Cobalt and its compounds

(as inhalable dusts or aerosols)

MAK value	**–**
Peak limitation	**–**
Absorption through the skin	**–**
Sensitization (1995)	**Sah**
Carcinogenicity (1971)	**Category 2**
Prenatal toxicity	**–**
Germ cell mutagenicity (2001)	**3A**

Substance	CAS number	Molecular formula
Cobalt metal	7440-48-4	Co
Cobalt (II) sulfide	1317-42-6	CoS
Cobalt (II) oxide	1307-96-6	CoO
Cobalt (II,III) oxide	1308-06-1	Co_3O_4
Cobalt (II) carbonate	513-79-1	$CoCO_3$
Cobalt (II) sulfate and comparable soluble salts	10026-24-1	$CoSO_4 \cdot 7\ H_2O$

New facts on carcinogenicity have become known since publication of the documentation in which cobalt and its compounds were classified as carcinogenic (Cobalt and cobalt compounds, Volume 3 of the present series). The most important of these is that the carcinogenicity of readily soluble cobalt sulfate has been demonstrated in inhalation tests with rats and mice. Owing to their particular physical, chemical and biological properties, hard metal dust and organic cobalt siccatives such as cobalt octoate and cobalt naphthenate are not included in this assessment.

1 Mechanism of Action

Cobalt and cobalt compounds were genotoxic *in vitro* and in the bone marrow of mice and hamsters. The genotoxic effect of cobalt ions probably takes place via the production

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of radical oxygen species, as 5 of 9 of the mutations found in tumour tissue in the carcinogenicity study of the NTP with cobalt sulfate in mice were G-T transversions in codon 12 of the K-ras oncogene. The authors interpret this transversion as supportive evidence that cobalt sulfate heptahydrate may indirectly damage DNA by oxidative stress (NTP 1998). This hypothesis is supported by direct proof that radical oxygen species are produced by the interaction between cobalt, tungsten carbide and oxygen in hard metal dusts (Lison *et al.* 1995). In human lymphocytes, the clastogenic effect of cobalt dust was weaker than that of a combination of cobalt and tungsten carbide (Anard *et al.* 1997, de Boeck *et al.* 1998, van Goethem *et al.* 1997).

The genotoxicity of other mutagenic agents was increased by cobalt ions (Beyersmann and Hartwig 1992) and cobalt dusts (de Boeck *et al.* 1998). Attention was drawn to this relationship by the inhibitory effect of cobalt ions on the repair of DNA damage (Kasten *et al.* 1997). In particular, the function of the XPA protein from mammalian cells participating in the nucleotide excision repair is inhibited by cobalt(II) ions (Asmuß *et al.* 2000). Evidence of a cocarcinogenic effect in animal studies, in which cobalt(II) oxide increased the carcinogenic effect of benzo(a)pyrene, corresponds to the comutagenic properties found (Steinhoff and Mohr 1991). Empirical evidence in humans also provides evidence for disturbed DNA repair due to cobalt. Both an increased number of DNA single strand breaks and reduced repair capacity for oxidative DNA damage in lymphocytes were found in a subgroup of 11 subjects from a group of 78 metal workers, who were exposed to > 4 g/m^3 cobalt at the work site (Oesch *et al.* 1999).

2 Toxicokinetics

2.1 Solubility data

Because of the carcinogenicity of soluble cobalt sulfate found in animal experiments, which must be attributed to the properties of cobalt ions, it is important to take the solubilities of other cobalt compounds in water and biological fluids into account. For pragmatic reasons, cobalt compounds are divided into two groups, those soluble in water at levels above 0.1 g/l, and those poorly soluble in water at levels below 0.1 g/l. The data available on the solubility of cobalt and its compounds can be found in Table 1.

Table 1. Solubility of cobalt und cobalt compounds

Substance	Molecular formula	CAS number	Solubility in H_2O (temperature)	Solubility in serum
Cobalt metal	Co	7440-48-4	poorly soluble [1]	200 mg/l (37 C)
Cobalt(II) oxide	CoO	1307-96-6	poorly soluble; 3.13 mg/l	273 mg/l (37 C)
Cobalt(III) oxide	Co_2O_3	1308-04-9	poorly soluble	
Cobalt(III) oxide · H_2O	$Co_2O_3 \cdot H_2O$	12016-80-7	poorly soluble; 0.84 mg/l (37 C)	53.9 mg/l (37 C)
Cobalt(II,III) oxide	Co_3O_4	1308-06-1	poorly soluble	
Cobalt(II) hydroxide	$Co(OH)_2$	21041-93-0	poorly soluble; 3.2 mg/l (18 C)	
Cobalt(III) hydroxide	$Co(OH)_3$	1307-86-4	poorly soluble; 3.2 mg/l (20 C)	
Cobalt(II) sulfide	CoS	1317-42-6	poorly soluble; 3.8 mg/l (18 C)	
Cobalt(II) carbonate	$CoCO_3$	513-79-1	soluble 1.1 g/l (15 C)	
Cobalt(II) nitrate · 6 H_2O	$Co(NO_3)_2$	10026-22-9	soluble 134 g/l (0 C)	
Cobalt(II) acetate	$Co(CH_3COO)_2$	71-48-7	soluble 380 g/l (25 C)	
Cobalt(II) sulfate	$CoSO_4$	10124-43-3	soluble 393 g/l (25 C)	
Cobalt(II) chloride	$CoCl_2$	7646-79-9	soluble 529 g/l (20 C)	

[1] solubility < 0.1 g/l; no exact numerical values available

The first group includes cobalt sulfate and other, comparable, inorganic cobalt salts, whereas cobalt metal, cobalt oxides, cobalt hydroxides and cobalt sulfide are in the second group. Nevertheless, in the case of cobalt metal in powder form, cobalt(II) oxide and cobalt(III) oxide hydrate, a higher solubility was found in blood serum when compared with that in water. This agrees with the data on the absorption of cobalt from inhaled hard metal and cobalt metal in exposed workers in the hard metal production industry, in cobalt foundries, and in cobalt electrolysis installations (Angerer et al. 1989, IARC 1990).

2.2 Absorption and Distribution

2.2.1 Metallic (elemental) cobalt

Elemental cobalt is absorbed into the lung tissue of exposed humans and results in increased concentrations of soluble cobalt in blood and urine (Angerer *et al.* 1989). In a study with rats, ultrafine cobalt particles (20 nm) attain solubility in the lungs within hours, larger particles (11 m) have pulmonary half-lives of 3–4 days (Edel *et al.* 1994).

2.2.2 Oxidic cobalt compounds

The poorly soluble cobalt(II,III) oxide has a good *in vitro* absorption rate in human and canine macrophages, and is solubilized intracellularly, whereby, with a half-life of 14 days, the rate of dissolution of 0.3 m particles is about ten times more rapid than that of particles sized 0.8 m (Kreyling *et al.* 1990). In dogs, *in vivo* half-lives between 6 and 80 days were measured for the dissolution of cobalt oxides in pulmonary macrophages (Kreyling *et al.* 1986). The solubilized cobalt is transferred into the blood, while the particulate fraction is transported to the larynx via mucociliary clearance and subsequently reaches the gastrointestinal tract by means of swallowing (Kreyling *et al.* 1993).

2.2.3 Sulfidic cobalt compounds

The phagocytosis of cobalt sulfides in Syrian hamster embryo cells depends on the crystalline form encountered and the surface charge. Crystalline, negatively charged particles are absorbed more rapidly than amorphous, positively charged ones (Abracchio *et al.* 1982).

2.2.4 Soluble cobalt compounds

After oral administration to **rats** (dose of cobalt 33.3 mg/kg body weight), cobalt(II) chloride was poorly absorbed in the intestine in conjunction with a primarily passive transport mechanism. Elimination was relatively rapid: 75 % of the absorbed dose was excreted within 36 hours (Ayala-Fierro *et al.* 1999). After intravenous injection of cobalt(II) chloride into rats, cobalt ions were quickly eliminated from the blood with an initial half life period of 1.3 hours. Also after subcutaneous injection of cobalt(II) chloride into rats, cobalt was eliminated from the blood plasma at a half-life of around 25 hours (Rosenberg 1993).

In male **rats**, a single intravenous injection of [^{57}Co]-cobalt(II) chloride was distributed in the blood, liver, lung, spleen and epididymides, but was not found in germ cells. The marked uptake of cobalt in the nuclei of liver (24.0 %) and kidney (19.5 %)

cells is important in the context of genotoxicity. The *in vitro* absorption of cobalt by rat sperm cells after treatment with [^{57}Co]-cobalt(II) chloride has been demonstrated (Edel *et al.* 1994).

After ingestion of a comparatively high cobalt dose (around 72 mg/kg body weight) in the form of cobalt(II) chloride in the drinking water for 10 weeks, male **mice** revealed an increase in the tissue concentrations of cobalt: the increase factors were 1.9 in the liver, 2.2 in the kidneys, 2.5 in the testes and 1.7 in the epididymides (Pedigo and Vernon 1993).

In another study, cobalt(II) chloride was administered to male **rats** in their diet for 14 days. Six animals per group received a total dose of 0, 5 or 20 mg/kg body weight. Increased cobalt concentrations in blood, brain, intestine, kidneys, liver, and testes were found after 69 days in the 5 and 20 mg/kg groups. The cobalt concentrations in the testes were increased in a dose-dependent manner by about ten to one hundred times that of the controls (cobalt at levels of 0.2 or 2 g/g tissue respectively) (Nation *et al.* 1983).

In a study with **sheep**, four male animals per group were fed daily for 70 days with cobalt doses of 0, 3.0 and 4.5 mg/kg in the form of gelatine capsules filled with cobalt(II) chloride. The cobalt dose was increased to 0, 10 and 15 mg/kg for a further 38 days. The animals were killed at the end of this period, and the cobalt concentrations measured in liver, kidneys and testes. These were increased in all three organs of the treated groups, but without significant differences between the lower and the higher dose group (Corrier *et al.* 1986).

3 Effects in Humans

3.1 Single exposures

On opening a bag containing cobalt phthalocyanine in powder form (Merox catalyst), a worker in a mineral oil refinery inadvertently received a considerable quantity of it in his mouth. Five months later, a giant cell tumour developed in his mouth (Schulz 1978).

3.2 Repeated exposures

3.2.1 Cobalt compounds in metal foundries

During 1983/1984 in a metal smelter located in Goslar (Germany), a field study was conducted in a population of 40 metal workers who had been exposed to cobalt. Their mean age was 42.7 ± 9.3 years and the total mean duration of exposure to cobalt was 11.3 ± 8.04 years. Owing to spatial circumstances, an additional exposure to nickel could not be excluded. The mean cobalt concentration in the air at the workplace was

313.6 ± 451.4 g/m^3 (Wegner *et al.* 1986). Table 2 summarizes the air concentrations and the corresponding serum levels for the different work areas involved.

Table 2. Cobalt concentrations in air and blood of persons exposed to a metal smelter (from Wegner *et al.* 1986)

Work area	Number of cases	Cobalt in air (g/m^3)		Cobalt in blood (g/l)	
		$\bar{x}$	s	$\bar{x}$	s
Reduction	12	49.1	84.0	0.49	2.6
Electrolysis	11	238.8	133.8	1.86	10.2
Grinding/sieving	6	1045.7	692.2	5.22	64.7
Salts	9	338.9	349.3	1.77	10.8

$\bar{x}$: mean value; s: standard deviation

The investigations performed in smelter workers, such as blood count, lung function tests and radiographic screening of the lungs, yielded no evidence for a cobalt-specific syndrome. It was possible to determine the cause of death in 67 out of a total 70 deceased former smelter workers who had been exposed to cobalt for at least ten years (Table 3). The age of smelter workers having died from lung cancer was 63.6 ± 10.03 years, thus being somewhat lower than the mean age at death of the total collective (65.7 ± 10.23 years); the length of employment in the smelter was, at 27.3 ± 9.07 years, markedly above the mean value of the total collective studied (20.9 ± 8.04 years). The percentage of deaths due to cancer in the collective was, at 43.3 %, markedly above the value for the population of the Federal Republic of Germany in 1981 (23 %). As a result of the lack of decisive information on study design, this study, only published in the form of an expanded summary in a symposium volume, must be regarded as being inadequate and not relevant for evaluation. Furthermore, a simultaneous exposure to nickel or a previous exposure to arsenic during work in the pesticides department of the plant cannot be excluded as cause for the increased level of cancer mortality. Finally, the proportion of smokers among the workers who died from lung carcinoma was relatively high.

Table 3. Number and percentage of specific causes of death in employees of a metal smelter (from Wegner *et al.* 1986)

Cause of death	Number and percentage of specific causes of death	Of whom smokers
Bronchial carcinoma	13/67 (19.4%)	12/13 (92.3%)
Stomach carcinoma	6/67 (9.0%)	5/6 (83.3%)
Other malignant tumours	10/67 (14.9%)	
Total number of malignant tumours	29/67 (43.3%)	
Respiratory diseases	5/67 (7.5%)	
Cardiovascular diseases	30/67 (44.8%)	
Other diseases	3/67 (4.5%)	

3.2.2 Cobalt metal

Evidence indicating a clastogenic effect of cobalt is found in humans. Both an increased number of DNA single strand breaks and a reduced repair capacity for oxidative DNA damage in lymphocytes was found in a subgroup of 11 persons from a group of 78 metal workers, who were exposed to > 4 g/m^3 cobalt at the workplace (Oesch *et al.* 1999). By contrast, no increase in micronuclei, DNA breaks or oxidative DNA damage in lymphocytes was found in a group of 24 workers exposed to cobalt (21.5 g cobalt/g creatinine in urine) and 29 workers exposed to hard metal dust (19.9 g cobalt/g creatinine in urine) versus control persons (1.7 g cobalt/g creatinine in urine) (de Boeck *et al.* 2000).

A study in a cohort of 1143 French workers in electrochemical cobalt production initially showed an increased mortality due to lung cancer (see Table 4) (Mur *et al.* 1987). The usefulness of this study in regard to cobalt is limited on account of the low number of cases (n = 4) and the presence of nickel and arsenic ions in the raw material processed (IARC 1990). During the extended follow-up period of this cohort, no additional cases of lung cancer mortality were observed in now 1148 workers, so that no increased risk of lung cancer mortality was cited in the upated analysis (3 cases, standard mortality rate (SMR) 1.16; 95 % confidence interval (CI) 0.24–3.40) (Moulin *et al.* 1993). These results are not conclusive for the classification of cobalt metal as a carcinogen.

In a historical cohort study, 4897 workers in the manufacture of stainless steel and steel alloys starting employment between 1968 and 1991 and working for periods of at least one year were investigated. A total of 54 cases of lung cancer mortality were recorded in the cohort (SMR 1.19; 95 % CI 0.89–1.55) (Moulin *et al.* 2000). An expert-based, semiquantitative exposure estimate for a large number of hazardous substances was carried out in a nested case-control study for the 54 cases of lung cancer mortality. Retrospectively, smoking habits were recorded for 71 % of the cases and controls. In the raw analyses adapted for smoking habits and other hazardous substances, none of the surrogate variables used for cobalt exposure showed an association between cobalt

exposure and lung cancer risk. The usefulness of this study is limited because the exposure estimates were based on a subjective estimate in the experts' interviews, no information was provided on the level of exposure to cobalt and no association between the lung cancer risk and exposure to chromium, nickel or asbestos could be observed.

3.2.3 Summary of epidemiological results

The epidemiological results available for the carcinogenicity of cobalt and its compounds in humans are summarized in Table 4. As a result of the, at least in part, considerably limited validity and precision of the few studies published, the available epidemiological data on cobalt metal cannot be used to assess a possible carcinogenicity of cobalt metal in humans.

Table 4. Epidemiological studies of lung carcinogenicity from cobalt and cobalt compounds

Cobalt metal/ cobalt compounds	Study collective	Cobalt exposure/ potential confounders	Observed deaths from lung cancer	Reference
Cobalt compounds	67 cases of death among workers in smelting: ore reduction, electrolysis, grinding and sieving, handling of cobalt salts	duration of employment/ tobacco smoking, arsenic, probably nickel	13/67 (14.9%)	Wegner *et al.* 1986
Cobalt metal	cohort of 1143 workers, exposure >1 year in electrochemical cobalt production, follow-up 1950–1980	exposure estimation of workplace/tobacco smoking, arsenic, nickel	4 cases, SMR 4.66; 95% CI 1.46–10.64	Mur *et al.* 1987
Cobalt metal	follow-up 1950–1988	see above	3 cases *, SMR 1.16; 95% CI 0.24–3.40	Moulin *et al.* 1993
Cobalt metal	historical cohort study (n = 4897) subjects exposed to cobalt in steel alloy production, start of employment 1968–1991, employment >1 year, nested case-control study	expert-based, semiquantitative exposure estimation for cobalt and numerous other hazardous substances, adjusted for smoking habits and other hazardous substances	54 cases, SMR 1.19; 95% CI 0.89–1.55; OR (cobalt) 0.44; 95% CI 0.17–1.16; adjusted for smoking habits, quartz and PAH	Moulin *et al.* 2000

* One death from lung cancer in the first follow-up could not be confirmed in the extended follow-up.

CI: confidence interval; OR: odds ratio; PAH: polycyclic aromatic hydrocarbons; SMR: standard mortality rate

3.3 Allergenic effects

3.3.1 Skin

Cobalt chloride is routinely tested in practically all patients with suspected contact dermatitits in the epicutaneous test. This is why a large number of findings are available on this substance, not all of which can be described here. Among the patients who reacted positively, however, a well-defined exposure to cobalt is only rarely found. For this reason the clinical importance of cobalt and cobalt salts as causes for an allergic contact dermatitits can only be assessed with difficulty. Isolated epicutaneous test reactions to cobalt salts are relatively rare (Cavelier *et al.* 1989, Fregert and Rorsman 1966, van Joost and van Everdingen 1982, Rystedt 1979). Sensitization to cobalt is more frequently found in young women with a nickel sensitization already present (Enders *et al.* 1988). The extent of this association apparently depends on the degree of sensitization to nickel and on the score of the test reaction to nickel sulfate (Brasch and Geier 1997, van Joost and van Everdingen 1982). To a lesser extent, reactions to cobalt chloride have also been found in women presenting a dichromate sensitization (Geier *et al.* 2000).

In the epicutaneous test, a 1 % preparation of cobalt chloride in petrolatum is generally used. A concentration of around 0.01–0.1 % cobalt chloride is considered to be the threshold value at which an allergic reaction is produced in the epicutaneous test (Rystedt 1979, Wahlberg 1973). Patients with marked sensitization also react to lower concentrations (Fischer and Rystedt 1983), and a reaction can be elicited by as low as 0.001 % cobalt chloride in damaged skin (Allenby and Basketter 1989).

A reaction to cobalt chloride occurred in 1.1 % of 567 and in 2.3 % of 1141 tested subjects of two studies conducted on a demographic basis (Nielsen and Menn 1992, Sch fer *et al.* 2001). By contrast, a positive reaction to cobalt chloride in larger test collectives with patients in dermatological clinics is found over a wide range between below 5 % and over 20 % of the patients (see Table 5).

Increased rates of sensitization to cobalt were found in bricklayers and construction workers (Uter *et al.* 2004), metal surface processors and printers (Uter *et al.* 2002) in a multifactorial analysis of the epicutaneous test findings from the clinics of the Information Network of Departments of Dermatology (IVDK). Sensitization to cobalt is frequently found, particularly in bricklayers and construction workers with chromate eczema, as they are probably also exposed to cobalt in the cement (Geier and Schnuch 1998, Guo *et al.* 1999, Irvine *et al.* 1994, Wong *et al.* 1998). According to a Finnish investigation, cobalt or cobalt salts were the primary cause in 41 out of 2543 workers suffering from occupational contact dermatitis. In this case printers, lathe operators, machinists, toolmakers or mechanics were principally involved. The authors estimated the incidence at 0.03 cases per 10000 work years (Kanerva *et al.* 2000). Other fields in which occupationally induced sensitizations to cobalt are reported principally concern hard metal production and processing (Dickel *et al.* 2001, Fischer and Rystedt 1983, Hartung *et al.* 1990, Shum and Gawkrodger 2002) as well as porcelain and ceramics manufacturing (Gaddoni *et al.* 1993, Piril and Geier 1964). Case reports, some of which

are very incompletely documented, cited contact with coins (Kanerva *et al.* 1998), cattle feed containing cobalt (Ratcliffe and English 1998, Tuomi and R s nen 1995), a solution containing cobalt used in metal engraving (Gawkrodger and Lewis 1993) and cobalt naphthenate (Bedello *et al.* 1984, Minamoto *et al.* 2002, Wahlberg and Wrangsj 1985) as being causes of cobalt sensitization. A probably airborne contact dermatitits has been reported in two diamond polishers (Dooms-Goossens *et al.* 1986).

The genesis of the light-induced reactions to cobalt salts cited in the literature (Camarasa and Alomar 1981, Manciet *et al.* 1995, Romaguera *et al.* 1982) is not sufficiently clarified.

After induction treatment with 25 % cobalt sulfate, 10 of 25 volunteers reacted upon provocation with 2.5 % cobalt sulfate in petrolatum in the maximization test (Kligman 1966).

According to the results of two *in vitro* studies, only a few of the investigated nickel-specific T-cell clones of patients sensitized to nickel could also be stimulated by cobalt chloride (Moulon *et al.* 1995, Pistoor *et al.* 1995).

Table 5. Reports of allergic reactions in epicutaneous testing with cobalt salts in patients with contact dermatitis or suspected contact allergy

Subjects tested	Concentration (vehicle)	Result	Contact/Remarks	Reference
1005 patients	1% cobalt chloride (petrolatum)	reaction in 87 of 1005 (8.7%)	test period: 1989	Aberer and Reiter 1991
12026 patients	1% cobalt chloride (petrolatum)	reaction in 570 of 12026 (4.7%)	test period: 1977–1983	Enders et al. 1988
1310 patients	1% cobalt chloride (petrolatum)	reaction in 126 of 1310 (9.6%)	test period: not specified; 76 1+, 31 2+, 19 3+; also reaction to nickel in 76/126	van Joost and van Everdingen 1982
230 patients with suspected occupational contact dermatitis	1% cobalt chloride (petrolatum)	reaction in 20 of 230 (8.7%)	test period: 1998–5/2001; there was a reaction to at least one test substance in 130 of 230 patients tested	Nettis et al. 2003
987 patients	2% cobalt sulfate (water)	reaction in 42 of 987 (4.3%)	reaction in 29 of 199 patients (14.6%) of a selected collective of patients, who were tested specifically with cobalt chloride or cobalt nitrate as components of a metal test block in addition to the standard series	Rammelsberg and Pevny 1986
964 patients with suspected metal intolerance	1% cobalt chloride (petrolatum)	reaction in 227 of 964 (23.6%)	criteria and degree of reaction not specified; no information on the relevance of reactions; all 227 patients also reacted to 2.5% nickel sulfate in petrolatum; reaction also in 6 of 200 control subjects	Romaguera et al. 1988
5708 females 3064 males; 6335 females 3500 males	1% cobalt chloride (petrolatum)	reaction in 6.6%, 3.5%, 6.5%, and 3.5%, respectively	test period: 1993–1994	Schnuch and Geier 1995
67322 patients	1% cobalt chloride (petrolatum)	reaction in 5.4%	test period: 1995–2001; reaction in 4.3% of 23331 female subjects ≥ 40 years old, in 3.1% of 13679 males ≥ 40 years old, in 8.7% of 15313 females < 40 years old and in 3.4% of 8874 males < 40 years old	Schnuch *et al.* 2004

3.3.2 Respiratory tract

Indications that cobalt and cobalt compounds have a sensitizing effect on the respiratory tract principally result from investigations conducted with workers in hard metal production and/or processing, and from diamond polishing.

The most important findings, which indicate a sensitizing effect of cobalt compounds on the airways, are from case studies (see Table 6). A provocation test with cobalt chloride was positive in 12 workers with asthma in the hard metal industry and was apparently carried out using a dosimeter with concentrations of 10^{-5} to 1 % cobalt chloride. Positive intracutaneous test reactions to cobalt were also found in eight patients, and six of these eight patients reacted in the radioallergosorbent test (RAST) with cobalt–HSA conjugate. These patients also produced positive reactions in the intracutaneous test with nickel sulfate; specific IgE to nickel–HSA conjugate were also detected (Shirakawa *et al.* 1988, 1989, 1990).

In one of four investigated patients with positive intracutaneous test results and specific IgE to cobalt–HSA conjugate, a positive result was obtained in the lymphocyte transformation test with 12 or 59 g/ml cobalt chloride (Kusaka *et al.* 1989). Owing to the low number of controls used in intracutaneous testing, an evaluation of these results is difficult as various (non-specific) types of skin reaction could here be causal. The positive provocation tests with cobalt chloride in exposed persons, in whom workplace-related asthmatic symptoms were found, provide an important indication for a specific, airway-sensitizing effect of cobalt salts. A certain number of the patients in these investigations had apparently already been described in a cross-sectional study (Kusaka *et al.* 1986b). Later investigations reported evidence of specific IgE in persons with symptoms of asthma exposed to hard metal or cobalt (Kusaka *et al.* 1996, Shirakawa and Morimoto 1993). As clinical study findings were not reported, evaluation is only possible to a limited extent. In addition, it is not transparent as to what extent workers from earlier investigations were possibly also included in the collective investigated. In another publication, the findings of nine patients are described in whom cobalt asthma had been diagnosed between 1982 and 1990 and whose lung function was again checked one and three years later. In the follow-up investigation a deterioration of the lung function and an increase in non-specific reactivity and symptoms was found only in one worker subjected to further exposure. In the remaining eight persons, who had not been exposed any longer, recovery (two patients), improvement (five patients) or stabilization (one patient) of symptoms and lung function was diagnosed (Pisati and Zedda 1994).

Table 6. Reports on series of cases with results from studies on employees with asthma exposed to cobalt

Persons investigated	Findings	Reference
12 employees with asthma in hard metal production and processing	all patients positive in provocation tests with $CoCl_2$; 4 immediate reaction, 5 delayed reaction and 3 dual reaction with a decrease of FEV_1 of at least 20%; in 6 of 12 employees RAST with Co–HSA conjugate positive; 8 intracutaneous test positive (decisive concentrations documented only for 5 tests: 1 0.1%; 2 0.01%; 2 10^{-5} %); reaction to 2% cobalt chloride in the intracutaneous test in 1 of 8 control subjects; 2 positive epicutaneous test; collective overlaps with Kusaka *et al.* 1986b	Shirakawa *et al.* 1988, 1989, 1990
18 employees with asthma in hard metal production and processing	9/9 provocation tests with 2 ml 1% $CoCl_2$ positive; 2 immediate reaction (FEV_1 decrease by 27% and 35%), 5 delayed reaction (FEV_1 decrease by 20%–38%), 2 dual reaction; 9 patients refused testing with a provocation test; epicutaneous tests in 4/18 positive, of which provocation test was positive in 2/9 patients; all findings in a period of 3 years were summarized; 319 of a total of about 600 persons employed at the time were exposed to hard metal (cobalt exposure determined in the different production areas: 3–1292 g cobalt/m^3 on average); collective overlaps with Shirakawa *et al.* 1988, 1989, 1990	Kusaka *et al.* 1986b
9 employees with cobalt asthma	8 delayed reactions and 1 dual reaction with a decrease of FEV_1 by at least 15% in the provocation test with 0.2–0.3 mg $CoSO_4/m^3$ in an exposure chamber (7 m^3)	Pisati and Zedda 1994

FEV_1: forced expiratory volume in the first second; HSA:= human serum albumin; RAST: radioallergosorbent test

An investigation reported symptoms of asthma in 9 persons from a company with around 1500 workers producing tungsten carbide. A workplace-related reduction of vital capacity and forced expiratory volume in the first second (FEV_1) was determined in one employee and in one case an exposure test with cobalt powder resulted in an airway reaction after one hour (no further details) (Coates *et al.* 1973). An earlier survey describes asthmatic complaints in seven of 120 exposed persons in a cobalt refinery, no further findings were reported (Key 1961).

Not usable for assessment is the statement in an earlier investigation in workers of a nickel refinery, to the effect that workplace-related asthmatic symptoms occurred in one of the workers engaged in filling cobalt chloride as part of his occupation (no further details) (Morgan 1983).

An investigation of workers in porcelain painting reported only that the workers exposed to cobalt had worse lung function values and complained more frequently about respiratory tract symptoms than the control persons. There was no correlation between the cobalt concentrations measured in blood or urine of the exposed persons (Raffn *et al.* 1988). In a cross-sectional study of more recent date in 194 diamond polishers, a lower average forced vital capacity and a lower average FEV_1 were detected in 92 high-exposure workers in comparison to 102 low-exposure workers and 59 control persons. Rhinoconjunctivitis and coughing were more frequent in cases of high exposure than in the comparison groups. Average workplace-related exposure values determined in the three groups were 0.4, 1.6 and 10.2 g/m^3 cobalt (Nemery *et al.* 1992). Further investigations also indicate increased asthmatic symptoms or worse lung function values in workers exposed to cobalt or hard metal (Fischbein *et al.* 1992, Gennart and Lauwerys 1990, Linna *et al.* 2003, Meyer-Bisch *et al.* 1989, Sprince *et al.* 1988, Swennen *et al.* 1993). Bronchial provocation tests or other immunological investigations were not performed in any of these studies. Therefore, these findings indicate at best the frequency of respiratory tract diseases in workers exposed to cobalt. For this reason they cannot be included for assessment of the airway-sensitizing effect of cobalt.

A large number of case reports are available (Table 7) in which proof of sensitization using skin or *in vitro* tests was for the most part not performed. The diagnosis in these reports is based on a positive provocation test with cobalt sulfate, which was nebulized in a chamber, but in many cases also on an exposure test with materials not characterized in more detail such as grinding dust, hard metal dust or cobalt dust. The test results are on the whole difficult to interpret because corresponding control tests in non-exposed persons were either not performed or not described in detail. The results of the epicutaneous tests performed are not usable for the assessment of the sensitizing effect on the respiratory tract. A case report of a diamond polisher with workplace-related asthma symptoms and workplace-related decrease of peak expiratory flow (PEF) (Wilk-Rivard and Szeinuk 2001) cannot be taken into account because of exposure to mixed substances and the absence of allergological investigations.

Table 7. Case reports of results from studies of employees with asthma exposed to cobalt

Subjects investigated	Findings	Reference
toolmakers (hard metal workpieces) with asthma; secretary with asthma, rhinitis and dermatitis	in the provocation test with Spinhaler , immediate reaction in both subjects and less severe reaction to hard metal dust delayed by about 3 and 7 h; in the scratch test and the epicutaneous test with $CoCl_2$, reactions in the secretary working in a hard metal production factory	Hartmann *et al.* 1982
2 hard metal grinders with asthma	1 dual and 1 delayed reaction with decrease of the FEV_1 by 25–30% after provocation with 0.27 mg $CoSO_4/m^3$, which was nebulized in a chamber; no reaction after corticoid pretreatment; patients are possibly also documented in Pisati and Zedda 1994 (Table 6)	Pisati *et al.* 1986
hard metal grinder with asthma and 3 hard metal grinders with alveolitis	PEF decrease after provocation with dust from the factory in the patient with asthma; workplace-related decrease in the vital capacity and the FEV_1 in one employee with alveolitis; positive epicutaneous tests in all patients; no further allergological examinations performed	Sj gren *et al.* 1980
2 employees in hard metal production with asthma (1 with rhinitis)	dual reaction in 2 patients (FEV_1 decrease: 24%/42% after 10 h and 17% after 50 minutes/19% after 9 h), each after a 5-minute provocation test with 100 g hard metal powder or with 50 g cobalt powder	Davison *et al.* 1983
employees in hard metal processing with asthma	provocation, performed only with a metal powder mixture from nickel, cobalt and chromium, was followed by a reaction delayed by 3h with a decrease in FEV_1 by 48%; no prick or intracutaneous test performed; 1+ reaction to 1% $CoCl_2$ and 3+ reaction to nickel in epicutaneous test; lymphocyte transformation test with nickel and cobalt positive (no further details); because of exposure to the metal mixture, data not suitable for assessment	de Hauteclocque *et al.* 2002
diamond polisher with asthma and alveolitis	dual reaction on provocation with abrasive dust (3 5 minutes, 1 h apart); increased non-specific bronchial hyperresponsiveness 24 h after provocation	van Cutsem *et al.* 1987
3 diamond polishers with asthma	in all patients marked but hard to classify immediate reactions (FEV_1 decrease up to 50%) in provocation test (total 3 5 minutes each, 1 h apart) with fine cobalt abrasive dust	Gheysens *et al.* 1985

Table 7. continued

Subjects investigated	Findings	Reference
employee with asthma from a glassware factory	no reaction to 1 % cobalt sulfate in provocation test; isolated delayed reaction with a decrease of FEV_1 by about 40% after 2-minute provocation via nebulization of 10% cobalt sulfate (total cobalt intake: 38 mg); increase of the non-specific airway hyperresponsiveness on the day after challenge (PC_{20} (methacholine): 25 mg/ml → 2.5 mg/ml); reaction to intradermal testing with 1% and 10% cobalt sulfate, but no reaction to these solutions in the prick test	Baik *et al.* 1995
employee with asthma (cobalt resinate filling process)	immediate reaction with an FEV_1 decrease of 26% and delayed reaction after 4 h in provocation test by decanting cobalt resinate powder (2 5 minutes 1 h apart); 2 h after a 20-minute provocation test with cobalt stearate, beginning decrease of FEV_1; after 6 h decrease of FEV_1 by about 30% and symptoms of dyspnoea; only an immediate reaction classified as irritative, and no delayed reaction after provocation with Tall resin	Pilli re *et al.* 1990

FEV_1: forced expiratory volume in the first second; PEF: peak expiratory flow

4 Animal Experiments and *in vitro* Studies

4.1 Allergenic Effects

4.1.1 Skin

No sensitization could be produced in Hartley guinea pigs in a Buehler test with occlusive application of 50 % cobalt chloride in a 0.2 % aqueous solution of tetrapropylene benzene sulfonate carried out for at least three hours six times at one week intervals. The author nevertheless states that, though the cobalt preparation produced marked folliculitis after repeated application and reactions having a similar degree after provocation treatment in both treated and control animals, the frequency was higher in treated animals (9 of 10 versus 2 of 5 in controls) (Buehler 1965). All more recent animal studies, summarized in Table 8, revealed only positive results.

In an incompletely documented, open epicutaneous test, five female Hartley guinea pigs which had been sensitized through open application of 1 % $CoCl_2$ $6H_2O$ in lanolin alcohol five times per week for four weeks also reacted to the 48-hour occlusive

provocation treatment with 2 % $NiSO_4$ $6H_2O$ in lanolin alcohol. Animals sensitized to nickel sulfate also reacted to cobalt chloride (Cavelier *et al.* 1989). However, the cross-reactions observed in this study were observed either not at all or only to a very limited extent in other studies (Lammintausta *et al.* 1985, Lid n and Wahlberg 1994, Wahlberg and Lid n 2000), or could not be demonstrated with enough clarity due to the mixed exposures carried out. After provocation treatment with 0.1 % cobalt sulfate, 3 of 10 and 7 of 10 guinea pigs reacted after intradermal induction with 0.1 % cobalt sulfate and epicutaneous induction with 2.5 % cobalt sulfate in an incompletely documented maximization test (Goodwin and Johnson 1985). In a local lymph node assay with groups of three BALB/c mice, positive results were obtained with 5 % cobalt chloride in dimethyl sulfoxide (DMSO) only after three induction treatments but not after a single induction treatment. A tripling of the lymphocyte proliferation occurred only after skin abrasion when a preparation consisting of 5 % cobalt chloride in ethanol was applied (Ikarashi *et al.* 1992). In a more recent study applying 0.5 %, 1 % and 1.5 % cobalt chloride in DMSO to groups of four CBA/Ca mice, a threefold increase in lymphocyte proliferation was determined, though it was not concentration-dependent (stimulation index (SI): 3.2, 3.7 and 2.8, respectively) (Basketter *et al.* 1999).

4.1.2 Respiratory tract

In one experimental study, guinea pigs were sensitized epicutaneously to cobalt chloride in the cumulative contact enhancement test (see Table 8), before they were exposed to cobalt chloride in aerosol form six hours per day for two weeks (on average 2.4 mg/m^3 of cobalt). There was a tendency to an increase in neutrophils and eosinophils in the bronchoalveolar lavage fluid when compared with the control animals (non-sensitized but exposed, as well as sensitized, non-exposed animals) (Camner *et al.* 1993). No sensitizing effect of cobalt on the respiratory tract can be deduced from these findings.

4.2 Reproductive toxicity

In this section, only those investigations are considered which are of importance in assessing the germ cell mutagenic effects of cobalt and cobalt compounds.

In a study with CD1 mice, sperm concentration and testicular weight were unchanged following three intraperitoneal cobalt(II)chloride injections at 200 mol/kg body weight (11.8 mg/kg body weight of cobalt). After the administration of cobalt(II) chloride in the drinking water for 13 weeks at cobalt doses of 23, 42 or 72 mg/kg body weight and day, a dose-dependent decrease in fertility, sperm concentrations and testicular weight occurred (Pedigo *et al.* 1988).

In a dominant lethal test (see Section 4.3) with B6C3F1 mice, the frequency of preimplantation losses was significantly increased after treatment of male animals with cobalt(II) chloride in their drinking water for 10 weeks (400 mg cobalt per litre, around 72 mg/kg body weight) and subsequent mating with untreated females. It is possible to attribute the preimplantation losses to a reduced sperm cell concentration and assess this

as reduction in fertility. After a recovery period of 6 weeks, the sperm parameters motility and progressive velocity, though not the concentration, had reverted to normal values (Pedigo and Vernon 1993).

Testicular degeneration and necrosis, degeneration of Sertoli cells, reduced spermatogenesis and the formation of giant cells (in spermatocytes and/or spermatids) were observed in Sprague-Dawley rats after dietary treatment with cobalt(II) chloride (around 20 mg/kg body weight of cobalt) for 98 days. No effects were seen in the interstitial Leydig cells (Corrier *et al.* 1985).

Table 8. Results of experimental studies with cobalt salts in guinea pigs

Method, strain, sex	Induction, i.d. injection volume, concentration (vehicle)	Induction, epicutan. day, type of application, concentration (vehicle)	Provocation, day, type of application, concentration (vehicle)	Number of animals with reaction	Remarks	Reference
optimization test, Pirbright white, ♀ + ♂	d 1 (2), d 3 and d 5, 100 l of 0.1% $CoCl_2$; d 8, d 10, d 12, d 15, d 17 and d 19, 100 l of 0.1% $CoCl_2$ in FCA (isotonic saline)	–	d 36, i.d., 100 l 0.1% (isotonic saline); d 50, 24 h occlusive, 0.5% $CoCl_2$ (petrolatum)	19/20 1/19	no reaction in 20 control animals after provocation with the respective vehicle; reading after 24 h (intradermal provocation) and after 48 h (epicutaneous provocation)	Maurer 1985; Maurer *et al.* 1980
adjuvant patch test, Hartley, ♀	d 1, 4 100 l FCA	d1, d 2 and d 3, 24 h occlusive after skin abrasion, 3% $CoSO_4$ (water); d 8, non-occlusive 10% sodium dodecylsulfate in petrolatum; d 9, 48 h occlusive, 0.2 ml 3% (water)	d 22, non-occlusive, 10 l 0.003–3% $CoSO_4$ (water)	0.003%: 0/5 0.01%: 2/5 0.03%: 5/5 0.1%: 5/5 0.3%: 5/5 1%: 5/5 3%: 5/5	no data on reactions in control animals; readings after 24, 48 and 72 h	Yanagi *et al.* 2001
	d 1, 4 100 l FCA	d 1, 72 h occlusive after skin abrasion, 4 0.1 ml 3% $CoSO_4$ (water); d 7, 48 h occlusive after skin abrasion, 0.4 ml 3% (water)	d 14, non-occlusive, 10 l 0.003–3% $CoSO_4$ (water)	0.003: 0/5 0.01%: 0/5 0.03%: 5/5 0.1%: 5/5 0.3%: 5/5 1%: 5/5 3%: 5/5		

Table 8. continued

Method, strain, sex	Induction, i.d. injection volume, concentration (vehicle)	Induction, epicutan. day, type of application, concentration (vehicle)	Provocation, day, type of application, concentration (vehicle)	Number of animals with reaction	Remarks	Reference
maximization test, Hartley, ♀	d 1, 2 100 µl each substance, substance in FCA and FCA, 1% $CoCl_2$ (water)	d 8, 48 h occlusive, 5% (petrolatum)	d 22, 24 h occlusive, 0.1%, 0.5% and 1% $CoCl_2$ (petrolatum)	0.1%: 7/24 0.5%: 18/24 1%: 23/24	reading after 72 h; reaction in 3/24, 20/24 and 24/24 animals after 48 h; reaction in 1/25 FCA-pretreated control animals to 1% $CoCl_2$ after 72 h; tendency to more severe reactions in sensitized animals than in control animals after subsequent i.d. provocation with 0.025–0.2% $CoCl_2$	Wahlberg and Boman 1978
maximization test, Dunkin-Hartley, ♀	d 1, 2 100 µl each substance, substance in FCA and FCA, 1% $CoCl_2$ (water)	d 8, 48 h occlusive, 5% (petrolatum)	d 22, 24 h occlusive, 0.1% and 0.3% $CoCl_2$ (petrolatum)	0.1%: 5/15 0.3%: 11/15	reading after 48 h; reaction to 0.1% and 0.3% $CoCl_2$ in 2/15 and 1/15 control animals respectively; setting of concentrations for induction and provocation in FCA-pretreated control animals; reaction to $NiSO_4$ in 1 of 11 sensitized animals; reaction in 30/30 animals to 0.3% $CoCl_2$ in the second study, carried out along the same lines but incompletely documented	Lidén and Wahlberg 1994, Wahlberg and Lidén 2000

Table 8. continued

Method, strain, sex	Induction, i.d. injection volume, concentration (vehicle)	Induction, epicutan. day, type of application, concentration (vehicle)	Provocation, day, type of application, concentration (vehicle)	Number of animals with reaction	Remarks	Reference
modified cumulative contact enhancement test, Dunkin-Hartley, ♀	–	d 1, 3, 8 and 10, 24 h occlusive, 5% $CoCl_2$ (water)	d 22, 24 h occlusive, 0.1%, 0.5% and 1% $CoCl_2$ (isotonic saline solution)	0.1%: 11/16 0.5%: 14/16 1%: 16/16	reading after 48 h; positive reaction in 11/16, 15/16 and 16/16 animals, respectively after 24 h; provocation not performed in control animals; no FCA was used in deviation from the original protocol; provocation concentrations contradictorily documented	Camner *et al.* 1993
open epicutaneous test, Hartley, not specified	–	5 d per week, non-occlusive, 15% $CoCl_2$ (water) (1st week) and 10% $CoCl_2$ (water) (2nd to 4th week)	2 weeks after final induction, 24 h occlusive, 1% $CoCl_2$ (petrolatum)	6/10	reading after 48 h; no reaction in 3 control animals; no reaction to 5% $NiSO_4$ in petrolatum; no reaction to 1% $CoCl_2$ in 10 animals treated with 25% nickel sulfate as induction	Lammintausta *et al.* 1985
open epicutaneous test, Dunkin-Hartley, not specified	–	3 weeks, daily non-occlusive; 0.1 ml, 0.1%; 0.3%; 1% or 3% $CoCl_2$ (water)	d 21, 24 h non-occlusive, 1% $CoCl_2$ (petrolatum) d 35, occlusive, 1% $CoCl_2$ (petrolatum)	0.1%: 5/6 0.3%: 4/6 1%: 3/6 3%: 3/6 0.1%: 4/6 0.3%: 3/6 1%: 4/6 3%: 5/6	no reaction in 6 control animals after non-occlusive provocation treatment; findings with 4.5%, 6% and 7.5% cobalt chloride for induction and with 0.1% and 0.3% cobalt chloride for provocation are not presented	Wahlberg *et al.* 2000

Table 8. continued

Method, strain, sex	Induction, i.d. injection volume, concentration (vehicle)	Induction, epicutan. day, type of application, concentration (vehicle)	Provocation, day, type of application, concentration (vehicle)	Number of animals with reaction	Remarks	Reference
single injection adjuvant test, not specified	d 1, 1 100 l 0.1% $CoSO_4$ in FCA	–	d 13, 6 h occlusive, 1% $CoSO_4$ (not specified)	7/10	no data for control animals; positive reaction in 9/10, 7/10 and 10/10 animals respectively after induction with 2 , 3 or 4 injections	Goodwin and Johnson 1985
modified single injection adjuvant test, not specified	d 1, 4 100 l 0.35% $CoCl_2$ in FCA	–	2 weeks after induction, 6 h occlusive, 3 provocations (Pr) performed; 1st Pr: 0.0001% and 0.001%; 2nd Pr: 0.01% and 0.1%; 3rd Pr: 1% $CoCl_2$ (water)	1st Pr: 0/10 each dose 2nd Pr: 1/10 and 3(2*)/10 3rd Pr: 10/10	*: questionable reaction; reaction to 1%, 0.1% and 0.01% in 10/10, 9/10 and 4/10 animals respectively in a 2nd group of 10 animals after provocation in reverse order; only one questionable reaction to 1% $CoCl_2$ was observed in both groups after addition of 1.3 equivalents of EDTA	Allenby and Basketter 1989

EDTA: ethylene diamine tetraacetic acid; FCA: Freund's complete adjuvant; i.d.: intradermal

4.3 Genotoxicity

4.3.1 *In vitro*

Table 9 presents an overview of studies with soluble cobalt(II) salts in bacteria and yeasts.

The results of the mutagenicity tests with soluble cobalt salts in *S. typhimurium* were mainly negative. Cobalt(II) chloride was mutagenic in *S. cerevisiae*. The genotoxicity studies with mammalian cells (Table 10) revealed that the soluble cobalt salts did not induce chromosome aberrations, but sister chromatid exchanges were increased as well as micronuclei and cell transformations to some extent.

In human fibroblasts, cobalt inhibited the DNA repair synthesis of DNA damage caused by UV-C irradiation. Cobalt ions inhibited the incision and the polymerisation step, while ligation was not affected (Kasten *et al.* 1997). Cobalt(II) ions especially inhibited the function of the XPA (*Xeroderma pigmentosum* group A) protein, a zinc finger protein involved in nucleotide excision repair (Asmuß *et al.* 2000). Soluble cobalt salts induced DNA strand breaks in various mammalian cells. A clastogenic effect of cobalt metal dust was observed in human lymphocytes in a study with hard metals. This effect was more severe with a combination of cobalt and tungsten carbide, as they occur in hard metals, than with elemental cobalt (Anard *et al.* 1997, de Boeck *et al.* 1998).

Table 9. Genotoxicity of soluble cobalt compounds in bacteria and yeast

Substance	Test system		Highest concentration	Result		Toxicity	Reference
				S9	+S9		
Cobalt(II) chloride	SMT	*S. typhimurium*					
		TA98	40 g/ml	+		50% GI at 40 g/ml	Wong 1988
		TA98	20 g/ml		n.i.	GI at10 mM	Tso and Fung 1981
		TA100	100 mM		n.i.		Mochizuki and Kada 1982
		TA102	40 g/ml			50% GI at 40 g/ml	Wong 1988
		TA1535	40 g/ml			50% GI at 40 g/ml	Wong 1988
		TA1537	40 g/ml	+		50% GI at 40 g/ml	Wong 1988
		TA1537	0.1 mM		n.i.	no details	Ogawa *et al.* 1986
		TA1538	20 g/ml		n.i.		Mochizuki and Kada 1982
		TA2637	0.1 mM		n.i.	no details	Ogawa *et al.* 1986
	Gene mutation in supF-tRNA gene of *E. coli*	cell-free treatment of a plasmid and transfection to *E. coli*	20 M	+	n.i.	not applicable	Ogawa *et al.* 1999
	Gene mutation ("petite" colonies)	*S. cerevisiae*	6 mg/ml	+	n.i.	unclear	Kharab and Singh 1987
Cobalt(II) sulfate	SMT	*S. typhimurium*					
		TA98	10 g/plate			slightly toxic	NTP 1998
		TA100	10 g/ plate	+	+	slightly toxic	NTP 1998
		TA1535	1 g/ plate				NTP 1998

GI: growth inhibition; n.i.: not investigated; SMT: *Salmonella* mutagenicity test

Table 10. Genotoxicity in mammalian cells *in vitro*

Test	Result	Highest concentration	Toxicity	Reference
Cobalt(II) chloride				
gene mutation				
– V79 hamster cells (hprt)	+	250 M	68%	Hartwig *et al.* 1990
– mouse lymphoma cells (tk)		57 g/ml	no details	Amacher and Paillet 1980
inhibition of DNA repair synthesis				
– human fibroblasts	+	200 M	55%	Kasten *et al.* 1997
SCE				
– mouse macrophage cell line	+	100 M		Andersen 1983
– human lymphocytes	+	10 M		Andersen 1983
micronuclei				
– mouse bone marrow cells		50 g/ml		Suzuki *et al.* 1993
– human lymphocytes	+	0.5 g/ml		Capomazza and Botta 1991
DNA breaks				
– human fibroblasts	+	10 mM		Hamilton-Koch *et al.* 1986
– CHO cells	+	10 mM		
– HeLa cells	+	250 M		Hamilton-Koch *et al.* 1986
– human leukocytes	+	50 M	no details	Hartwig *et al.* 1990
– human lymphocytes	+	6 g/ml		McLean *et al.* 1982 de Boeck *et al.* 1998
chromosome aberrations				
– human lymphocytes		0.5 g/ml		Capomazza and Botta 1991
Cobalt(II) nitrate				
chromosome aberrations				
– human fibroblasts		0.08 M	subtoxic	Paton and Allison 1972
– human leukocytes		0.08 M	subtoxic	Paton and Allison 1972
Cobalt(II) acetate				
chromosome aberrations				
– human lymphocytes		2.4 M	no details	Vorosholin *et al.* 1978
Cobalt metal				
micronuclei				
– human lymphocytes	+	6 g/ml		van Goethem *et al.* 1997
DNA strand breaks				
– human lymphocytes	+	6 g/ml	no details	Anard *et al.* 1997
– human lymphocytes	+	6 g/ml		de Boeck *et al.* 1998
Cobalt(II) sulfide, crystalline				
DNA strand breaks				
– CHO cells	+	10 g/ml	no details	Robison *et al.* 1982
morphological cell transformation – SHE cells	+	10 g/ml	toxic	Costa *et al.* 1982

CHO: cell line from Chinese hamster ovary; SCE: sister chromatid exchange; SHE: Syrian hamster embryo

4.3.2 *In vivo*

4.3.2.1 Somatic cells

The *in vivo* genotoxicity data are shown in Table 11.

Table 11. Genotoxicity in mammals *in vivo*

Substance	Test	Administration route and dose	Effect	Reference
Cobalt(II) chloride	aneuploidy in ♂ hamsters – in bone marrow – in germ cells	intraperitoneal 400 mg/kg body weight distributed over 9 d	+* +*	Farah 1983
	chromosome aberrations in bone marrow of mice	oral 20–80 mg/kg body weight	+* dose-dependent	Palit *et al.* 1991
	micronuclei in bone marrow of mice after 30 hours	intraperitoneal 25–90 mg/kg body weight	+ dose-dependent	Suzuki *et al.* 1993
Cobalt(II) sulfate heptahydrate	K-ras mutation in lung neoplasms of mice	inhalation, 3 mg/m^3	+	NTP 1998

* Positive control missing

Cobalt(II) chloride induced aneuploidies, especially hyperploidies, in bone marrow cells after intraperitoneal injection in male hamsters. The total dose of 400 mg cobalt(II) chloride/kg was close to the toxic range, the effects described were relatively slight and, in view of the small number of cells evaluated, not well validated (Farah 1983).

In mice, a single oral cobalt(II) chloride dose of 20–80 mg/kg body weight caused a dose-dependent increase in chromosome aberrations in the bone marrow (Palit *et al.* 1991). The maximum effect was very pronounced with 21.6 % aberrant cells.

After intraperitoneal injection of cobalt(II) chloride to mice, a dose-dependent increase in micronuclei was found in polychromatic erythrocytes within 30 hours (Suzuki *et al.* 1993).

4.3.2.2 Germ cells

To study a possible induction of aneuploidy in germ cells, cobalt(II) chloride was administered intraperitoneally to Syrian hamsters 7 times within 9 days (total dose 400 mg/kg body weight). There was an interval of 9 days between the start of treatment and removal of the testes. The incidence of hyperploid first meiotic metaphases increased significantly in the group treated with cobalt(II) chloride. No difference was observed in the second meiotic metaphases (Farah 1983). Due to the fact that about 11 to 13 days are needed between the final division prior to initiation of the meiotic prophase and the first meiotic metaphase, a treatment period of 9 days is not sufficient for an analysis of aberrant chromosome distributions in the spermatocytes. The author states that the cells must have been in the pachytene stage at the start of the treatment, i.e. already in the meiotic prophase. Since there were no cell divisions between the start of

the treatment and the examination, no chromosome aberrations could have been induced. Therefore, the results of this study are not useful.

In a dominant lethal test, 10 male B6C3F1 mice were mated with virgin females at a ratio of 1:2 during 2 weeks after a 10-week treatment with cobalt(II) chloride (about 71.1 mg/kg body weight) at a dose of 400 mg/l drinking water. After mating with the treated males, the number of pregnant animals in the corresponding females was decreased to 18 of 31 (control: 29 of 32) and also the number of live embryos per female was reduced to 6.5 (control 8.3). Preimplantation loss per female animal was significantly increased to 2.4 (0.43 in controls). No postimplantation losses occurred, whereby the number of pregnant females investigated was too small to verify a statistical significance. The preimplantation losses can be interpreted as being due to the reduced sperm concentration expressed by reduced fertility, and presumably have no genotoxic cause (Pedigo and Vernon 1993).

4.4 Carcinogenicity

Studies of the carcinogenicity of cobalt compounds are summarized in Table 12.

4.4.1 Cobalt metal

Local sarcomas have been induced by cobalt implants and intramuscular injection of cobalt powder (Heath 1954, 1956). These findings are an indication of a possible carcinogenic effect of cobalt metal.

4.4.2 Oxidic cobalt

The incidence of pulmonary tumours was not significantly increased in male hamsters after inhalation of cobalt(II) oxide (Wehner *et al.* 1977). Local tumours were found after intramuscular injection of cobalt(II) oxide in male rats, but not in female mice (Gilman and Ruckerbauer 1962). After intraperitoneal injection, cobalt(II) oxide produced local tumours in male and female rats, and a few lung tumours after intratracheal instillation (Steinhoff and Mohr 1991). These findings indicate a possible carcinogenic effect of cobalt(II) oxide.

Another part of the aforementioned study investigating the combined effect of cobalt(II) oxide and benzo(*a*)pyrene was conducted with a smaller number of animals (20 per group) in female rats (Steinhoff and Mohr 1991). The results indicate that cobalt enhances the carcinogenic effect of benzo(*a*)pyrene and are to be considered in conjunction with the inhibition of DNA repair by cobalt ions (see below).

Table 12. Carcinogenicity of cobalt compounds (according to IARC 1991)

Species	Duration, application	Dose	Tumour incidence	Tumour type*	Reference
Cobalt metal					
rat ♂	1 , intramuscular	0 mg	0/10		Heath 1954, 1956
		28 mg	4/10	local sarcomas	
rat ♀	1 , intramuscular	0 mg	0/10		Heath 1954, 1956
		28 mg	5/10	local sarcomas	
Cobalt(II) oxide					
hamster ♂	7 h/d, 5 d/w, 17–21 months, inhalation	0 g/l	1/51 2/51	malignant tumour benign tumours	Wehner *et al.* 1977
		10 g/l	2/51 1/51	malignant tumour benign tumour	
mouse ♀	1 , intramuscular	0 mg	0/48		Gilman and Ruckerbauer 1962
		10 mg	0/46		
rat ♂	1 , intramuscular	0 mg/kg bw	0/20		Gilman and Ruckerbauer 1962
		30 mg/kg bw	5/10	local malignant tumours	
rat ♂, ♀	3 , intraperitoneal	0 mg/kg bw	1/20	local malignant tumours	Steinhoff and Mohr 1991
		200 mg/kg bw	14/20		
rat ♂	1 /2 weeks, 2 years, intratracheal	0 mg/kg bw	0/100		Steinhoff and Mohr 1991
		2 mg/kg bw	1/50	benign squamous cell tumour	
		10 mg/kg bw	5/50	3 adeno-carcinomas 2 adenomas	
rat ♀	1 /2 weeks, 2 years, intratracheal	0 mg/kg bw	0/100		Steinhoff and Mohr 1991
		2 mg/kg bw	1/50	adenoma	
		10 mg/kg bw	1/50	carcinoma	
Combination of cobalt(II) oxide with benzo(a)pyrene (B(a)P)					
rat ♀	1 /2 weeks, 2 years, intratracheal	0 mg/kg CoO, 0 mg/kg B(a)P	0/20		Steinhoff and Mohr 1991
		10 mg/kg CoO, 20 mg/kg B(a)P	8/20	squamous cell tumours	
			1/20	adenocarcinoma	
		0 mg/kg CoO, 20 mg/kg B(a)P	1/20	squamous cell tumours	

Table 12. continued

Species	Duration, application	Dose	Tumour incidence	Tumour type*	Reference
Cobalt(II) sulfide					
rat ♂, ♀	1 /thigh, intramuscular	0 mg	no details		Gilman 1962
		20 mg	28/29	local sarcomas 35/58 at injection sites	
Cobalt(II) chloride					
rat ♂	2 5 d, 9 d interval, subcutaneous	0 mg/kg	0/19		Shabaan *et al.* 1977
		40 mg/kg	6/16 8/11	local sarcomas after 8 and 12 months, respectively	

* lung tumours, unless otherwise indicated
bw: body weight

4.4.3 Sulfidic cobalt

For cobalt(II) sulfide, only one study with intramuscular injection in rats is available, in which local sarcomas were observed in 28 of 29 animals. Control animals were not investigated (Gilman 1962).

4.4.4 Water soluble cobalt(II) salts

Cobalt(II) chloride induced local sarcomas after subcutanous injection into rats at high toxic doses (Shabaan *et al.* 1977). Lung tumours have been induced in mice by intraperitoneal injection of cobalt(II) acetate (Stoner *et al.* 1976). Since the tumour incidence was already 7 of 19 in controls, this study is not useful. A comprehensive inhalation study has been conducted with cobalt(II) sulfate (Table 13).

There was some evidence of carcinogenicity in the lungs of male F344/N rats and clear evidence of carcinogenicity in the lungs of female F344/N rats, as well as male and female B6C3F1 mice. In the same study, cobalt sulfate induced phaeochromocytomas in the adrenal glands of female rats. This indicates that soluble cobalt can induce systemic tumours. Additional mechanistic information was obtained from the analysis of mutations in the K-ras oncogene in lung neoplasms of cobalt sulfate-exposed mice. The enhanced frequency of G to T transversions in codon 12 of the K-ras gene in cobalt sulfate-induced neoplasms compared to controls is supportive evidence that cobalt sulfate may indirectly damage DNA by oxidative stress (NTP 1998).

Table 13. Results of the NTP study on the carcinogenicity of cobalt sulfate in rats (NTP 1998)

Species:	F344/N rats, 50 ♂, ♀ per group
Application:	inhalation, whole animal exposure chamber
Concentration:	0, 0.3, 1.0, 3.0 mg cobalt sulfate heptahydrate/m^3 (0, 60, 200, 600 g cobalt/m^3)
Duration:	6 hours/day, 5 days/week, 105 weeks
Toxicity:	0.3 mg/m^3 and above: ♂, ♀: interstitial fibrosis

		Cobalt sulfate-heptahydrate concentration [mg/m^3]			
		0	0.3	1.0	3.0
Surviving animals after 24 months	♂	17/50 (34%)	15/50 (30%)	21/50 (42%)	15/50 (30%)
	♀	28/50 (56%)	25/49 (51%)	26/50 (52%)	30/50 (60%)
Lungs					
hyperplasia of the alveolar epithelium	♂	9/50 (18%)	20/50 (40%)*	20/48 (42%)*	23/50 (46%)**
	♀	15/50 (30%)	7/49 (14%)	20/50 (40%)	33/50 (66%)
atypical hyperplasia of the alveolar epithelium	♀	0/50 (0%)	0/49 (0%)	3/50 (6%)	5/50 (10%)*
metaplasia of the squamous epithelium	♀	0/50 (0%)	1/49 (2%)	8/50 (16%)*	3/50 (6%)
metaplasia of the alveolar epithelium	♂	0/50 (0%)	50/50 (100%)**	48/48 (100%)**	49/50 (98%)**
	♀	2/50 (4%)	47/49 (96%)**	50/50 (100%)**	49/50 (98%)**
bronchoalveolar adenomas	♂	1/50 (2%)	4/50 (8%)	1/48 (2%)	6/50 (12%)
	♀	0/50 (0%)	1/49 (2%)	10/50 (20%)**	9/50 (18%)*
bronchoalveolar carcinomas	♂	0/50 (0%)	0/50 (0%)	3/48 (6%)	1/50 (2%)
	♀	0/50 (0%)	2/49 (4%)	6/50 (12%)*	6/50 (12%)*
bronchoalveolar adenomas or carcinomas	♂	1/50 (2%)	4/50 (8%)	4/48 (8%)	7/50 (14%)*
	♀	0/50 (0%)	3/49 (6%)	16/50 (32%)**	16/50 (32%)**
Nose					
hyperplasia of the lateral wall epithelium	♂	2/50 (4%)	14/50 (28%)	21/49 (42%)	20/50 (40%)
	♀	1/50 (2%)	8/49 (16%)	26/50 (52%)	38/50 (76%)
metaplasia of the lateral wall squamous epithelium	♂	1/50 (2%)	3/50 (6%)	5/49 (10%)	8/50 (16%)
	♀	1/50 (2%)	1/49 (2%)	4/50 (8%)	10/50 (20%)
olfactory epithelial atrophy	♂	8/50 (16%)	24/50 (48%)**	42/49 (86%)**	48/50 (96%)**
	♀	5/50 (10%)	29/49 (59%)**	46/50 (92%)**	47/50 (94%)**
olfactory epithelial metaplasia	♂	5/50 (10%)	1/50 (2%)	5/49 (10%)	30/50 (60%)**
	♀	2/50 (4%)	2/49 (4%)	3/50 (6%)**	40/50 (80%)**

Table 13. continued

Larynx					
metaplasia of the squamous epithelium of the epiglottis	♂	0/50 (0%)	10/49 (20%)**	37/48 (77%)**	50/50 (100%)**
	♀	1/50 (2%)	22/49 (45%)**	39/50 (78%)**	48/50 (96%)**
Adrenals					
benign, complex or malignant phaeochromocytomas	♂	15/50 (30%)	19/50 (38%)	25/49 (51%)*	20/50 (40%)
	♀	2/48 (4%)	1/49 (2%)	4/50 (8%)	10/48 (21%)*

* $p \leq 0.05$ (Fisher's exact test)
** $p \leq 0.01$ (Fisher's exact test)

Table 14. Results of the NTP study on the carcinogenicity of cobalt sulfate in mice (NTP 1998)

Species:	B6C3F1 mice, 50 ♂, ♀ per group
Administration:	inhalation, whole animal exposure chamber
Concentration:	0, 0.3, 1.0, 3.0 mg cobalt sulfate heptahydrate/m^3 (0, 60, 200, 600 g cobalt/m^3)
Duration:	6 hours/day, 5 days/week, 105 weeks

		Cobalt sulfate heptahydrate concentration [mg/m^3]			
		0	0.3	1.0	3.0
Surviving animals after 24 months	♂	22/50 (44%)	31/50 (62%)	24/50 (48%)	2050 (40%)
	♀	34/50 (68%)	37/50 (74%)	32/50 (64%)	28/50 (56%)
Lungs					
Bronchoalveolar adenomas	♂	9/50 (18%)	12/50 (24%)	13/50 (26%)	18/50 (36%)*
	♀	3/50 (6%)	6/50 (12%)	9/50 (18%)	10/50 (20%)*
Bronchoalveolar carcinomas	♂	4/50 (8%)	5/50 (10%)	7/50 (14%)	11/50 (22%)*
	♀	1/50 (2%)	1/50 (2%)	4/50 (8%)	9/50 (18%)**
Bronchoalveolar adenomas or carcinomas	♂	11/50 (22%)	14/50 (28%)	19/50 (38%)	28/50 (56%)**
	♀	4/50 (8%)	7/50 (14%)	13/50 (26%)*	18/50 (36%)**
Nose					
olfactory epithelial atrophy	♂	0/50 (0%)	0/50 (0%)	29/48 (60%)**	48/49/98%)**
	♀	0/50 (0%)	2/50 (4%)	12/49 (24%)**	46/48 (96%)**
olfactory epithelial hyperplasia	♂	0/50 (0%)	0/50 (0%)	0/48 (0%)	10/50 /20%)**
	♀	0/50 (0%)	0/50 (0%)	0/49 (0%)	30/48 (63%)**
Larynx					
metaplasia of the squamous epithelium	♂	0/48 (0%)	37/49 (76%)**	48/48 (100%)**	44/49 (90%)**
	♀	0/50 (0%)	45/49 (92%)**	40/47 (85%)**	50/50 (100%)**

* $p \leq 0.05$ (Fisher's exact test)
** $p \leq 0.01$ (Fisher's exact test)

5 Manifesto (MAK value/classification)

Cobalt sulfate proved to be carcinogenic in an inhalation study in rats and mice. In mechanistic studies, the cobalt ion was identified as the effective agent. Therefore, all cobalt compounds readily soluble in water (solubility > 0.1 g/l) are classified in Carcinogen category 2. The poorly soluble sulfidic and oxidic cobalt compounds as well as metallic cobalt are also bioavailable. Thus, the toxicologically active cobalt ion is released from these substances as well. An increased incidence of single strand breaks in the lymphocytes of exposed persons and an inhibition of DNA repair were found after exposure to metallic cobalt. In a valid study performed with rats only, cobalt(II) oxide induced lung tumours in the male animals. On the basis of these data, and in analogy to the readily soluble cobalt compounds, metallic cobalt and sulfidic and oxidic cobalt compounds are also classified in Carcinogen category 2.

Effects of cobalt on the lung function of exposed workers were observed consistently at cobalt concentrations as low as 0.05 mg/m^3 (Alexandersson 1979a, 1979b). Acute, reversible effects (respiratory tract irritation, reduced forced vital capacity) were described for healthy persons after short-term exposure to cobalt concentrations of 0.038 mg/m^3 (Kusaka *et al.* 1986a). After average exposures below these concentrations, there were still some individual cases of allergic alveolitits and work-related asthma (Kusaka *et al.* 1986b, Sj gren *et al.* 1980). Reports on cardiac dysfunctions (ECG changes) in hard metal workers after exposure to cobalt concentrations of 0.01 mg/m^3 are not convincing, since these findings were not observed at higher exposure levels (Alexandersson and Atterh g 1980). From these data, it is not possible to derive a NOAEL (no observed adverse effect level) for toxic effects, especially in the respiratory tract. Neither can, from the epidemiological data and genotoxicity studies available, a threshold level be derived which would protect against carcinogenic effects.

Cobalt(II) chloride induced micronuclei and structural chromosome aberrations in human lymphocytes *in vitro*, aneuploidy in the bone marrow cells of Syrian hamsters and structural chromosome aberrations and micronuclei in the bone marrow cells of the mouse *in vivo*. Cobalt dust inhibited DNA repair in lymphocytes of workers exposed to cobalt. In the dominant lethal test, no structural chromosome aberrations in germ cells were detected. There are no other valid *in vivo* studies available on genotoxicity in germ cells. It is known from studies on metabolism that soluble cobalt is able to pass the blood/testis barrier and reaches the testes and epididymides. Its bioavailablity in germ cells has also been demonstrated. Cobalt and cobalt compounds are classified in Category 3A for germ cell mutagens on the basis of their genotoxicity and bioavailability in germ cells.

The contact sensitizing effect of cobalt compounds has been demonstrated in numerous clinical studies and in animal experiments both with and without adjuvant. Although only a few data are available, there are nevertheless clear indications of an increase in the incidence of asthmatic diseases in exposed persons, especially in hard metal production or processing, which are very likely due to exposure to cobalt. Evidence of an immunological mechanism is provided by the fact that sensitization in the intracutaneous test and specific IgE have been demonstrated. The dual or isolated delayed reactions observed in the provocation test with cobalt, cobalt compounds and

hard metals are additional indications of an immunological mechanism. Therefore, the designation Sah for cobalt and cobalt compounds has been retained. There are no findings of sensitizing effects of cobalt alloys that suggest designation with Sa or Sh is justified. Nevertheless, the assessment of cobalt alloys from which cobalt is bioavailable should very likely be similar to that of the metal.

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