobalt binds to serum proteins (particularly the albumin fraction) and subsequently accumulates in the liver, kidney, heart, and pancreas (39, 46, 59, 78, 90, 106, 183, 293, 299). Autoradiographic studies after intravenous administration of cobalt have shown that there is no detectable uptake by the CNS, except for the choroid plexus (46, 90, 293). Other studies have also demonstrated that the fraction of the administered dose found in the brain is very small the first hours or the first few days after intravenous injection of cobalt (59, 106). However, the tissue distribution appears to vary both with the route of administration, dose, and duration of the experiment (78).

Whole-body autoradiographic studies in pregnant mice have shown that cobalt (cobalt chloride) administered intravenously accumulates in cartilaginous structures of the mother and in the fetal skeleton (90, 293). It was also found that the cobalt content in the maternal myocardium 16 days after intravenous injection was twice that in the liver. In inhalation experiments where dogs were exposed to cobalt oxides, relatively high concentrations of cobalt were also detected in skin, bones and cartilaginous structures (25, 169).

Studies of trace metals in normal human tissue has shown relatively high concentrations of cobalt in liver, kidney, heart, and spleen, whereas low concentrations are found in serum, brain and pancreas (245, 328). In experiments where radioactive cobalt chloride was administered intravenously, the concentration of cobalt in the liver was 8-fold higher than the average whole-body concentration 3 hours after the injection, and elevated activity was recorded in the liver even after 1000 days (291). Post mortem analysis of tissue from patients with cobalt-chromium prostheses also suggest that cobalt is concentrated in the liver, heart and kidney (209). Furthermore, relatively high concentrations of cobalt has also been found in the heart of cases with cardiomyopathy that has been caused either by excessive consumption of cobalt-containing beer (303) or by industrial exposure to cobalt (24, 135, 154).

In vitro studies with cobalt and hard-metal dust have shown that cobalt is more soluble in lung homogenate and plasma than in physiological saline. At the subcellular level, cobalt is particularly located in the lung cytosol, where 56% is associated with low molecular weight components and 34% is associated with proteins. The high fraction associated with low molecular weight components, which are considered diffusible, may explain the low concentration of cobalt in the lung of some cases with hard-metal lung diseases (79).

Together, these studies show that absorbed cobalt is rapidly distributed in the body and accumulates particularly in the liver, kidney, and heart.

6.3. Elimination

Absorbed and intravenously administered cobalt is predominantly eliminated by urinary excretion (46, 60, 64, 78, 106, 155, 184, 240, 291). Biliary excretion

accounts only for 4-14% of the administered dose (i.v. injection) in animal studies (46, 54, 184). However, the amount eliminated in the faeces may be lower due to reabsorption of cobalt in the intestine (54). The faecal excretion rate in dogs inhaling mixed cobalt oxides or cobalt nitrate was one order of magnitude less than urinary excretion (169).

Urinary cobalt has been monitored in Swedish hard-metal workers (4,6). The concentration of cobalt decreased rapidly during the first 24 h in periods off work, which indicates rapid excretion. The fast, initial decline was followed by a more long-lasting, slow decrease in the cobalt concentration. Urinary cobalt in the workers were still higher than control values after 4 weeks holiday. Elevated urinary cobalt levels were also found in a case of hard-metal pneumoconiosis 4 months after exposure had ceased (70). Recent studies with cobalt exposed workers and subjects without occupational exposure to cobalt indicate that urinary excretion occurs more rapidly in persons without a history of cobalt exposure (221).

Experiments with oral or intravenous administration of cobalt chloride in humans have shown that an average of 22% of the dose is eliminated in the first days urine, and elimination via faeces constitutes on average only 20% of the amount excreted by the kidneys (291). Furthermore, whole-body clearance after oral or intravenous administration of cobalt chloride follows a multiexponential curve. The biological half-life for the fast, initial component in two subjects ranged from 0.37 to 0.71 d and that of the long-term (4^{th}) component was about 800 d (291). In a case of a worker who accidentally ingested radioactive cobalt chloride, the biological half-lives for the fast, intermediate and slow component of the whole-body clearance curve were 0.47 d, 2.7 d, and 59 d, respectively (220). Urinary excretion varies considerably among individuals and is usually increased in fasting subjects and in subjects with iron deficiency (243, 292). Furthermore, there is evidence that females excrete cobalt much faster than males (53).

The concentration of cobalt in lung tissue from cases with hard-metal pneumoconiosis is often low or within normal limits (e.g. 63, 67, 164, 203, 239, 270), which suggests that elimination from the lungs is rapid. Animal experiments have shown that the majority of inhaled metallic cobalt and soluble cobalt compounds (CoO, $Co(NO_3)_2$) is removed from the lung and excreted within few days (96, 169, 319). For example, in rats exposed to ultrafine cobalt particles, the biological half-life for the fast and slow component of the lung clearance curve was 53 h and 156 h, respectively, and 75% of the initial lung burden was eliminated within the first 3 days (177). Similarly, all cobalt oxide (CoO) was essentially eliminated from the lung 6 d after inhalation exposure in Syrian golden hamsters (319). In contrast to the more soluble cobalt compounds, inhaled Co_3O_4 is cleared more slowly (25, 169).

A series of studies on animals and human volunteers have documented large interspecies differences in clearance of Co_3O_4. Larger animals were found to have slower lung clearance than the smaller rodents and clearance was also shown to be age-dependent (22, 58, 168). The biological half-life for clearance of 0.9 μm

Co_3O_4 particles was 240 d for the baboon, 90 d for dogs, and 35 d for rats. In humans, only about 50% of the initial lung burden was cleared six months after exposure (91).

Data from humans with accidental inhalation exposure to ^{60}Co (and its oxide), have shown half-lives for long-term lung clearance in the order of 664 d to 17 y (124, 228). Interpretation of these studies is, however, complicated by the fact that the nature of the inhaled compounds was not established.

7. Biological Monitoring

Some of the studies on cobalt in blood and urine have been summarized in Table 5. In individuals without occupational exposure to cobalt, the concentration of cobalt in the blood ranges from 0.2 to 1.9 µg/l and urinary cobalt levels range from 0.3 to 2 µg/l. The individual variation is considerable and smokers tend to have higher concentrations than non-smokers, which is due to cobalt in tobacco (6, 11). In subjects with occupational exposure to cobalt, both urinary and blood cobalt levels are markedly elevated. Exposed smokers, again, have higher urinary cobalt concentrations than similarly exposed non-smokers (4).

Several studies have shown a correlation between cobalt in urine (or blood) and airborne cobalt in the work environment (6, 11, 97, 134, 297, 307). For example, in a large Japanese study of 175 hard-metal workers (134), the correlation coefficient for cobalt in blood vs. air was 0.96 ($P < 0.001$) and that for cobalt in urine vs. air was 0.99 ($P < 0.001$). Using the data in this study, an average exposure level of 0.050 mg/m^3 (current Danish OEL) results in a urinary cobalt concentration of 34.4 µg/l. This value agrees reasonably well with those reported in other studies (e.g. 4, 297). Some studies, however, have failed to demonstrate a clear relationship between airborne cobalt and cobalt in the urine (208, 274, 275). The degree of correlation appears to depend on which time during the workweek blood samples are taken (276). Furthermore, lack of correlation between urinary and air cobalt levels has been explained by significant cutaneous absorption of cobalt in dusty workplaces (274).

Obviously, blood and urinary cobalt levels are also likely to depend on the nature of the cobalt compounds that the workers have been exposed to. This seems to be supported by the fact that plate decorators exposed to insoluble cobalt blue (cobalt aluminate) have normal urinary cobalt levels, whereas those exposed to semi-soluble cobalt blue dye (cobalt-zinc silicate) have 10-fold higher urinary cobalt levels (257). Moreover, Lison et al (195) have recently demonstrated that there is no significant correlation between air cobalt concentration and urinary or blood cobalt in workers exposed to cobalt oxides. By contrast, there was a very good correlation between the concentration of cobalt in the air and cobalt in urine and blood for workers with exposure to cobalt metals, salts, and hard metals.

Since urinary cobalt declines rapidly when exposure ceases (4, 6, 276), the concentration in urine samples taken at the end of the workshift appears to be a good indicator of current exposure level.

Table 5. Urinary and blood cobalt levels (mean ± SD) in subjects with or without occupational exposure to cobalt.

Study group	Air Co level (mg/m^3)	Urinary Co (µg/l)	Blood Co (µg/l)	Ref
Hard-metal workers:				
Powder handlers	0.186 ± 0.108	148 ± 14	10.8 ± 0.3	(134)
Wet grinders	0.092 ± 0.092	68 ± 87	4.3 ± 3.9	
Shapers	0.050 ± 0.035	41 ± 60	5.2 ± 3.1	
Sinter workers	0.028 ± 0.030	10 ± 10	2.6 ± 1.0	
Hard-metal workers:				
Non-smokers	0.06	35 ± 64		(4)
Smokers	0.06	52 ± 64		
Non-smokers	0.005-0.01	17 ± 83		(4)
Smokers	0.005-0.01	38 ± 68		
Hard-metal workers:				
Wet grinders	0.055	34 ± 7		(297)
Dry grinders	0.021	12 ± 6		
Cobalt foundry workers:				
Grinders	1.05	438	47.9	(17)
Electrolysis	0.239	113	18.6	
Reduction	0.049	19	4.9	
Plate decorators	0.050	77 ± 177	2.2 ± 3.7	(258)
Office workers	-	2 ± 1	1.9 ± 1.1	(134)
Office workers:				
Non-smokers	-	0.3 ± 0.5	0.5 ± 0.3	(4,11)
Smokers	-	0.6 ± 0.5	0.5 ± 0.3	
Unexposed controls	-	0.9 ± 2.2	0.2 ± 0.1	(258)

Note: The study groups have been exposed to different types of cobalt componds, e.g. metallic Co (hard-metal workers, cobalt foundry workers), cobalt blue dyes (plate decorators), and unspecified cobalt compounds (foundry workers).

While cobalt in blood and urine may reflect recent exposure, it has been suggested that the concentration of cobalt in hair and nails could be used as an index of exposure in past periods (30, 70, 135). For example, the cobalt concentration in pubic hair and toe nails of a case with hard-metal pneumoconiosis was 4,200 ng/g and 31,560 ng/g, respectively (normal values: 420 and 25 ng/g) (70). However, the reliability of these values is questionable due to the possibility of direct surface contamination.

8. Mechanism of Toxicity

Cobalt appears to affect several biochemical processes through interference with macromolecules and enzyme systems. Cobalt may also compete with other metal ions for absorption from the gastrointestinal tract, thereby producing deficiency of essential elements. Liver and kidney tissue from rats and mice treated with cobalt show marked depression of respiratory activity (68, 75), and isolated mitochondria from the heart have decreased ability to oxidize fatty acids and pyruvate (321). This action may be due to complex formation between the cobalt ion and sulfhydryl groups of dihydrolipoic acid, the coenzyme required for oxidative decarboxylation of pyruvate and alpha-ketoglutarate (2, 3,75, 317). However, cobalt does not invariably inhibits all —SH enzymes (187).

It has also been documented that cobalt has an indirect effect on cytochrome P-450 catalyzed reactions by inhibiting heme biosynthesis (inhibition of ALA synthetase activity) and inducing heme degradation (induction of heme oxygenase) (19, 51, 201, 284). In contrast to the findings in acute experiments, there is evidence that long-term administration of cobalt salts may produce an increase in the cytochrome P-450 and heme content in the liver (149). Cobalt ions have also been found to oxidize cellular glutathione and they are able to produce reactive hydroxyl-like species in the presence of hydrogen peroxide (188, 198). Moreover, there is ample evidence that cobalt interferes with DNA replication and repair (e.g. 13, 102, 117, 205, 311).

The mechanism of cobalt-induced lung injuries (hard-metal lung diseases) is poorly understood. It has been suggested that the chronic inflammatory response as well as the systemic changes (weight loss) is due to cobalt-induced release of a tumour necrosis factor from sensitized mononuclear cells in the lung (265). Furthermore, it is also possible that the pulmonary toxicity of cobalt may be related to oxidative stress resulting from generation of reactive oxidant species from endogenous hydrogen peroxide (226). Hard-metal asthma appears to involve both immunologic and nonimmunologic mechanisms (286).

There appears to be several factors affecting the toxicity of cobalt. Animal experiments with inhalation of different soluble metal salts suggest that the specific pulmonary effects of cobalt (formation of type II cell noduli with secondary effects on alveolar macrophages) are potentiated by simultaneous exposure to nickel or chromium (139-141).

Results of intratracheal implantation experiments in rats indicate that the pulmonary toxicity of cobalt is enhanced by simultaneous instillation of tungsten carbide (180). This is supported by *in vitro* studies showing increased solubility of cobalt in the presence of tungsten carbide and higher cytotoxic potential of tungsten carbide-cobalt mixtures compared to cobalt metal alone (196, 197).

Epidemiological studies have shown that the combination of smoking and exposure to cobalt increases the frequency of respiratory symptoms and also appears to affect respiratory function more severely than cobalt exposure alone (5, 73, 307).

In vitro experiments have shown that pretreatment of cells with zinc induces formation of cytosolic metallothionein (metal-binding protein), which effectively protects against the cytotoxicity of cobalt (199).

Dietary amino acids and proteins protects against the acute oral toxicity cobalt salts (320). Furthermore, the cardiotoxic effects of cobalt are much more severe in protein deficient animals (266).

9. Effects in Animals and *in Vitro* Studies

9. 1. Acute toxicity

The acute oral toxicity of cobalt and cobalt compounds is generally low (190, 300). The lowest observed lethal doses after oral administration of metallic cobalt range from 750 mg/kg in rabbits to 1500 mg/kg in rats (190). In a comparative study with several cobalt compounds (cobalt fluoride, cobalt oxide, cobalt phosphate, cobalt bromide, cobalt chloride, cobalt sulphate, cobalt nitrate and cobalt acetate) the oral LD-50 values in rats ranged from 150 mg/kg to 708 mg/kg. However, when calculated on the basis of the cobalt ion, the values were roughly identical for all compounds (294). The oral LD-50 value for cobalt naphthenate in rats has been reported to be 3.9 g/kg (264).

In experimental animals acute poisoning is manifested by diarrhea, cutaneous vasodilatation, edema, decline in body temperature, tremors, progressive loss of muscular tone, and shock (69, 112, 294, 300, 320). Post mortem histopathological findings in rats include hyperemia (liver and kidneys), hemorrhage and edema (294).

Metallic cobalt powder introduced by intratracheal injection in rats and guinea pigs has proven to be acutely toxic by producing pneumonitic changes, pulmonary edema and hyperemia (69, 278). Similarly, rats and other animals exposed by inhalation to high concentrations of cobalt dust for a few hours were found to have considerable edema of the lungs with multiple hemorrhages (112). Pulmonary edema and congestion have also been observed in rats exposed for 3 hours to aerosols containing cobalt chloride (131).

9. 2. Short-term inhalation exposure

The effect of short-term exposure to ultra-fine cobalt particles (2.7 mg/m^3 for 5 h; or 2.1 mg/m^3, 5 h/d for 4 d) has been studied in rats (177). The exposed animals showed airway inflammation with hypertrophy and proliferation of bronchiolar epithelium and damage to cilia. Lung tissue responded with inflammation, interstitial edema, ballooning of type I cells, and proliferation of fibroblasts and type II cells. The histological changes were, however, reversible within 28 days.

9. 3. Long-term inhalation exposure and intratracheal administration studies

Intratracheal instillation and long-term inhalation experiments have particularly been performed in order to establish the role of cobalt in hard-metal interstitial lung fibrosis. It appears from experiments made in the fifties that cobalt and cobalt containing hard-metal dust induce various lung changes whereas pure tungsten carbide is comparatively inert.

Histopathological observations of the lungs of guinea pigs, 12 months after intratracheal injection of cobalt powder (2 successive doses of 5 mg, or a single dose of 25 or 50 mg) revealed interstitial cellular infiltration, clusters of multinucleate cells, proliferation of lymphoid tissue, and some fibrotic changes in alveolar septae and around larger blood vessels (278). More or less similar changes, as well as hyperplasia and metaplasia of bronchial epithelium, have been observed in guinea pigs up to 12 months after instillation or inhalation of tungsten carbide-cobalt dust mixtures (279). In contrast, the histological changes observed after intratracheal injection of pure tungsten carbide in rats were small and comparable to that of inert dust (180, 212).

More recent experiments with intratracheal implantation of hard metal dust in rats seem to confirm the previous findings in guinea pigs, although the reaction in the rat is less severe (165). Furthermore, it appears that tungsten carbide may enhance the pulmonary toxicity of cobalt as seen in the implantation experiments with rats by Lasfargues et al (180). They found that cobalt (10 mg/kg) produced a moderate inflammatory response, whereas an identical amount together with tungsten carbide produced severe alveolitis and fatal pulmonary edema. Tungsten carbide alone induced only a mild macrophage reaction with no edema. These experiments are supported by *in vitro* studies with alveolar macrophages which show that mixtures of tungsten carbide and cobalt are more cytotoxic than cobalt alone and that pure tungsten carbide is not cytotoxic (196).

Experiments where miniature swines were exposed to cobalt dust (0, 0.1, and 1.0 mg/m^3, 6 h/d, 5 d/w) for 3 months have demonstrated a dose-related decrease in lung compliance, and ultrastructural observations revealed thickening of alveolar septae with marked deposition of collagen (156). In addition to the respiratory effects, there was evidence of effects on the heart (decline in the QRS voltage in ECG recordings). Inhalation of cobalt oxide in hamsters (10 mg/m^3, 7 h/d, 5 d/w) for the entire life span has also been shown to give rise to lung fibrosis with hypertrophy and hyperplasia of the alveolar epithelium (318).

Lung changes can also be induced by inhalation of soluble cobalt aerosols. For example, exposure of rabbits to cobalt chloride (0.4-2 mg/m^3, 6 h/d, 5 d/w, for 4-6 weeks or 14-16 weeks) produces interstitial inflammation of the lung and hyperplasia and nodular accumulation of type II cells, as well as an increase in macrophages, fibronectin content, and lysozyme activity in lavage fluid from the lungs (31, 44, 138, 139, 142, 144, 145). Experiments with guinea pigs suggest that animals which have been sensitized by dermal contact to cobalt have different lung tissue reactions to inhaled cobalt chloride than non-sensitized animals (43). In contrast to the experiments with cobalt chloride, no effects could be seen on

alveolar macrophages after exposure of rabbits to metallic cobalt (0.2 and 1.3 mg/m^3, 6 h/d, 5 d/w, 4-6 w) (143).

Bucher et al (38) exposed rats and mice to aerosols of cobalt sulphate heptahydrate (0, 0.3, 1.0, 3.0, 10, and 30 mg/m^3)[1], 6 hours daily, 5 days per week for 13 weeks. The most significant effects in the respiratory system at the low exposure levels (0.3 and 1.0 mg/m^3) were inflammation and squamous metaplasia of the epithelium in the larynx and inflammation and histiocytic infiltration in the lung. Both rats and mice in the high-dose groups (10 and 30 mg/m^3) showed inflammation of the nose, degeneration of the olfactory epithelium, ulcers and inflammatory polyps in the larynx, lung fibrosis, and hyperplasia of alveolar epithelium. In addition to the respiratory effects, hematological changes (increased hematocrit and decreased platelet number) were seen in the high-dose groups of rats. Female rats in the two high-dose groups also showed increased triiodothyroxin levels. The cardiomyopathy seen in some of the rats exposed to 30 mg/m^3 was not considered treatment-related, since this was also observed in the control group. No consistent dose-related changes were seen in hematology of mice.

Exposure of rabbits to cobalt fumes (1.5 mg/m^3, 6h/d, 5d/w) for up to 24 weeks did not produce changes in red blood cell counts, hemoglobin, and hematocrit (301). However, the animals showed changes in serum proteins (increase in total protein and alpha globulin fraction).

9. 4. Toxic effects after oral, i.v., and i.p. administration

This section summarizes the various organ effects seen in animal experiments with oral dosing (gavage studies, feeding studies), intravenous (i.v.) administration, and intraperitoneal (i.p.) administration. While effects on the respiratory system are dominating in inhalation experiments, systemic administration produces toxic effects particularly in the heart, blood-forming organs, and in the thyroid gland.

9. 4. 1. Cardiovascular system

Degenerative heart lesions comparable to those in humans have been produced in several animal species by administration of cobalt salts. The pathological changes, which varies somewhat between species, are characterized by findings such as pericardial effusion, loss of striation, dissolution of myofibrils, intracellular vacuoles, increase in lipid content, and focal fibrosis without inflammatory cells (74, 107, 110, 192, 215, 266, 273). Furthermore, ECG recordings show lowered amplitude or complete loss of the QRS complex (215, 273). These changes have been observed in rats and guinea pigs after oral administration of cobalt sulfate (usually 20-25 mg/kg/d for 2-8 w), in rats after intraperitoneal injection of cobalt nitrate (5 mg/kg, 7 doses), and in rabbits after subcutaneous injections of cobalt chloride (15-25 mg/kg/d). At the ultrastructural level, cardiac cells are charac-

[1] equivalent cobalt concentrations: 0, 0.11, 0.367, 1.1, 3.67, 11.0 mg Co/m^3.

terized by fragmentation and loss of myofibrils, abnormal mitochondria, multivesicular vacuoles, and dilatation of sarcoplasmatic reticulum (110, 192, 215). Some of these changes develop few hours after the first dose as seen in experiments where cobalt nitrate was administered intraperitoneally (5 mg/kg) to rats (192). Accumulation of cobalt in the heart muscle as well as cardiomyopathy is aggravated by protein deficiency (266, 320).

In contrast to these findings, light microscopy revealed no abnormalities in pigs' myocardium after oral administration of cobalt (as cobalt chloride) in doses of 20 mg/kg/d for 6 weeks (39). Furthermore, Pehrsson et al (250) measured several hemodynamic parameters in rats given oral doses of cobalt sulfate (40 mg/kg/d) for 8 weeks, but they were unable to demonstrate any disturbances in cardiac function. This was in spite of a 30-fold increase in the cobalt concentration in the heart of the dosed animals.

9. 4. 2. Blood and blood-forming organs

It is well documented that administration of cobalt chloride results in increased red blood cell number, hemoglobin concentration and hematocrit in experimental animals (e.g. 37, 128, 283, 312). This effect appears to be mediated by increases in renal erythropoietin factor activity and plasma erythropoietin (290). Experiments with rats have shown that cobalt chloride (2.5-10 mg/kg/d for up to 32 w) produces considerable hyperplasia of the bone marrow as well as structural changes in the malpighian corpuscles of the spleen (128). However, the effect on the spleen may be secondary to the cobalt-induced polycythemia. The increased red blood cell number and hemoglobin concentration seen after cobalt chloride administration in rats were not accompanied by increased hemolysis or blood volume (312).

Administration of cobalt chloride has also been shown to induce marked elevations in plasma lipids (total fatty acids, triglycerides, cholesterol, lipid phosphorous) as well as increases in alpha globulin fractions and total serum proteins (301, 329). Furthermore, the alpha-helix component of fibrinogen from rabbits treated with cobalt is increased by about 30% compared to fibrinogen from untreated animals (87).

9. 4. 3. Thyroid gland

The effect of cobalt on the thyroid gland in animal experiments appears to be variable. Kriss et al found that intraperitoneal injection of cobalt chloride (0.2- 2.8 mg) in chickens produced dose related suppression of ^{131}I uptake without colloid depletion (171). Thyroid hyperplasia and colloid depletion have been observed in guinea pigs given cobalt chloride (8 mg/kg/d, i.p.) for 30 days (18). In contrast to these findings, addition of cobalt chloride to the drinking water in concentrations sufficient to induce polycythemia did not produce inhibition of ^{131}I uptake in rats (283). No treatment-related changes were found in histopathology of the thyroid from guinea pigs given repeated subcutaneous injections of cobalt chloride (20 mg/kg, variable number of doses) for up to 70 days (74).

9.4.4. Liver, pancreas and kidneys

The effects of cobalt alone or in combination with alcohol have been studied in guinea pigs (74). The animals were given cobalt chloride by subcutaneous injections in doses of 20 mg/kg three times weekly for 24-70 days ("low-dose") or as injections every other day for two weeks and then daily for another four days ("high-dose"). In the low-dose group, the animals showed fatty degeneration in the periphery of liver lobuli and vacuolation of cells in the center. In the high-dose group, there were necrotic changes in the liver. Liver changes consisting of venous congestion together with an increased number of lipid droplets or atrophy of hepatocytes have also been observed after administration of cobalt chloride in rabbits (15-25 mg/kg/d, s.c. for 9-13 days) and in dogs (28 mg/kg/d, i.v. infusion twice weekly for 10 weeks) (110, 273).

Dogs receiving cobalt chloride (10-13 mg/kg, single i.v. injection) show an acute increase in the blood glucose level and selective autolysis of alpha cells in the pancreatic islets (182). Similar changes have been seen in guinea pigs after intraperitoneal injection of cobalt chloride (33). In a study on rats, single injections of cobalt chloride (20, 35, 40 or 45 mg/kg) also produced increases in the blood glucose level (dose dependent), but no pathological changes were seen in the pancreatic islets, except for a slight increase in nuclear area of the beta cells (132). In addition to the effects on the pancreatic islet, severe damage has also been found in the exocrine part of pancreas after subcutaneous or intraperitoneal injection of cobalt chloride in guinea pigs (33, 74). The observed damage consisted of atrophy of acini, dissociation of cells, and focal necrosis.

There is comparatively little information on effects of cobalt on the kidneys. In the experiments in which cobalt chloride was administered to dogs by intravenous infusion, the kidneys were found to be congested and there were signs of hydropic degeneration (273). Some metabolic parameters in renal tissue may also be affected by the presence of cobalt ions as seen in experiments with isolated rat glomeruli (310).

9. 4. 5. Other organs

In animal experiments it has been found that oral administration of cobalt chloride in doses of 20 mg/kg/d (but not at 5 mg/kg/d) for 69 days may affect operant responding (lever pressing) in rats (225). Furthermore, *in vitro* electrophysiological studies have documented that cobalt affects neuronal function (83, 172, 323).

9. 5. Mutagenicity and genotoxicity

With a few exceptions only *soluble* cobalt(II) compounds have been investigated for genotoxic and mutagenic effects. There are two reports dealing with the insoluble cobalt(II) sulphide (61, 262), and one report dealing with cobalt blue (34). No information is available on the mutagenicity of metallic cobalt and cobalt oxide.

9. 5. 1. Effects in bacteria

Bacteria have been considered as insensitive to the genotoxic effect of cobalt and other metallic compounds. The insensitivity of bacteria has been explained by the lack of bioavailability or uptake into the cell since cobalt and other metals may precipitate with phosphates or other compounds in the culture media thereby rendering them inactive in toxicity and mutagenicity test.

The results from mutagenicity tests of soluble cobalt(II) salts in bacteria are inconsistent. The genotoxic response of these compounds depends on the test organisms, the strain, and the experimental conditions (34). Several negative results in the *Salmonella*/microsome assay with cobalt concentrations up to 1 mM/plate have been reported (20, 214, 236, 237, 313) (see also 133 for review). In these negative assays different test conditions were used (spot test, standard plate assay and fluctuation test), and in one study trimetaphosphate was used instead of orthophosphate to prevent precipitation of cobalt phosphate (20), but no positive mutagenic effect was found. The following test strains were used in these studies: TA98, TA100, TA1535, TA1537. In another study (325), cobalt was found mutagenic to the frame shift *Salmonella* strains TA98 and TA1537 without addition of S9 mix, but not with addition of S9 mix.

In two recent studies, cobalt chloride was found mutagenic in *Salmonella typhimurium* under modified test conditions using the frameshift strain TA97a (34, 242). When the preincubation assay was used, cobalt chloride was much more mutagenic than in the standard plate assay (also with standard phosphate buffer). Other metal salts have also been detected as mutagens when the phosphate buffer was replaced with deionized water or Hepes buffer (242). These two studies show that metals *can* be detected as mutagens in bacteria when proper test conditions and test strains are used. On the other hand, cobalt chloride was found inactive in the lambda prophage induction test in *E. coli* $WP2_S(\lambda)$ (267). Conflicting results have also been found with soluble cobalt salts in the *Bacillus subtilis* rec +/- growth inhibition test (150, 232). In the study with positive results, a preincubation procedure was used.

Cobalt form complexes with biological heteroaromates like histidine (40), adenine (194), 9-aminoacridine, harman, and norharman (236). In addition, cobalt(II) salts has a comutagenic effect on several mutagenic and non-mutagenic heteroaromatic compounds in the frameshift strains TA1537 and TA2637 of *S. typhimurium* (235, 236, 238). In these studies modified test media without phosphate were used. Cobalt(II) chloride have also been shown to have an antimutagenic effect on recognized mutagens like N-methyl- N'-nitro-N-nitrosoguanidine (MNNG) in *E. coli* and on Trp-P-1 in *S. typhimurium* (148, 214).

In a recent study it was concluded that cobalt chloride can act either as an inhibitor or as an inducer of the SOS repair functions in *E. coli* depending on the experimental conditions (186). When cobalt chloride act as an inhibitor of the SOS system, by blocking the protein synthesis, it is also antimutagenic to UV-induced mutagenesis. However, these results were obtained only when the metal

was present during the experimental period. When *E. coli* cells were treated with cobalt chloride for a short period of time, induction of the SOS system was seen.

Only one study on the genotoxic effect of *insoluble* cobalt compounds in procaryotes has been reported (34). In this study, cobalt blue used in the Danish porcelain industry was tested in different strains of *S. typhimurium* in a modified standard plate assay at Co concentrations up to 110 µg/plate. Phosphate buffer was replaced with an acetate buffer (pH=5) in order to dissolve the cobalt blue dye. Cobalt blue was found more mutagenic in TA97a than equimolar concentrations of soluble cobalt chloride under the same test conditions. Furthermore, adenine was antimutagenic to cobalt blue (equimolar concentrations).

9. 5. 2. Effects in yeast

Cobalt chloride is a potent inducer of respiratory deficiency (mitochondrial mutations) in yeast cells (80, 160, 193, 256). In growing, but not in stationary *Saccharomyces cerevisiae* D7 the water insoluble cobalt blue (34) and the soluble cobalt chloride induce point mutations (34, 159). Moreover, cobalt chloride induced gene conversion in growing *S. cerevisiae* D7 cells (34, 159) as well as an increase (not statistically significant) of aneuploidy in *S. cerevisiae* D61M (34).

9. 5. 3. Effects in plants

Various cobalt compounds (cobalt chloride, cobalt nitrate, cobalt sulfate) have been shown to have an effect on the chromosomal structure and cell division in root tips of *Vicia faba* (125, 166), and chromosomal aberrations and aneuploidy have been observed in *Allium cepa* (105).

9. 5. 4. Mammalian cells

Soluble cobalt(II) salts have been studied in many mammalian test systems. Cobalt induced DNA strand breaks in mammalian (HeLA) cells. The induction is time-dependent, with the highest number of breaks after 4 h incubation at a concentration as low as 50 µM $CoCl_2$ (117). In Chinese Hamster Ovary (CHO) cells, DNA strand breaks were also induced at a 2000 µM cobalt chloride concentration (111). McLean et al (205) also found DNA strand breaks in human white blood cells by using Fluorescence Analysis of DNA Unwinding at a low cobalt chloride concentration (50 µM). Cobalt chloride induced point mutations at the HPRT locus in V79 Chinese hamster cells with a 4.2-fold increase in spontaneous mutation frequency at 100 µM (117). A smaller increase (2.3-fold) was found in the same cell type (V79 Chinese Hamster cells) with 0.2 mM cobalt chloride by using 8-azaguanidine resistant mutants as marker for point mutations. Cobalt chloride failed to induce trifluorothymidine-resistant mutants in L5178Y/TK cells (14). (The short incubation time of 3 h should be noted compared to 20 h incubation time in the positive study of Miyaki et al (213)). Cobalt(II) salts caused a dose-dependent inhibition of DNA synthesis in phytohemagglutinin (PHA) stimulated human peripheral blood lymphocytes (311). Soluble cobalt compounds have also been found to be weak inducers of

6-thioguanine-resistant colonies in FM3A cells (mouse mammary carcinoma cells) (219).

Although cobalt chloride is a strong inducer of micronuclei in human lymphocytes, only a weak clastogenic effect (or no effect) was observed with human fibroblasts, leucocytes and lymphocytes (45, 247). These results indicate that cobalt chloride may induce aneuploidi in isolated human cells (45).

Cobalt(II) acetate enhanced viral transformation in Syrian hamster embryo cells (49), and cobalt(II) chloride and acetate have been found to induce sister chromatid exchanges (SCE) in Chinese hamster V79 cells. Moreover, these compounds have an enhancing effect on UV-induced SCE and mutations at the HPRT locus in mammalian cells (118). Data from this study also indicate that these genetic effects are due to an interaction with DNA excision repair rather than a direct DNA damaging effect (118). However, in another study, cobalt chloride had an antimutagenic effect on 8-azaguanine resistant mutations induced by gamma-rays in Chinese hamster V79 cells, and no effect was seen on UV-induced mutations (327).

Two studies on water *insoluble* cobalt sulphide showed that crystalline, but not amorphous cobalt sulphide is phagocytized by Chinese hamster ovary (CHO) cells and Syrian hamster embryo cells in a concentration-dependent fashion. The crystalline form of cobalt sulphide induced strand breakage and cell transformation (61, 262).

9. 5. 5. Effects in vivo

The genotoxic effect of cobalt chloride on somatic and germ cells was investigated in male hamsters. Ten male Syrian hamsters were given seven intraperitoneal injections of cobalt chloride over 9 days (total dose of 0.4 g/kg). The treatment induced a statistical significant increase of aneuploidi in both somatic and germ cells compared to 13 control animals (84).

The ability of cobalt chloride to induce chromosomal aberration in mice *in vivo* was studied by Palit et al (244). Cobalt chloride was administered orally to mice at doses of 20, 40 and 80 mg/kg body weight (corresponding to 2.5, 5 and 10% of the predetermined LD-50). The frequency of chromosomal aberrations was observed after 6, 12, 18 and 24 hours. Five test animals were used per set (time and dose) together with 5 control animals in each group. A statistically significant increase was found in chromosomal aberrations (both including and without gaps) and in the number of chromosomal breaks per cell, and there was evidence of dose-response relationship.

In a recent study the effect of cobalt on the induction of micronuclei by other mutagens was studied *in vitro* and *in vivo* (305). Cobalt chloride up to 50 µg/ml did not induce a statistically significant increase in micronuclei *in vitro* either with or without S9 mix. *In vivo*, cobalt chloride (25, 50 and 90 mg Co/kg) induced a dose-dependent and statistically significant increase in micronucleated polychromatic erythrocytes (MPCE) when administered as a single intraperitoneal dose. Pretreatment with cobalt chloride (50 mg/kg) enhanced the incidence of micronuclei induced by benzo(a)pyren and 2-naphtylamine. Also cobalt chloride

had a comutagenic effect on 1,1-dimethylhydrazine, which did not itself induce a significant increase of MPCE. The synergistic effect of cobalt and other mutagens might be due to the ability of cobalt to accelerate erythropoiesis.

In summary, both soluble and insoluble cobalt compounds seem to be weak genotoxic agents, although the data is rather limited for the insoluble compounds. The genotoxic response in *in vitro* systems is very much dependent on experimental conditions, and some of the conflicting data in bacteria can be explained by differences in bioavailability and exposure time (34, 117). In other words, when appropriate test conditions are used cobalt compounds are also genotoxic in procaryotes. Cobalt causes DNA strand breakage and a possible mechanism for this effect could be production of singlet oxygen and hydroxyl radicals (326). Besides the direct interaction with DNA, the genetic effect of cobalt compounds could be due to a decrease in the fidelity of DNA polymerization (102). Thus, there is sufficient evidence to conclude that cobalt is mutagenic both in procaryotes and in mammalian cells *in vivo* or after long-term *in vitro* exposure.

9. 6. Carcinogenicity

The carcinogenicity of cobalt and cobalt compounds has recently been reviewed (133, 137, 191). Both soluble and insoluble cobalt compounds have been investigated for possible carcinogenic effects in long-term animal experiments with various species (rabbits, rats, mice, guinea pigs and hamsters). However, in contrast to genotoxicity studies, most of the carcinogenicity data concern insoluble cobalt compounds (metallic cobalt, cobalt alloys, cobalt oxide and insoluble cobalt salts). The administration route is usually by intramuscular injection, but other routes of administration have been used. The results from experiments with soluble and insoluble cobalt compounds are discussed separately in the following section and are also summarized in Tables 6 and 7.

9. 6. 1. Insoluble cobalt compounds

Metallic cobalt powder was tested in 20 rats in one experiment with a single intramuscular injection (28 mg). In the exposed group, three male rats and two female rats developed local fibrosarcomas, whereas none of the control animals developed tumours. One of the male rats developed lymph node metastasis (119). This study has later been repeated with 30 exposed and 10 unexposed animals. Seventeen of the exposed animals developed malignant tumours (mainly rhabdomyosarcomas) and no tumours were observed in the control animals (121). In another study, in which 28 mg cobalt powder was injected into the thorax, 8 of 20 rats died shortly after the injection and four of the survivors developed sarcomas in or near the heart (122). A single dose of 10 mg cobalt powder did not induce tumours in a group of 18 rats after intrarenal injection (136).

Different cobalt containing alloys have also been investigated. Cobalt-chromium-molybdenum alloy was tested in hooded rats by intramuscular injection of 28 mg powdered alloy in horse serum (particle size 0.1-1 µm). In three

Table 6. Summary of animal carcinogenicity data with cobalt and *insoluble* cobalt compounds.

Compound	Species	Adm. route [1]	Amount/dose	Tumour type	Tumour incidence (controls) [2]	Tumour incidence (exposed) [2]	Ref.
Cobalt metal	Rat, hooded	I.m.	28 mg	Local sarcoma	0/20	5/20	(119)
	Rat, hooded	I.m.	28 mg	Local sarcoma	0/20	17/30	(121)
	Rat, hooded	I.t.	28 mg	Thoracic tumour	-	4/12	(122)
Cobalt alloys:							
Co-Cr-Mo:							
100-250 µm particles	Rat, Wistar	I.m.	28 mg	Local tumour	0/50	0/51	(206)
0.5-50 µm particles	Rat, Wistar	I.m.	28 mg	Local tumour		0/61	(206)
0.5-50 µm particles	Rat, Hooded	I.m.	28 mg	Local tumour		0/53	(206)
	Guinea pig	I.m.	28 mg	Local tumour		0/46	(206)
0.1-1 µm particles	Rat, hooded	I.m.	28 mg	Local sarcoma	-	23/80	(306)
Co-Cr/W/Ni/C/Mn/Si	Rat, Sprague-Dawley	I.m.	rod	Local tumour	0/30	0/90	(94)
Co-Al-Cr spinel	Rat, Sprague-Dawley	I.p.	200 mg/kg	Lung tumour	1/20	2/20	(298)
		I.t.	10 mg/kg	Local tumour	0/200	3/100	

Table 6. contd

Compound	Species	Adm. route [1]	Amount/dose	Tumour type	Tumour incidence (controls) [2]	Tumour incidence (exposed) [2]	Ref.
Cobalt oxide	Rat, Wistar	I.m.	30 mg	Local sarcoma	0/10	5/10	(103)
	Rat, Wistar	I.m.	20 mg	Local sarcoma		13/29 sites	(102)
	Mouse, Swiss	I.m.	10 mg	Local sarcoma	0/48	0/46	(103)
	Rat, Sprague-Dawley	S.c.	1000 mg/kg	Local, malignant	0/20	9/20	(298)
		I.t.	390 mg/kg	Pulmonary			(298)
				benign	0/100	2/100	
				malignant	0/100	4/100	
		I.p.	200 mg/kg	Local, malignant	1/20	14/20	(298)
		I.t.	78 mg/kg	Pulmonary, benign	0/100	2/100	(298)
Cobalt sulphide	Rat, Wistar	I.m.	20 mg	Local sarcoma	-	35/58 sites	(102)

1) Intramuscular (I.m.), intraperitoneal (I.p.), subcutaneous (S.c.), intratracheal (I.t.)
2) If nothing else is noted, the figures represent the number of tumour bearing animals/total number of treated animals (survivors)

Table 7. Summary of animal carcinogenicity data with *soluble* cobalt compounds.

Compound	Species	Adm. route 1)	Amount/ dose	Tumour type	Tumour incidence (controls) 2)	Tumour incidence (exposed) 2)	Ref.
Cobalt chloride	Rat, Wistar	S.c.	40 mg/kg	Subcut. sarcoma	0/19	8/11 (after 12 mo observation)	(285)
		S.c.	40 mg/kg	Subcut. sarcoma	0/19	6/16 (after 8 mo observation)	
Cobalt naphthenate	Mouse	I.m.	0.2 ml	Muscular		8/30	(234)
	Rabbit	Various	?	Pleural mesothelioma, hemangioendothelioma, osteochondroma, muscular		8/12	(233)
Cobalt(II) acetate	Mouse	I.p.	95 mg/kg	Pulmonary	7/19	8/20	(302)
			237 mg/kg		7/19	8/20	
			475 mg/kg		7/19	10/17	

1) Intramuscular (I.m.), intraperitoneal (I.p.), subcutaneous (S.c.), intratracheal (I.t.)
2) If nothing else is noted, the figures represent tumour bearing animals/total number of treated animals (survivors)

experiments with a total of 80 female rats, 23 developed sarcomas at the injection site (123, 306). No control group was reported. In another study, particles of cobalt-chromium-molybdenum alloy was tested by intramuscular injection (28 mg) in Wistar rats, hooded rats and Dunkin Hartley guinea pigs (206). In this study, larger particles of two different size ranges (0.5-50 µm and 100-250 µm) were used. The particles were implanted intramuscularly by surgical techniques. No malignant tumours developed at the operation site in either test or control animals in a lifetime period. The discrepancies between these two studies may be explained by the fact that different strains of rats were used, as well as different particle size. The smaller particles may induce tumours more readily than the larger particles because of higher dissolution rate.

Polished rods of three different cobalt containing alloys were implanted intramuscularly in three groups of 15 male and 15 female Sprague-Dawley rats, and a similar number of animals served as controls. No tumours developed at the implantation site neither in the exposed nor in the control animals (94). Cobalt-aluminium-chromium spinel produced a few local malignant tumours (2/20) after intraperitoneal injection (3 x 200 mg/kg) in rats. Furthermore, after intratracheal installation of cobalt-aluminium-chromium spinel (390 mg/kg), 3 of 100 rats developed malignant pulmonary tumours (298).

Cobalt(II) oxide was tested in Swiss mice and Wistar rats by intramuscular injection of 30 mg, 5 µm particles, dissolved in Penicillin G. Five out of 10 rats in the test developed malignant tumours (rhabdomyosarcomas) at the injection site, whereas none of the control animals developed tumours. Metastases involving the lymph nodes and lungs occurred in four of the animals. The latency period was relatively short in all cases (6 month in average). In contrast, no tumorigenic effect was seen in mice with even longer observation time (103). In a later study on rats by the same author (102), similar test conditions were used and the tumour incidence (rhabdomyosarcomas) was 13/29 injection sites in 24 out of the 32 surviving animals. Iron and copper oxides did not induce tumours under the same test conditions. Furthermore cobalt oxide did not induce tumours in Swiss mice in this study either.

After subcutaneous injection of 5 x 2 or 1 x 10 mg cobalt oxide/kg/week (total dose 1000 mg/kg) in two groups of 10 rats each, 5 and 4 animals developed local malignant tumours in the two groups, respectively, whereas none appeared in the control group. In the same study, intraperitoneal injections of 3 x 200 mg cobalt oxide/kg produced malignant intraperitoneal tumours in 14 of 20 rats, and one out of 20 control animals had tumours (298).

Only one study on intratracheal installation of cobalt oxide exists (298). In this study, rats were divided into two dose groups. The low-dose group received single doses of 2 mg/kg (total dose 78 mg/kg) and the high-dose group received single doses of 10 mg/kg (total dose 390 mg/kg). A dose-dependent carcinogenic effect was found in the lungs: 2 benign pulmonary tumours among 100 animals in the low-dose group and 2 benign and 4 malignant pulmonary tumours among 100 rats in the high-dose group.

Alternating intratracheal installations of cobalt oxide (total dose 470 mg/kg) and benzo[a]pyren (total dose 200 mg/kg) produced 9 malignant pulmonary tumours in 20 rats, whereas with benzo[a]pyren alone only 1 malignant tumour was developed in 20 rats (298).

In a study limited by poor survival, golden hamsters, administered cobalt oxide dust by inhalation, showed no increase in the incidence of pulmonary tumours (318). It should be noted that the respiratory tract of golden hamsters is less sensitive to the local carcinogenic action of metals than the respiratory tract of rats (298).

Only one relevant study on the carcinogenicity of cobalt sulphide is available (102). Intramuscular injection of cobalt sulphide (20 mg) in rats produced a high incidence of tumours (35/58 injection sites). No control group was reported. Histologically, most of the tumours were of the rhabdomyosarcoma type and metastases were very frequent (55%). Furthermore, cobalt sulphide produced more tumours and the tumours were more often metastasizing than after cobalt oxide treatment under the same test conditions.

9. 6. 2. Soluble cobalt compounds

Cobalt(II) chloride was tested in two experiments with 20 rats in each group. The animals received daily subcutaneous injections of cobalt chloride (40 mg/kg) for periods of five days followed by nine days without dosing. In one group, which was observed for twelve months, 8 of 11 treated rats developed subcutaneous fibrosarcomas (four were located distant from the injection site), whereas none of the control animals injected with saline had tumours. In the second group, which was observed for 8 months, 6 of the 16 survivors developed subcutaneous fibrosarcomas, with one located distant from the injection site (285).

There are two studies on the carcinogenic effect of cobalt naphthenate in rabbits and mice (233, 234). Both studies are, however, incompletely reported concerning dose, schedule, duration of experiment, control group, etc. The compound was apparently given by various routes of administration (intravenous, intramuscular, intrapleural and intrahepatic injections). In the experiments with mice, 8 of 30 animals developed skeletal muscle tumours after intravenous injections of cobalt naphthenate. In the rabbits, tumours developed at the injections site in 8 out of 12 animals. The tumours included pleural mesothelioma, hemangioendothelioma of the liver, osteochondroma of the ear, and skeletal muscular tumours.

The effect of *cobalt(III) acetate* has been studied in Strain A mice by multiple intraperitoneal injections. After 30 weeks lung tumours were found in all treated groups (8/20, 8/20, 10/17) as well as in the control group (7/19). There was no significant increase in tumour incidence in the treated groups compared to the control group (302).

In summary, the effects of intratracheal instillation of cobalt oxide and the consistent occurrence of tumours (mostly rhabdomyosarcomas) at the injection site indicate that cobalt and cobalt compounds have a weak carcinogenic effect in animal experiments. However, many of the studies lack information on survival and control groups. Furthermore, the route of administration in most of the

experiments is not particularly relevant for the occupational setting. (IARC considers the evidence for carcinogenicity in experimental animals as *sufficient* for metallic cobalt and cobalt oxide; *limited* for cobalt-chromium-molybdenum alloys, cobalt sulfide, and cobalt chloride; and *inadequate* for other tested compounds (133)).

9. 7. Reproductive and developmental toxicity

9. 7. 1. Reproductive effects

Reproductive effects have been found in rodents given cobalt by various routes of administration. For example, male rats maintained on a diet containing 265 ppm cobalt for up to 98 days show decreased testicular volume, vascular congestion, and degenerative changes in the testicular tissue (216). Marked reduction in testicular weight was also reported in male rats given daily oral doses of cobalt (20 mg/kg) for 69 days (225). Similarly, male mice given 400 ppm cobalt (as $CoCl_2$) in the drinking water for up to 33 weeks have decreased testicular weight, and fertilization rate and sperm motility were reduced after 11 and 13 weeks of treatment (248, 249). In a histopathological study of mice which had been exposed to 400 ppm cobalt in the drinking water for 13 weeks, severe degenerative changes were seen in the seminiferous tubules (vacuolation of Sertoli cells, accumulation of necrotic debris, reduction in size of germinal epithelium) (16). Furthermore, the histological observations revealed collagen deposition around tubules and changes in the endothelium of the vasculature.

In addition to the experiments with oral administration or injection of cobalt compounds, reproductive effects have also been reported in mice (but not rats) after inhalation exposure to cobalt sulfate aerosols for 13 weeks (38). Sperm motility was found to be reduced after exposure to 3, 10 or 30 mg/m^3 and atrophy of testes was observed in animals exposed to 30 mg/m^3. Female mice exposed to 30 mg/m^3 had significantly longer oestrous cycles.

The mechanism by which cobalt exerts its action on the testes is not clear. It has been speculated that cobalt interferes with metals essential for spermatogenesis (16), or produces tissue hypoxia due to congestion of blood vessels in the testes and deposition of peritubular collagen (216). It appears that simultaneous administration of zinc chloride may prevent the cobalt-induced testicular damage seen in mice (15).

9. 7. 2. Developmental toxicity

The effect of *in utero* exposure to cobalt compounds has been studied in several species. Experiments with pregnant rats receiving daily oral doses of cobaltous chloride (25, 50, or 100 mg/kg) on day 6-15 of gestation did not reveal any treatment-related embryotoxic or teratogenic effects (246).

In pregnant hamsters, both subcutaneous and intraperitoneal injection of cobaltous acetate (40-160 mg/kg, s.c.; 40-70 mg/kg, i.p) on day 8 of gestation

produced dose dependent increases in fetal resorption, and CNS defects were observed at some of the dose levels (95).

Experiments with pregnant mice have shown that intraperitoneal injections of cobaltous chloride (25 mg/kg) or sodium cobaltinitrite (50 mg/kg) on day 10 or 11 of gestation produce a high incidence of cleft palate in the fetuses (151, 152). Wide (1984) gave pregnant mice intravenous injections of 0.1 ml 5 mM cobalt chloride (1.2 mg Co/kg) on day 3 or 8 of gestation and found no effect on implantation frequency, weight of fetuses, or number of resorptions (322). It was, however, found that cobalt administration on day 8 interfered with the process of ossification.

In a study of embryonic development in mice where the males had been exposed to 400 ppm cobalt in drinking water for 10 weeks before mating with untreated females, it was shown that the treatment had no effect on embryonic development *in vitro* (249). However, cobalt treatment of the males changed the percentage of pregnant mice and number of live embryos per female. It was concluded that cobalt affects preimplantation losses by compromising the fertility of treated males.

In addition to these experiments there are some data related to the embryonic development of cobalt exposed frogs and chickens. A concentration dependent increase in the frequency of malformations was found in embryos of the frog *Xenopus laevis* that had been incubated in media containing cobalt chloride at concentrations ranging from 1.8 to 56 µmol/L (about three orders of magnitude below those causing embryolethality) (255). In chickens, injections of cobalt into the yolk or air sac were found to be both toxic and teratogenic (100, 173). The observed effects included reduced body size, twisted limbs, skeletal defects, and eye abnormalities.

9. 8. Other studies

In vitro experiments have shown effects of cobalt (as metal or as ions) on growing cells (e.g. 78, 120), steroid producing cells (229), cultured fibroblasts (27, 28, 66), macrophages (196), isolated rat glomerulus (310), and nerve cells (83, 172, 323).

10. Observations in Man

10. 1. Acute effects

There are practically no descriptions of acute poisoning after oral ingestion of cobalt or cobalt compounds in humans. Gastrointestinal effects (abdominal pain, vomiting) and neutropenia has been reported in a case of a 6-y-old child who ingested about 2.5 g cobalt chloride (223).

Acute respiratory effects have been reported in some studies. Kusaka et al (174) exposed hard-metal workers and non-occupationally exposed subjects to cobalt

containing hard-metal dust for 6-7 hours. The control subjects reported airway irritation and showed a significant decline in FVC after exposure to hard-metal dust with cobalt in concentrations of 0.038 mg/m^3. In contrast, neither irritation nor significant changes in ventilatory function were seen in the hard-metal workers after exposure to a cobalt concentration of 0.124 mg/m^3. This finding is somewhat at variance with the observation of a decline in lung function both during shift and over the workweek in Swedish hard-metal workers exposed to 0.06 mg Co/m^3 (4, 5).

10. 2. Skin irritation and sensitization

Cobalt is a potent skin sensitizer and since cobalt is a constant impurity in nickel, cobalt allergy is often associated with sensitivity to nickel (1). Allergic contact dermatitis due to cobalt has been reported from different types of industries such as the hard-metal industry, pottery industry, rubber industry, and construction industry (e.g. 89, 92, 96, 158, 161, 252, 282).

The prevalence of positive reactions to cobalt chloride in eczema patients have been reported in several studies. Rystedt found a positive reaction in 286 (7.1%) out of 4034 tested patients, but isolated reactions to cobalt was found only in 50 (1.2%) of the patients (271). Similarly, the frequency of sensitivity to cobalt in 834 Italians suspected of having allergic contact dermatitis was 7.1% with a higher relative incidence among the women (48). In a German study of 5811 eczema patients seen over the years from 1975 to 1989, 9.3% had positive reactions to cobalt chloride, and there was a tendency for an increase in the incidence of cobalt allergy during the observation period (109). In a Polish study of 2653 dermatitis patients, the frequency of allergy to cobalt in 4-year periods (1977-1988) ranged from 24.9% to 35.5% with no evidence of increase in the incidence (162).

A study of 50 decorators and enamellers in the Italian ceramics industry revealed 8 subjects (16%) with positive patch tests to cobalt chloride. The sensitization was considered due to the use of cobalt as a pigment in blue, green and black colours (93).

The cement eczema seen among construction workers is in part due to cobalt allergy. The studies summarized by Pirilä and Kajanne (253) show that the frequency of sensitivity to cobalt in cases with cement eczema varies considerably and may correlate with the cobalt concentration in the cement. For example, a very high percentage (76%) of bricklayers with cement eczema in Barcelona are hypersensitive to both chromium and cobalt (42). In contrast, the relatively low prevalence of cobalt sensitivity (1.5%) seen among 272 Asian construction workers has been related to the small content of soluble cobalt in the cement used in that area (104). In an American study, the total cobalt content in 42 different cement samples was shown to be less than 0.5 µg/g, and none of 95 tested workers with cement exposure had positive reactions to cobalt (251). Furthermore, there is a single case report of a bricklayer with severe dermatitis on sun-

exposed areas which was demonstrated to be due to photosensitization to cobalt (41).

The contact dermatitis in the hard-metal industry is of the erythematous, papular type (282), but is not always due to cobalt allergy. For example, in a study of 360 hard-metal workers it was reported that 16 had contact eczema, but only three were allergic to cobalt (289). Fisher and Rystedt (89) tested 853 hard-metal workers (485 men and 368 women) and found that 62 (7.3%) had positive reactions to cobalt. On retesting, 39 (9 men and 30 women) had positive reactions and isolated cobalt allergy was found in 24 subjects. The greatest risk of cobalt allergy was found among workers engaged in grinding and etching. The greater frequency of cobalt allergy among women was explained by concomitant non-occupational exposure to nickel (272).

Since cobalt is an impurity in nickel alloys, jewellery, earrings, and metal objects constitutes a potential source of non-occupational exposure to cobalt. Patients with cobalt allergy may have a clinical appearance described as nickel dermatitis (203). Subjects who are allergic to nickel are 20 times more likely to be allergic to cobalt than those not allergic to nickel (1). Patch testing of subjects classified as allergic to cobalt has shown that the minimum concentration of cobalt chloride that elicits a positive test reaction ranges from 10 to 10,000 ppm (2.2 - 2260 ppm cobalt ion) (13). Furthermore, plating of cobalt containing metals with a layer of chrome (1 µm) does not appear to prevent a skin reaction in cobalt allergic subjects (50). Exposure to cobalt from personal care items and detergent and cleaning products is considered insignificant since the cobalt content generally is below 5 ppm (26).

Exposure to cobalt can also occur from dental prostheses and artificial joints, and some patients responding adversely to surgical implants have positive skin reactions to cobalt (85, 146).

10. 3. Effects of repeated exposure on organ systems

Effects on the respiratory system appears to be dominating in persons with occupational exposure to cobalt. However, due to the use of cobalt compounds as therapeutic agents there is a considerable amount of information on toxic effects in other organ systems, which will also be discussed below.

10. 3. 1. Respiratory system

Effects in hard-metal workers - Inhalation of cobalt containing dust occurs particularly in the hard-metal (cemented tungsten carbide) industry and it is generally agreed that cobalt is the major etiological factor in the development of the so-called hard-metal lung diseases (23, 29, 62, 67, 71, 280). These diseases include three major types of reactions: hypersensitivity pneumonitis, interstitial lung fibrosis, and asthmatic reactions (62).

Hypersensitivity pneumonitis (allergic alveolitis) and lung fibrosis are considered part of a continuum that ranges from pure alveolitis to irreversible fibrosis. The classical symptoms seen in heavily exposed hard-metal workers are

characterized by weight loss, cough, wheezing, and dyspnoea on exertion. Chest radiographs show reticulo-nodular densities and lung biopsies reveal interstitial cellular infiltrates consisting of lymphocytes and plasmocytes followed by deposition of collagen and elastic tissue. Lung function tests show restrictive ventilatory impairment as indicated by decreases in vital capacity (FVC) and forced expiratory volumes (FEV). Another characteristic finding is arterial hypoxia and a reduced cabon monoxide diffusion capacity during rest or exercise. These changes have been observed in numerous cases (e.g. 21, 29, 56, 57, 63, 67, 88, 115, 116, 164, 200, 212, 239, 241, 280, 288).

One particular pathological finding associated with hard-metal exposure is the presence of large, multinucleated cells in the alveolar spaces (giant cell interstitial pneumonia) (e.g. 67, 239, 308). Furthermore, elemental analysis of lung tissue from workers with hard-metal lung fibrosis have demonstrated the presence of tungsten and tungsten carbide in high amounts (56, 67, 164, 200, 239, 260, 270, 288). In contrast, the cobalt content in lung tissue is often comparatively low or cannot be detected (56, 63, 67, 70, 114, 116, 164, 200, 239, 260, 270). The duration of exposure before symptoms appear may range from a few months to many years (56). Usually, the condition deteriorates slowly with continuous dust exposure, but in milder cases there may be improvements in lung function during periods off work or with change of job (63, 67, 280, 288).

The clinical pattern seen in hard-metal workers with asthmatic reactions is that of a typical occupational asthma. The symptoms include dry cough, wheezing, chest tightness, exertional dyspnea, and rhinitis. Partial or complete recovery occurs during weekends and holidays and there is an immediate relapse on returning to work. Furthermore, significant improvements are noted after wearing a respirator or after installation of exhaust ventilation systems. There are no radiological abnormalities, but lung function tests show an obstructive pattern with decreased FEV (67, 176, 179, 280, 286, 287).

The latency period from the first exposure to development of asthma in 18 cases ranged from 3 months to 10 years (176). Bronchial provocation tests have been important in establishing the role of cobalt in hard-metal asthma. While cobalt or cobalt containing dust produce a positive reaction (asthmatic symptoms or decreased FEV) in workers with hard-metal asthma (67, 113, 254, 286, 287), no effects are seen with pure tungsten carbide (55, 67). On the other hand, it has also been demonstrated that inhalation of nickel may produce a fall in FEV in patients with hard-metal asthma (287).

Ventilatory impairment of the obstructive type has been documented in a series of studies on Swedish hard-metal workers with exposure to comparatively low cobalt levels (4, 5,10). Ventilatory function declined during the working day and during the week, and improvements occurred over the weekend. The decline was most marked in the high-exposure group (0.06 mg Co/m^3), particularly among smokers, but a tendency for decrease in lung function during the week was also noted in workers with exposure to 0.01 mg Co/m^3. While lung function was

Table 8. Effects of cobalt and cobalt compounds on the respiratory system in animal inhalation experiments

Species	Exposure level [1]	Duration	Effect	Reference
Guinea pigs	WC/Co (3:1) 2,800-10,600 particles/cm^3	8 h/d, 51/2 d/w 20 d (+5 d unexposed)+10 d	Acute pneumonitis; 80% died during or after the exposure	(69)
Rats, mice, hamsters, rabbits	metallic Co "high conc."	6 h/d 1-4 d	Lung hemorrhage and edema; many deaths.	(112)
Rats	metallic Co 2.1-2.7 mg/m^3	5 h/d, 1 or 4 d	Airway inflammation, edema, damaged cilia; proliferation of fibroblasts, bronchial epithelium, and type II cells	(177)
Rabbit	metallic Co 1.3 mg/m^3	6 h/d, 5 d/w, 4-6 w	No effect on alveolar macrophages	(143)
Miniature swine	metallic Co 1.0 mg/m^3	6 h/d, 5 d/w, 3 mo	Alveolar septal thickening, deposition of collagen (EM), decreased lung compliance	(156)
Rabbit	metallic Co 0.2 mg/m^3	6 h/d, 5 d/w, 4-6 w	No effect on alveolar macrophages	(143)
Miniature swine	metallic Co 0.1 mg/m^3	6 h/d, 5 d/w, 3 mo	Alveolar septal thickening and deposition of collagen (EM)	(156)
Rats	Co^{++} (as $CoSO_4$) 3.67 mg/m^3	6 h/d, 5 d/w, 13 w	Degeneration of olfactory epithelium, ulcers and inflammation, polyps in larynx, lung fibrosis	(38)
Mice	Co^{++} (as $CoSO_4$) 3.67 mg/m^3	6 h/d, 5 d/w, 13 w	Nasal inflammation, degeneration of olfactory epithelium, alveolar epithelium hyperplasia	(38)
Rats, mice	Co^{++} (as $CoSO_4$) 0.11 mg/m^3	6 h/d, 5 d/w, 13 w	Inflammation and squamous metaplasia of larynx, histiocytic infiltration of alveoles	(38)
Rabbits	Co^{++} (as $CoCl_2$) 0.9, 2.0 mg/m^3	6 h/d, 5 d/w, 14-16 w	Lung lavage fluid: Increased fibronectin content and lysozyme activity. (LOEL: 0.9 mg/m^3)	(31)
Rabbits	Co^{++} (as $CoCl_2$) 0.5 mg/m^3	6 h/d, 5 d/w, 4-6 w	Alveolar epithelium: Hyperplasia of type II cells	(142)
Rabbits	Co^{++} (as $CoCl_2$) 0.4, 2.0 mg/m^3	6 h/d, 5 d/w, 14-16 w	Interstitial lung inflammation, nodular accumulation of type II cells, changes in macrophage structure and function. (LOEL: 0.4 mg/m^3)	(144,145)

1) Concentration of cobalt or cobalt ions is as reported or has been calculated from authors data

normalized over weekends in the low-exposure groups, the high-exposure group had a persistent reduction in lung function. Furthermore, workers in the high-exposure group had a higher frequency of mucous membrane irritation than controls (see also Table 9).

Most clinical and radiological surveys indicate a low prevalence of hard-metal lung diseases. In a study of 255 hard-metal workers in UK in 1962, only one worker had fibrosis, but several had slight changes in their chest radiographs suggesting early fibrosis. Furthermore, only four cases were discovered during routine visits to the factory over 15 years (29). A survey in USA (1971-1973) discovered only 9 cases of fibrosis and 9 subjects suffering from respiratory sensitization among 1500 hard-metal workers (55, 56). In a Japanese survey (1983) of 319 hard-metal workers, 18 cases (5.6%) were found to have occupational asthma and chest radiographs showed diffuse shadowing in only three workers (0.9%). However, the cause of pneumoconiosis in these cases was not established conclusively (176). In a more recent cross-sectional study of 1039 hard-metal workers in USA, 26 (2.6%) had abnormal chest radiographs, but only 7 (0.7%) were diagnosed as having an interstitial lung disease (295). In a French study of 425 workers exposed to hard-metal dust, no cases of fibrosis were discovered, but minor abnormalities in chest radiographs were more frequent in exposed men than in controls (208). Some of these studies appear to show a correlation between the cobalt concentration and the prevalence of hard-metal asthma and lung fibrosis (176, 295).

Effects in other cobalt-exposed workers - While there are numerous studies dealing with workers exposed to hard-metal dust, there are comparatively few dealing with subjects exposed to cobalt alone. Diamond polishers are exposed to dust which primarily contains cobalt and diamond fragments. The dust originates from the use of grinding disks made from abrasive microdiamonds embedded in cobalt which was introduced in the seventies (71, 178, 315). Case reports have documented that diamond polishers, as well as others using diamond-cobalt abrasive tools, may develop cobalt-induced asthma and interstitial lung diseases (fibrosing alveolitis, giant cell interstitial fibrosis) similar to those seen in hard-metal workers (47, 72, 99, 227). In cases with fibrosis, the cobalt content in lung tissue is markedly elevated (72, 227). Furthermore, a study of 48 workers engaged in the production of diamond-cobalt circular saws has demonstrated a moderate restrictive ventilatory impairment (decreased FVC and FEV) which correlated with the duration of exposure (97).

Cases of diffuse interstitial lung fibrosis and a high prevalence of bronchitis and asthma-like symptoms have also been described in workers with exposure to dust containing cobalt carbonate in a cobalt catalyst plant (259). Workplace concentration of cobalt in this study ranged from 0.4 to 0.7 mg/m^3.

In addition to the observations on hard-metal workers and diamond polishers, a detailed study of workers in a Finnish cobalt and zinc producing plant has been reported (268). In this study it was found that the risk of occupational asthma was increased about 5 times in workers with exposure to cobalt sulfate compared to

controls. However, there was no evidence of increased risk of chronic bronchitis in workers with 6-8 years of exposure to cobalt concentrations ranging from 0.050 to 0.1 mg/m^3.

Recently, a detailed survey of 82 cobalt refinery workers in Belgium has been reported (307). The workers had been exposed to various cobalt salts, cobalt oxide, and metallic cobalt (0.125 mg Co/m^3) for 8 years. No radiological abnormalities were found, and lung function tests did not indicate ventilatory impairment. However, respiratory symptoms (dyspnoea and wheezing) were more common in exposed workers and particularly among exposed smokers.

Lung function and respiratory symptoms have also been studied in plate decorators exposed to cobalt blue dyes (258). The study group comprised 46 exposed women with an average of 11 years of employment (range 2-25 y) and 51 unexposed women. Workplace recordings showed that the decorators had been exposed to cobalt in concentrations of about 0.8 mg/m^3 (0.068-8.61 mg/m^3), but at the time of the study, airborne cobalt levels were considered to be just around the occupational exposure limit, (OEL=0.05 mg/m^3). There were significantly more complaints of upper respiratory tract irritation, cough and expectoration in the exposed compared to controls. Furthermore, there was a tendency of a higher frequency of asthma-like symptoms in the exposed group (11 vs. 2%). Lung function tests showed increased airflow resistance in the exposed, but the changes were not related to blood or urinary cobalt levels.

10. 3. 2. Cardiovascular system

Cardiac effects after occupational exposure - Case reports relating cardiomyopathy to industrial exposure to cobalt are rare in spite of the massive exposure that has occurred in the hard-metal industry. Cardiomyopathy has been described in two workers who had been exposed to dust from cobalt-containing ores at a mineral assay laboratory (135), in a "metal worker" with 4 years of exposure to cobalt (24), and in a hard-metal worker who was exposed for 4 years while weighing and mixing tungsten carbide and cobalt powders (154). All cases showed enlargement of the heart and histopathological abnormalities consisting of hypertrophic or degenerating vacuolated myocardial cells and fibrotic areas. Moreover, the cardiac tissue had markedly elevated concentrations of cobalt. It has been suggested that the low number of cases could be due to misclassification of the disease (135), or that the cases otherwise could represent chance occurrence of idiopathic congestive cardiomyopathy (129).

Cardiac function has been studied in 30 hard-metal workers with an average of 10 years exposure (129). No evidence of systolic left ventricular dysfunction was observed. However, a weak but significant inverse correlation was found between duration of employment and the left ventricular ejection fraction. Moreover, a subgroup with abnormal chest radiographs had relatively lower right ventricular ejection fractions during exercise compared to those having normal radiographs.

A more or less similar study has recently been conducted with 31 hard-metal workers from Italy, who had an average of 10.4 y exposure to 0.009-13.6 mg Co/m^3 (65). ECG, blood pressure, and heart rate was normal in all subjects.

However, those who were diagnosed as having hard-metal lung diseases (n=12) had significantly lower left ventricular ejection fraction during rest and exercise compared to the subgroup of healthy hard-metal workers. Moreover, within the subgroup with hard-metal lung diseases, cases of cardiomyopathy with doubtful aetiology were found.

In a Swedish study of hard-metal workers (7), it was found that wet grinders exposed to an average of 0.01 mg Co/m^3 had an increased frequency of ECG changes (depressed ST- and T-waves, arrythmia) compared to unexposed controls, whereas no changes were seen in powder handlers exposed to higher concentrations (0.06 mg Co/m^3). However, the difference between wet grinders and controls disappeared after four weeks holiday (8). In contrast to these findings, no ECG abnormalities were reported in a study of plate decorators with an average of 11 years of exposure to cobalt blue dyes (0.068-8.61 mg Co/m^3). The pulse rate, however, was significantly higher in exposed vs. controls (258).

Cardiac effects after oral exposure - The most important effect of cobalt and cobalt compounds on the circulatory system is cardiomyopathy. Numerous cases of cardiomyopathy occurred among heavy beer drinkers in the sixties in Belgium, Canada, and USA after cobalt (as sulfate or chloride) was added to the beer to improve the stability of the foam (3, 204, 217, 218). In Canada, cases appeared one month after cobalt sulfate was added and no new cases developed after withdrawal of cobalt. Although excessive alcohol intake and nutritional deficiency may have contributed to the development of cardiomyopathy in beer drinkers, cobalt is considered the essential factor (157, 217).

The heart disease seen in beer drinkers was manifested by the following symptoms and signs: epigastric pain, nausea and vomiting, anorexia, cyanosis, distended jugular veins, low blood pressure, and various ECG abnormalities. Chest radiographs showed cardiomegaly and there was evidence of pericardial effusion. Furthermore, most of the patients had hematocrit values in the high normal range or were polycythemic (3, 157, 204, 218). Histopathological findings (light microscopy) were normal in some cases while others showed myocardial hypertrophy, degeneration of myofibres, and in some cases interstitial fibrosis (3, 35, 157, 204). However, all biopsies showed extensive ultrastructural changes such as swollen mitochondria, abnormal sarcoplasmatic reticulum and abundant glycogen granules (3, 35). In addition, the cobalt concentration in the myocardium was about 10 times that found in normal cardiac tissue (303).

Cardiomyopathy has also been described in a hemodialysis patient who was given cobalt chloride for anemia (202). In this case, the signs included cardiomegaly and arrhythmia, and post mortem findings showed patchy myocardial necrosis, vacuolated muscle fibres and elevated cobalt levels in the myocardium.

10. 3. 3. Blood and blood-forming organs

Hematological parameters have been studied in plate decorators with an average of 11 years exposure to cobalt blue dyes (258). Cobalt exposure was considered heavy as indicated by 85-90 times higher urinary cobalt concentrations in exposed

subjects compared to controls. No differences in hematocrit were found between exposed and controls. However, small but non-significant changes were noted when the decorators resumed work after a period off work. Theses changes did not correlate with urinary cobalt.

In a study of cobalt refinery workers with exposure to various cobalt salts, cobalt oxide and metallic cobalt, a small but significant reduction was seen in hematocrit and hemoglobin content, whereas the number of white blood cells were increased (307). The reduction in hematocrit in this study is contrary to that which would have been expected from animal studies and observations in humans with systemic administration of cobalt salts.

Due to its hematopoietic effect, cobalt has previously been used in treatment of various types of anaemia (e.g. 32, 77, 108, 170, 281). Cobalt was usually administered as daily oral doses of cobalt chloride (25-300 mg) and most subjects were found to respond with an immediate increase in red blood cell number, hemoglobin, and hematocrit. On withdrawal of cobalt, all values returned to pre-therapeutic levels within few months (32, 77, 281).

Polycythemia or hematocrit values in the high normal range were commonly seen in cases of beer-drinkers' cobalt-induced cardiomyopathy (3, 157, 218). Some of these cases were also found to have increased blood volume.

10. 3. 4. Thyroid

Prescott et al (257) have provided evidence which suggests that occupational exposure to cobalt may affect thyroid hormone metabolism. They studied thyroid function in two groups of plate decorator exposed to cobalt blue dyes and compared the results with that in unexposed controls. Group 1 (n=36) was exposed to insoluble cobalt aluminate for an average of 14.6 years while group 2 (n=25) was exposed to the semisoluble cobalt-zinc silicate for 16.2 years. Group 1, which had normal urinary cobalt levels, did not differ significantly from the control group in any of the studied parameters. In group 2, urinary cobalt was increased 10-fold and the serum thyroxine level was significantly increased. Furthermore, group 2 showed a tendency for lower thyroid volume. In a previous study of plate decorators, however, no abnormalities in thyroid function were found (258). In contrast to these findings, a significant decrease in serum thyroxine levels was noted in a study of cobalt refinery workers (307).

In addition to these reports, there are some studies indicating that oral administration of cobalt salts has an effect on the thyroid gland. For example, goiter or decreased thyroidal ^{131}I uptake has been found in children and adults receiving cobalt chloride as a hematopoietic stimulant (77, 108, 170, 261, 281). In non-anaemic patients receiving cobalt chloride (150 mg/d, 2 weeks), ^{131}I uptake was also found to decline rapidly, but returned to normal levels after cobalt administration was discontinued (263).

Histopathological observations of thyroid tissue from 14 Quebec beer drinkers, who died from cardiomyopathy induced by cobalt sulfate, revealed significant changes in 11 of the cases. The changes, which occurred without clinical evidence

of thyroid dysfunction, included reduced follicle size, epithelial hyperplasia, and colloid depletion (35, 269).

10. 3. 5. Other organs

Symptoms referable to the gastrointestinal tract (anorexia, nausea, vomiting, constipation) have been reported in some patients to whom large doses of cobalt chloride were administered as therapy for anemia (e.g. 32, 77, 281). Otherwise, no reports of specific effects on the gastrointestinal tract were found.

There are a couple of case reports suggesting that cobalt may have an effect on the nervous system or sense organs. A 35-y-old woman, who had received cobalt chloride for about 6 months as therapy for anaemia, developed many adverse effects including bilateral nerve deafness (281). The symptoms receded when cobalt was discontinued. Another case report describes a 48-y-old man with decreased visual acuity, hearing loss, tinnitus and occasional vertigo (207). The man had been exposed to cobalt powder for 20 months and on examination he was found to have high blood cobalt levels (234 µg/l). His condition improved, but 11 months after stopping work there was still a residual hearing deficit.

Jordan et al (147) studied memory function in 12 former hard-metal workers, who complained of poor memory. They had been exposed to tungsten carbide, cobalt, and an unspecified organic solvent. The exposed subjects were found to have deficits in memory and attention compared to 26 healthy, unexposed workers. Considering the selection criteria and exposure history, this finding is hardly surprising and does not point to cobalt as the causative agent.

10. 4. Genotoxic effects

The literature search revealed only on study dealing with genotoxic effects after occupational exposure to cobalt (98). The study group included 26 workers which were compared to 25 matched controls. Workplace measurements showed cobalt concentrations in the range of 0.11-0.164 mg/m^3 in 1986 and 0.01-0.012 mg/m^3 in 1989. There was a statistical significant increase in SCE score in the exposed group compared to the control group. The level of serum tumour markers (carcinoembryonic antigen and tissue polypeptide antigen) was also elevated in the exposed compared to controls, but the difference was not statistically significant. The workers had also been exposed to two other potentially genotoxic metals (nickel and chromium) and it is therefore impossible to conclude which of the agents that was responsible for the observed effects.

10. 5. Carcinogenic effects

Only few relevant epidemiological studies of cancer risk in cobalt exposed workers are available. Some case studies and smaller epidemiological studies have been published and reviewed recently (cf. 133, 137), but the evidence of carcinogenicity in these is inconclusive due to small study groups or confounding factors.

Table 9. Key studies showing dose-effect and dose-response relationship in humans with occupational exposure to cobalt or cobalt compounds

Study group	Exposure [1,2]	Duration	Effect/response [3]	Ref.
46 plate decorators vs. 51 controls	0.8 (0.068-8.61) (cobalt blue dyes)	11 y (2-25 y)	Airway irritation, cough, and asthma-like symptoms more frequent in exposed vs controls. Increased airflow resistance and higher pulse rate in exposed.	(258)
319 hard-metal workers	I: 0.688, (0.006-6.4) II: 0.03-0.126	9.4 y (1-29 y)	3 cases (1%) with lung fibrosis. 18 cases (5.6%) of occupational asthma (higher prevalence in group I than in group II).	(176)
1039 hard-metal workers	I: > 0.1. II: 0.05-0.1 III: < 0.05	7.0 y	Increased frequency of abnormal chest radiographs in group I (5.1 x). 15.4-18.1% with work-related wheeze in group I and II. 9.2% with wheeze in group III.	(295)
425 hard-metal workers vs.88 controls	0.03-0.272	14 y	Mild clinical, radiological, and functional abnormalities in exposed.	(208)
48 production workers (diamond-cobalt saws) vs. 23 controls	0.015-0.135	6 y (0.2-32 y)	Ventilatory parameters (FEV_1, FVC, MEF75) significantly lower in exposed vs. controls.	(97)
42 hard-metal workers vs. 84 controls	0.126 (0.006-0.61)	10 y (2-20 y)	All ventilatory parameters lower in exposed vs. controls; significant only for FEV_1.	(174)
82 cobalt refinery workers vs. 82 controls	0.125 (various Co compounds)	8 y (0.3-39.4 y)	Dyspnoea and wheezing more frequent among exposed. No evidence of radiological abnormalities or ventilatory impairment. Changes in thyroid hormones and hematology.	(307)
225 cobalt production workers vs. 161 controls	0.05-0.1 (cobalt sulfate)	7.3 y	Respiratory symptoms significantly more frequent in exposed vs. controls. No evidence of respiratory impairment. Increased risk (7.3 x) of work-related asthma (separate study).	(268)
42 hard-metal workers	0.085 (0.017-0.610)	6 h (acute)	No irritation. No significant changes in ventilatory parameters.	(174)

Table 9. contd

Study group	Exposure [1,2]	Duration	Effect/response [3]	Ref.
291 hard-metal workers vs. 126 controls	I: 0.005-0.06 II: 0.06 III: 0.012 IV: 0.008 V: 0.003 VI: 0.002	7-11 y	Higher frequency of mucous membrane irritation in all exposure groups vs. controls. Ventilatory impairment (decreased FEV_1, FEV%, MMF) in high-exposure group (II). Decrease in lung function during working day and week (group II). No radiological abnormalities.	(4,5,10)
60 plate decorators vs. 48 controls	0.05 (cobalt blue dyes)	15 y	Increased serum thyroxine levels and tendency for lower thyroid volume in subgroup exposed to soluble cobalt blue dye.	(257)
15 healthy subjects	0.038 (0.014-0.076) (hard-metal dust)	6 h (acute experiment)	Airway irritation. FVC significantly decreased after exposure.	(174)
3 cases (hard-metal workers)	0.018-0.031	10-17 y	Work-related asthma (verified by positive bronchial provocation test).	(176)
362 powder metal workers vs. external referent population	0.017 (0.001-0.466) (mixed dust exposure)	21.7 y	Prevalence of abnormal radiographs (0.6%) comparable to referent population. FEV_1 and FVC comparable to or higher than predicted. Higher prevalence of chronic cough in exposed smokers.	(73)
146 hard-metal workers vs. 126 controls	I: 0.06 II: 0.01	7-10 y	Higher frequency of ECG abnormalities in low-exposure group (II, wet grinders), but not in high-exposure group (I). (No difference between exposed and controls after 4 w holiday).	(7,8)
4 cases (wet grinders)	< 0.01 (Co^{++} in coolants)	3-4 y	Allergic alveolitis.	(288)
3 cases (hard-metal workers)	< 0.008	1-7 y	Reduced ventilatory function. Biopsy (2 cases) showing fibrosis.	(295)

1) Mean cobalt concentration in mg Co/m^3; values in parentheses indicate range. In cases where more than one exposure group have been considered, these have been indicate by Roman numerals. Otherwise, the group means have been calculated from authors data.
2) Due to methodological differences, values may not be directly comparable.
3) FEV_1, forced expiratory volume; FEV%, FEV_1 in per cent of FVC; FVC, forced ventilatory capacity; MEF75, mean expiratory flow at 75%; MMF, maximal midexpiratory flow.

10. 5. 1. Occupational exposure

In a Swedish study from the hard-metal industry 3163 workers, with at least one year of exposure to cobalt containing hard-metal dust at one of three hard-metal manufacturing plants in 1940-1982, were included (127). The workers were followed during the period 1951-1982. The study group was divided into four exposure groups: < 0.002 mg/m^3, 0.001-0.005 mg/m^3, 0.01-0.03 mg/m^3, 0.01-11 mg/m^3. There were 292 deaths (including 73 tumor cases) among persons under 80 years of age during the study period. Standardized mortality ratios (SMR) were calculated using national rates. Seventeen cases of lung cancer were found compared to 12.7 expected (SMR 134; 95% CI 77-213). For workers with more than 10 years of exposure and a latency period of more than 20 years , a statistically significant increase in lung cancer was seen, i.e., seven cases were observed compared to 2.5 expected in all exposure categories (SMR 278; 95% CI 111-572). In the two lowest exposure groups, three cases were observed vs. 1.3 expected, and four cases of lung cancer were observed in the two highest exposure groups versus 1.2 expected. The workers has also been exposed to other components of hard-metal dust, but not to other known human carcinogens, and smoking habits were not different from those of the male Swedish population (12).

The mortality in a cohort of 1143 workers in a French electrochemical plant producing sodium and cobalt was studied by Mur et al (224). The cohort consisted of all men (24.9% migrants) who had worked in the plant for a minimum of one year between 1950 and 1980. Two hundred and thirteen persons of the cohort died before 1981, 80% of known causes. After adjustment for unknown causes of death there was a significantly higher incidence of lung cancer among workers only employed in the cobalt production (SMR 466; 95% CI 146-1064). This study suffers from the very low number of cases and the possibility that migrants may have a different rate of lung cancer compared to the French population which was used for reference in calculating SMR values. Moreover, the workers in the cobalt production were also exposed to unknown levels of other human carcinogens (nickel and arsenic). A recent follow-up of this study with a subcohort of native French workers did not support the hypothesis of a relationship between lung cancer and cobalt exposure (222).

10. 5. 2. Implanted medical devices

At least 10 cases of malignant tumours, mostly sarcomas, have been reported after surgical implantation of cobalt containing prostheses (61, 133). One cohort study has been reported with 1358 persons who received a total hip replacement in the period 1966-73 (101). The patients were followed for an average of 10.5 years after surgery (6 mo - 17 y), and the overall cancer incidence during the first 10 years was lower than expected. However, 10 or more years after surgery, the cancer incidence was significantly increased (57 observed vs. 35,6 expected; SMR 160 ; 95% CI 122 - 209). No specific information on the composition of the hip prosthesis was available in this study.

In conclusion, there is only one epidemiological study (127) pointing to an increased cancer risk in persons with occupational exposure to cobalt. However, with the lack of well-performed animal inhalation studies and detailed human genotoxicity data, it cannot be concluded at present whether cobalt should be considered carcinogenic to humans. It should be noted that IARC (133) finds the human data *inadequate*, but due to *sufficient evidence* for some compounds in animal experiments (metallic cobalt powder, cobaltous oxide) IARC concludes that cobalt and cobalt compounds are *possibly carcinogenic to humans (Group 2B)*.

11. Dose-Effect and Dose-Response Relationships

11. 1. Animal data

Exposure to cobalt in high concentrations produces respiratory tract inflammation, pneumonitis, lung hemorrhages, and edema which is fatal. At medium concentration range (2-11 mg Co/m^3), and exposure periods ranging from days to several weeks, experiments with rats and mice have shown various effects on the lung and airways such as inflammation, degeneration of olfactory epithelium, proliferation of fibroblasts, and fibrosis (see Table 8 for details and references). Systemic changes consisting of polycythemia and testicular atrophy have also been found at this exposure level. At concentrations from about 0.4 to 2 mg Co/m^3 several studies have documented changes in alveolar macrophage structure and function as well as ultrastructural changes in the lung. Histological changes in the lung, as seen by light microscopy or electron microscopy, have been found in rats, mice and miniature swine after about 3 months exposure to metallic cobalt (or cobalt ions) at concentrations around 0.1 mg/m^3, which is the current LOEL. Thus, a NOEL has not yet been established in animal experiments.

11. 2. Human data

11. 2. 1. Respiratory effects

The key studies showing dose-effect or dose-response relationship have been summarized in Table 9. Some studies have clearly documented that the prevalence of asthma and respiratory symptoms is related to the concentration of cobalt in the work environment (e.g. 4, 5, 176, 295), or that performance in ventilatory tests declines with duration of exposure (length of employment) (97). For example, in a study of 48 production workers (diamond-cobalt circular saws) with exposure to cobalt (0.135 mg Co/m^3 in mixing room and 0.015 mg Co/m^3 in oven room), respiratory dysfunction (reduced FVC, FEV_1, MEF75) was seen more commonly in the exposed groups (both smokers and non-smokers) than in

non-exposed controls. Furthermore, the spirometric parameters correlated negatively with duration of exposure (97).

In a study of 290 hard-metal workers, a significant association was established between peak expiratory flow rate (but not FVC, FEV_1, or FEV_1/FVC) and duration of employment in one of the two subgroups (296). Similarly, respiratory symptoms and abnormalities in spirometric tests and chest radiographs were more common in 425 hard-metal workers with exposure to cobalt in concentrations of 0.03-0.270 mg/m^3 than in 88 unexposed controls (208). However, there was no correlation between indices of lung function and duration of exposure.

Alexandersson studied respiratory symptoms and lung function in 291 Swedish hard-metal workers compared to 126 unexposed controls (4, 5). Based on job and workplace recordings, the study group was divided into different exposure groups (A, 0.005-0.01; B, 0.06; C, 0.012; D, 0.008; E, 0.003; F, 0.002 mg Co/m^3; and K, control). No abnormalities were seen in chest radiographs. There was a significantly higher frequency of mucous membrane irritation (eye, nose, pharynx) in all exposure groups compared to the unexposed controls. Chronic bronchitis and ventilatory impairment (decreased FEV_1, FEV%, MMF) were seen only in the high-exposure group (B). Furthermore, in this group, performance in lung function tests declined during the working day and improvements were noted over the weekend. The difference between FEV_1 in exposed and controls correlated significantly with both urinary and blood cobalt levels, but only in smokers in the high-exposure group.

A Japanese study of 319 hard-metal workers has demonstrated that asthma occurs more commonly among subjects exposed to high cobalt levels (176). Among 21 powder workers exposed to an average cobalt concentration of 0.688 mg/m^3 (range 0.006-6.4), 38% (8 subjects) were found to have asthma, whereas only 4.5% (10 subjects) had asthma in a group of 221 shapers, grinders and sinter workers, who were exposed to lower average cobalt concentrations (0.03-0.126 mg/m^3). In this study, the overall prevalence of asthma was 5.6% (18 cases out of 319 studied). In a large American survey (295), it was found that the prevalence of work-related wheeze was higher among individuals exposed to cobalt in excess of 0.05 mg/m^3 compared to those exposed at lower concentrations. Furthermore, the relative odds of abnormal chest radiographs was 5.1 times for individuals with exposure to cobalt higher than 0.1 mg/m^3 compared to those exposed to cobalt below 0.1 mg/m^3.

In contrast to these findings, it was not possible to establish any effect of length of employment on respiratory function in a study of 362 workers in a plant producing permanent magnets by powder metallurgy (73). The workers were exposed to comparatively low concentrations of cobalt (0.017 mg/m^3; range, 0.001-0.466 mg/m^3), rare metals (neodymium, samarium), and silica (0.009 mg/m^3). When correcting for age and smoking habits, no difference in respiratory function could be detected between workers with more than 22 years of employment and workers with shorter periods of employment. Furthermore, the prevalence of abnormal radiographs was comparable to that of an external referent population,

and spirometric parameter (FEV_1, FVC) were slightly higher than predicted (healthy worker effect).

Roto (1980) have studied Finnish cobalt production workers who had been exposed to cobalt/cobalt sulfate for an average of 7.3 years. Workplace recordings over several months showed airborne cobalt levels ranging from 0.05 to 0.1 mg/m^3. Spirometric data showed no evidence of impaired lung function, but the frequency of respiratory symptoms was significantly higher in cobalt workers than in unexposed controls (no correlation with duration of employment). Furthermore, the risk of work-related asthma among cobalt workers was 7.3 times that in unexposed controls (268).

Hogstedt and Alexandersson (1987 and 1990) have reported on mortality in Swedish hard-metal workers (126, 127). A retrospective evaluation of the cobalt exposure level was performed and the study population was divided in "low" (0.001-0.01 mg Co/m^3) and "high" (>0.01 mg Co/m^3) exposure groups. In a preliminary analysis (1901 male workers), an excess of lung cancer was found in the subcohort with long-term exposure, but there was no obvious relation to exposure level (126). In the follow-up study (3163 male workers), it was reported that there was no increased risk of death in the group as a whole (SMR=96). However, the high-exposure group had an increased risk of death from ischemic heart diseases and respiratory diseases including lung fibrosis. SMR for lung cancer (278) was significantly elevated for those with long duration of employment and there was a tendency for increased risk in the high-exposure group (SMR=333) compared to the low-exposure group (SMR=227).

The frequency of respiratory complaints (including asthma-like symptoms) were significantly higher in plate decorators exposed to cobalt blue dyes (0.8 mg/m^3; range, 0.068-8.61 mg/m^3) compared to controls (258). Furthermore, lung function tests showed increased airflow resistance in the exposed. The findings were not related to blood or urinary cobalt levels. A study of thyroid function in the plate decorators was performed after working conditions had been improved (average exposure level: 0.05 mg Co/m^3). In the subgroup exposed to soluble cobalt blue dye (cobalt-zinc silicate), urinary cobalt was markedly elevated and serum thyroxine levels was significantly increased and there was a tendency for lower thyroid volumes. Again, none of the parameters correlated with urinary cobalt levels or duration of exposure (257).

In a study of cobalt refinery workers with an average of 8 years exposure to various cobalt salts, cobalt oxide, and metallic cobalt (0.125 mg Co/m^3), the prevalence of respiratory complaints were higher than in controls (307). Furthermore, reduction of the FEV_1/VC ratio and dyspnoea were related to the concentration of cobalt in air and urine. The prevalence of abnormal biological analyses (serum thyroxine, TSH, WBC and RBC number) were also significantly higher than in controls, but these parameters did not correlate with cobalt in urine or duration of exposure.

Effects on the respiratory system have been reported at very low cobalt concentrations in some studies. For example, healthy subjects exposed for 7 hours

to hard-metal dust (0.8 mg/m^3) with cobalt in concentrations of 0.038 mg/m^3 reported airway irritation and had significantly lowered FVC (174). In contrast, no effects were seen in hard-metal workers acutely exposed to higher dust concentrations (total dust, 1.4 mg/m^3; cobalt, 0.085 mg/m^3). The hard-metal workers, however, had lower values in ventilatory tests than the healthy controls. In one of the Swedish studies on hard-metal workers (10), it was reported that there was a tendency for decrease in lung function during the week in a subgroup of workers with an exposure to about 0.01 mg Co/m^3.

Sjögren et al have described 4 cases of allergic alveolitis among wet grinders in a Swedish hard-metal plant (288). The cobalt concentration in the wet grinding area of the factory was below 0.01 mg/m^3 and usually ranged from 0.002 to 0.004 mg/m^3. The exposure was considered to be due to inhalation of aerosols of coolant fluids containing dissolved cobalt ions, which are more toxic than metallic cobalt. According to the authors these were the only cases of the disease that had occurred among a total 3000 hard-metal exposed workers over the years. Work-related asthma, as documented by positive cobalt challenge tests, has been found in 3 cases of hard-metal workers in Japan, who reportedly had been exposed to cobalt concentrations of no more than 0.018 to 0.031 mg/m^3 (176). Interestingly, two of these also appeared to have worked as wet grinders. Similarly, Sprince et al (295) found evidence of interstitial lung disease in three hard-metal workers with average lifetime exposure to cobalt in concentrations below 0.008 mg/m^3.

11. 2. 2. Cardiac effects

In addition to the data on respiratory effects, there are also studies on cardiac function and ECG changes in relation to cobalt exposure. In a study of Swedish hard-metal workers, Alexandersson and Atterhög (7) found that wet grinders exposed to an average of 0.01 mg Co/m^3 had an increased frequency of ECG changes (depressed ST- and T-waves, arrythmia) compared to unexposed controls, whereas no changes were seen in powder handlers exposed to higher concentrations (0.06 mg Co/m^3). The ECG changes did not appear to be related to the duration of employment, since the difference in frequency of abnormalities in workers with long-term exposure (> 7-8 y) and matched controls was similar to that in workers with shorter exposure periods. The authors concluded that the changes seen in wet grinders were probably not due to cobalt. However, a follow-up study demonstrated that the differences in ECG recordings between wet grinders and controls disappeared after four weeks holiday (8).

In contrast to these findings, no differences in ECG recordings were seen in heavily exposed plate decorators (0.8 mg Co/m^3) compared to controls, except for higher pulse rate in the exposed (258). The pulse rate, however, was not correlated with blood or urinary cobalt.

Cardiac function has also been evaluated in a group of 30 American hard-metal workers by gated cardiac blood pool imaging (129). Although the workers had been exposed to cobalt for an average of 10 years (no exposure level reported), there was no evidence of cardiac dysfunction. However, a weak but significant

inverse correlation was found between left ventricular function and duration of exposure.

12. Evaluation of Human Health Risks

12.1. Groups at extra risk

Wet grinders exposed to dissolved cobalt in aerosols of coolants appear to have an increased risk of lung diseases (288, 295). Whether this is due to enhanced toxicity of the cobalt ion vs. metallic cobalt, or is due to a synergistic effect of cobalt and coolant (or microorganisms in coolants) needs to be documented.

Animals studies, as well as observations in humans, suggest that smokers and groups with simultaneous exposure to other types of dust (e.g. diamonds, tungsten carbide) may have an increased risk of lung and airway diseases, particularly the interstitial lung diseases (see f.ex. 307). Moreover, females may be at higher risk due to higher absorption of cobalt (see 53).

12. 2. Assessment of health risks

The most important health risks associated with exposure to cobalt and cobalt compounds in the occupational setting are skin sensitization (allergic contact dermatitis), interstitial lung diseases, and obstructive lung diseases. The risk of asthma and asthma-like symptoms, as well as the risk of abnormal radiological findings, increases at exposure levels above 0.05 mg/m^3 (268, 295). While effects on the heart, blood, and thyroid gland have been observed in experimental animals and in humans after oral or i.v. administration of cobalt salts, there are only isolated reports on systemic effects after occupational exposure to cobalt.

Cobalt and cobalt compounds are mutagenic in several microbial test systems. Furthermore, cobalt and some cobalt compounds have been show to be carcinogenic in experimental animals after intramuscular injection or intratracheal instillation. However, from the available epidemiological studies it is not possible, at present, to draw firm conclusions on the carcinogenic risk of cobalt exposure in the work environment.

12. 3. Scientific basis for an occupational exposure limit

Effects on lung function has consistently been demonstrated at exposure levels down to 0.05 mg Co/mg^3. Acute, reversible effects (irritation, decreased FVC) have been shown in healthy subjects exposed to 0.038 mg Co/m^3. At average exposure levels below this value, there are isolated cases of allergic alveolitis and work-related asthma. Cardiac effects (ECG changes) reported in hard-metal workers at 0.01 mg/m^3 are not convincing as they do not occur at higher exposure levels. In addition, it should be noted that a well performed study on powder

metal workers (mixed dust exposure) did not demonstrate any respiratory effects at an average cobalt concentration of 0.017 mg/m^3, except for chronic cough in exposed smokers.

In the occupational setting where inhalation exposure is dominating, the critical effects are those related to the lungs and respiratory tract. Thus, an air concentration of 0.05 mg Co/m^3 may be taken as the LO(A)EL and 0.01 mg Co/m^3 may be considered the LOEL for occupationally exposed humans. It is possible, however, that particularly sensitive persons, or workers with exposure to dissolved cobalt (cobalt ions in aerosols of coolants) may react adversely at even lower concentrations. Furthermore, additional consideration should be given to the fact that cobalt is a skin sensitizing agent and possibly also carcinogenic.

13. Research Needs

It has been suggested that dissolved cobalt has enhanced toxicity compared to metallic cobalt dust. This needs further documentation both in experimental animals and in humans with occupational exposure to dissolved cobalt compounds. Furthermore, information on synergistic effects of cobalt and other inhalation exposures (e.g. nickel, tungsten carbide, aerosols of coolants) are needed.

The isolated reports on cases of cardiomyopathy seen in cobalt exposed workers in a mineral assay laboratory and powder metal workers (24, 135, 154) should prompt further studies with particular attention to cardiovascular diseases. Similarly, recent observations suggesting a possible effect of cobalt on thyroid function in exposed workers (257, 307) should be followed up by more detailed studies.

There is also a need for more information on the possible genotoxic effects in workers with exposure to cobalt and cobalt compounds. Well-performed epidemiological studies with a large study population and control of confounding factors (mixed exposure) are also needed in order to evaluate the cancer risk of occupational exposure to cobalt. In this context it should be noted that an epidemiological study of cancer and mortality rate in Danish plate decorators exposed to cobalt blue dyes is in progress (see 52).

Finally, future studies should pay more interest to exposure characterization, i.e., chemical form of exposure, size distribution of particles in dust, etc.

14. Summary

Midtgård U, Binderup ML. 114. Cobalt and cobalt compounds. The Nordic Expertgroup for Criteria Documentation of Health Risks from Chemicals. *Arbete och Hälsa* 1994;39:1-65.

Cobalt and cobalt compounds are industrially important and there are numerous reports on serious health effects that can be ascribed to cobalt exposure in the work environment. This document summarizes the major scientific aspects relevant for setting an occupational exposure limit for cobalt.

The major route of exposure in the work environment is through inhalation, but skin contact with cobalt containing products (cement) is also important in some types of jobs. The absorbed cobalt is distributed by the blood and accumulates in the liver, kidney, heart, and pancreas. Excretion is predominantly via the kidneys and is characterized by a fast, initial elimination followed by a more long-lasting component. There seems to be a good correlation between cobalt exposure and cobalt in blood or urine, but the degree of correlation depends on the individual cobalt compound (soluble or insoluble) and the time of sampling.

Animal experiments and human data have shown that cobalt has an effect on most organs. Particularly relevant for the occupational setting are the effects on the respiratory system (asthma, interstitial lung diseases), which have been seen in hard-metal workers and in diamond polishers using cobalt-diamond abrassive disks. Skin reactions (allergic dermatitis) have been reported in construction workers who have contact with cement. In addition, cobalt has an effect on the heart and hematopoietic system, and recent studies also suggest that the thyroid function may be affected in persons with occupational exposure to cobalt (ceramic plate decorators). Finally, cobalt has been found to be mutagenic in most test systems and there is evidence suggesting that cobalt and cobalt compounds are possibly carcinogenic. However, the epidemiological cancer data are very limited and further studies are needed to evaluate the carcinogenic risk of occupational cobalt exposure.

The effects on the respiratory system can be considered the critical effects. The lowest observed adverse effect level (LOAEL) in humans is 0.05 mg Co/m^3 and the lowest observed effect level (LOEL) is around 0.02 mg Co/m^3. However, it is possible that particularly sensitive persons may react at even lower exposure levels.

Key words; Asthma, cancer, cobalt, cobalt cardiomyopathy, genotoxicity, hard-metal disease, health effects, kinetics, occupational exposure, occupational hazards, review, toxicology.

15. Summary in Danish

Midtgård U, Binderup ML. 114. Kobolt og koboltforbindelser. Nordiska Expertgruppen för Kriteriedokumentation av Kemiska Hälsorisker. *Arbete och Hälsa* 1994;39:1-65.

Kobolt og koboltforbindelser har stor industriel betydning, og der findes mange rapporter om alvorlige helbredseffekter, som kan tilskrives eksponering for kobolt i arbejdsmiljøet. Dette dokument omhandler de vigtigste videnskabelige aspekter, der er relevante for fastsættelse af en grænseværdi i arbejdsmiljøet.

Den vigtigste form for eksponering i arbejdsmiljøet er gennem inhalation, men hudkontakt med produkter, der indeholder kobolt (cement) er også af betydning i visse typer af beskæftigelse. Det optogne kobolt distribueres med blodet og akkumuleres i lever, nyrer, hjerte og bugspytkirtlen. Udskillelsen, der hovedsagelig foregår gennem nyrerne, er karakteriseret ved en i starten hurtig udskillelse, der følges af en mere langsam elimination. Der synes at være en god korrelation mellem kobolteksponering i arbejdsmiljøet og koboltkoncentrationen in blod og urin. Graden af korrelation afhænger dog af, hvilke koboltforbindelser man er eksponeret for, og tidspunktet hvor blod- og urinprøverne tages.

Dyreforsøg og humandata har vist, at kobolt har en effekt på de fleste organer. Særlig relevant i arbejdsmiljømæssig sammenhæng er effekterne på åndedrætsorganerne (astma og lungefibrose), som bl.a. er kendt fra koboltekseponerede hårdmetalarbejdere og diamantslibere, som bruger polérskiver bestående af mikro-diamanter indlagt in en koboltmatrix. Hudreaktioner (allergisk dermatitis) ses bl.a. hos bygningsarbejdere, som har kontakt med cement. Derudover har kobolt en effekt på hjerte og bloddannende væv, og nyere undersøgelser antyder også, at skjoldbruskkirtlens funktion kan være påvirket hos arbejdere med kobolteksponering (plattemalere). Endelig skal det nævnes, at kobolt er fundet mutagent i de fleste testsystemer, og der er evidens for, at kobolt og koboltforbindelser muligvis er kræftfremkaldende. Dog er de epidemiologiske data meget begrænsede, og yderligere undersøgelser er påkrævet for at kunne vurdere cancerrisikoen af kobolt i arbejdsmiljømæssig sammenhæng.

Effekterne på åndedrætsorganerne må anses for at være de kritiske effekter. Det laveste observerede (uønskede) effektniveau hos mennesker (LOAEL) er 0,05 mg Co/m^3 og det laveste observerede effektniveau (LOEL) er omkring 0,02 mg Co/m^3. Det er dog muligt, at særligt følsomme personer kan reagere ved endnu lavere eksponeringsniveauer.

Nøgleord:Arbeidsmiljø, cancer, eksponering, genotoxicitet, helbredsrisici, hårdmetallungesygdomme, kardiomyopati, kinetik, kobolt, koboltasthma, review, toksikologi.

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Appendix 1.

Permitted or recommended maximum levels of cobalt (elemental and inorganic compounds, as Co) in air.

Country	ppm	mg/m^3	Comments	Year	Ref.
Denmark	-	0.05		1988	1
Finland	-	0.05		1993	2
Iceland	-	0.05	S	1989	3
Netherlands		0.05		1994	4
Norway	-	0.05	S	1989	5
Sweden	-	0.05	S	1993	6
USA (ACGIH)	-	0.02	A3	1994-95	7
(NIOSH)	-	0.05		1990-91	8

A3: animal carcinogen
S: senziticing

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CRITERIA DOCUMENTS FROM THE NORDIC EXPERT GROUP

The Criteria Documents are in a Scandinavian language, with summary in English. Those marked with * are in English. Those marked with D are published in collaboration with the Dutch Expert Committee for Occupational Standards (DECOS). Those marked with N are published in collaboration with NIOSH, USA.

Acetaldehyde	Arbete och Hälsa 1986:25
Acetone	Arbete och Hälsa 1986:39
Acetonitrile	Arbete och Hälsa 1989:22, 1989:37*
Acrolein	Arbete och Hälsa 1991:45
Acrylates	Arbete och Hälsa 1983:21
Acrylonitrile	Arbete och Hälsa 1985:4
Allyl alcohol	Arbete och Hälsa 1986:8
Aluminium	Arbete och Hälsa 1992:45, 1993:1*
Ammonia	Arbete och Hälsa 1986:31
Arsenic, inorganic	Arbete och Hälsa 1981:22, 1991:9, 1991:50*
Arsine	Arbete och Hälsa 1986:41
Asbestos	Arbete och Hälsa 1982:29
Benomyl	Arbete och Hälsa 1984:28
Benzene	Arbete och Hälsa 1981:11
Boric acid, Borax	Arbete och Hälsa 1980:13
1,3-Butadiene	Arbete och Hälsa 1994:36*
1-Butanol	Arbete och Hälsa 1980:20
Cadmium	Arbete och Hälsa 1981:29, 1992:26, 1993:1*
7/8 Carbon chain aliphatic monoketones	Arbete och Hälsa 1990:2*D
Carbon monoxide	Arbete och Hälsa 1980:8
Chlorine, Chlorine dioxide	Arbete och Hälsa 1980:6
Chloromequat chloride	Arbete och Hälsa 1984:36
4-Chloro-2-methylphenoxy acetic acid	Arbete och Hälsa 1981:14
Chlorophenols	Arbete och Hälsa 1984:46
Chromium	Arbete och Hälsa 1979:33
Cobalt	Arbete och Hälsa 1982:16
Copper	Arbete och Hälsa 1980:21
Creosote	Arbete och Hälsa 1988:13, 1988:33*
Cyclohexanone, Cyclopentanone	Arbete och Hälsa 1985:42
n-Decane	Arbete och Hälsa 1987:25, 1987:40*
Deodorized kerosene	Arbete och Hälsa 1985:24
Diacetone alcohol	Arbete och Hälsa 1989:4, 1989:37*
Diesel exhaust	Arbete och Hälsa 1993:34, 1993:35*
2-Diethylaminoethanol	Arbete och Hälsa 1994:25*N
Diethylamine, Diethylenetriamine, Dimethylamine & Ethylenediamine	Arbete och Hälsa 1994:23*
Diisocyanates	Arbete och Hälsa 1979:34, 1985:19
Dimethyldithiocarbamates	Arbete och Hälsa 1990:26, 1991:2*
Dimethylethylamine	Arbete och Hälsa 1991:26, 1991:50*
Dimethylformamide	Arbete och Hälsa 1982:28
Dimethylsulfoxide	Arbete och Hälsa 1991:37, 1991:50*
Dioxane	Arbete och Hälsa 1982:6
Epichlorohydrin	Arbete och Hälsa 1981:10
Ethyl acetate	Arbete och Hälsa 1990:35*D
Ethylbenzene	Arbete och Hälsa 1986:19
Ethylene bisdithiocarbamates	Arbete och Hälsa 1993:24, 1993:35*
Ethylenediamine	Arbete och Hälsa 1994:23*