Occupational Medicine 2010;**60:**301–306
Advance Access publication on 22 March 2010 doi:10.1093/occmed/kqq023

Cobalt asthma—a case series from a cobalt plant

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Background Cobalt has been shown to induce mainly asthma, allergic contact dermatitis and hard metal disease. The data on cobalt asthma are mainly based on case reports.

Aims To characterize all the cases of occupational cobalt asthma encountered in a cobalt plant at the time of diagnosis and 6 months later. We also evaluated the incidence of cobalt asthma in different departments on the basis of data on occupational exposures.

Methods We identified cases of cobalt asthma confirmed with specific bronchial challenge tests in the Kokkola cobalt plant in Finland where exposure levels have been regularly monitored.

Results Between 1967 and 2003, a total of 22 cases of cobalt asthma were diagnosed in the cobalt plant. On challenge tests, mostly late or dual asthmatic reactions were observed. The incidence of cobalt asthma was the highest in the departments with the highest cobalt exposure levels. All cases of cobalt asthma were encountered in departments where irritant gases were present in the ambient air in addition to cobalt. At the time of the follow-up examination 6 months later, non-specific hyperreactivity had mostly remained at the same level or increased.

Conclusions The incidence of cobalt asthma correlated with the exposure levels of cobalt in corresponding departments. An irritating effect of gaseous compounds may enhance the risk of cobalt asthma and even the smallest amounts of cobalt may be harmful to susceptible workers. Symptoms of asthma may continue despite the fact that occupational exposure to cobalt has ceased.

Key words Cobalt exposure; occupational asthma.

Introduction

Occupational exposure to cobalt dust has been mainly associated with asthma [1,2], allergic contact dermatitis [3] and hard metal disease [4,5]. Large epidemiological studies on cobalt asthma are lacking probably because of the rareness of the disease. Our knowledge of cobalt asthma is largely based on case reports. One study reports both bronchial asthma and contact dermatitis due to metallic cobalt in the same patient [6]. Several reports deal with diamond polishers' cobalt asthma [1,7,8]. Van Custem *et al.* [9] have reported combined asthma and alveolitis induced by cobalt in a diamond polisher.

Exposure to cobalt can be evaluated based on ambient air samples from the workplace or biological monitoring tests. Cobalt production workers have been shown to have many times higher urinary cobalt values than, for example, hard metal blade sharpeners [10,11]. If there is a dose–response effect between the exposure and risk of asthma, cobalt production workers could be anticipated to be exposed to a high risk of occupational asthma.

Previously, Roto [12] studied cobalt production workers and their risk of asthma in the same cobalt plant where the cases of this report originated. He demonstrated a 5-fold increased risk of general asthma among workers exposed to cobalt compared to non-exposed workers [12]. He reported six cases of cobalt asthma verified by specific inhalation challenge tests by the year 1980. Another questionnaire study conducted in the same cobalt plant reported significantly more suspected cases of work-related asthma among cobalt exposed workers than among controls [11]. These studies demonstrate that cobalt exposure is related to an increased risk of asthma in this cobalt plant.

This study was conducted to analyse all the cases of cobalt asthma encountered in the Kokkola cobalt plant and diagnosed in the Finnish Institute of Occupational Health

with specific inhalation provocation tests. We gathered the clinical data at the time of diagnosis and during a follow-up visit 6 months later in the patient files. We also evaluated the significance of exposure to cobalt and to irritant gases in the workplace air in relation to the risk of cobalt asthma.

Methods

The study took place in the Kokkola cobalt plant in Finland. The cases were identified in the cobalt plant's occupational health care registers, and the patient files were retrospectively reviewed. The diagnosis was confirmed in clinical examinations with specific inhalation challenge tests performed at the Finnish Institute of Occupational Health in Helsinki (FIOH). Fourteen patients participated in the follow-up examinations in the FIOH 6 months after diagnosis. The follow-up data were completed from the records of the occupational health care unit of the cobalt plant.

Spirometry was performed using a 3000-Kifa Bernstein spirometer (Instrumenta, Partille, Sweden) until 1987. At that time, the reference values of Berglund *et al.* [13] were used. A pneumotachograph spirometer connected to a microcomputer (Medikro MR909, Kuopio, Finland) and the Finnish reference values of Viljanen [14] were used from 1988.

Before 1991, a modified method by Laitinen [15] was used in the histamine challenge test. From 1992, the histamine challenge test was performed following the method of Sovijärvi *et al.* [16]. The provocative dose of 1.6% histamine diphosphate causing a 15% reduction in forced expiratory volume in 1 s (FEV1) (PD_{15}) was measured. The hyperresponsiveness was graded as strong with PD_{15} <0.10 mg, moderate when PD_{15} was 0.11–0.40 mg and mild when PD_{15} was 0.41–1.6 mg.

Specific bronchial provocation tests were performed in an 8-m^3 challenge chamber according to the international guidelines [17]. The exposure time was 30 min in both the referent and in the active test. In the active test, CoCl (0.1–1 ml/l) was used in 15 cases and $CoSO_4$ powder in 2 cases. In nine cases, the reaction was confirmed with a provocation test with cobalt powder dust or with the dust from sulphatizing roasting process. In five cases, only cobalt powder or dust from sulphatizing roasting was used. In the referent test, lactose powder was used in 17 cases, and the dilution fluid was used in 5 cases as a placebo. Patients were monitored for 24 h after each challenge. A portable, pocket-size spirometer (One Flow; STI MEDICAL, Saint Romans, France) was used to record peak expiratory flow (PEF) measurements and, after 1993, also FEV1 measurements. The clinical symptoms and lung auscultation were recorded as well. The reaction was classified as immediate if there was a decrease of ≥20% in the FEV1 or PEF during the first post-challenge hour, a delayed reaction causing a similar decrease in FEV1 or PEF after the first post-challenge hour and a dual reaction as a combination of these two reactions.

Twenty common environmental allergens were scratch chamber tested until 1978 (Bencard, UL and Dome, Division of Miles Laboratories Ltd, Buckinghamshire, UK) and were skin prick tested from 1979. Skin prick tests (SPT) for cobalt and common environmental allergens (ALK-Abello A/S, Copenhagen, Denmark) were performed as described by Kanerva *et al.* [18]. Histamine hydrochloride (10 mg/ml) was used as positive control. The concentration of cobalt chloride was 1 mg Co^{2+}/ml.

The cobalt plant of this study is located in Kokkola on the western coast of Finland. During 1967–2003, ~700 workers worked at the cobalt plant, including workers hired for 6 months or longer. Person-years in different departments were counted based on the number of workers at the end of each year. Incidence density was calculated as follows: number of new cases in each department per person-years [19].

Between 1966 and 1987, cobalt powder was produced from pyrite ore concentrate. After 1987, cobalt powder, inorganic cobalt and nickel compounds were produced using by-products of metallurgic industry as raw material (Figure 1).

In the sulphatizing roasting, dust in the ambient air was shown to contain 15–20% iron, 1% zinc, 0.4% cobalt and 0.2% nickel, whereas in the leaching building, the dust consisted of metal sulphides and sulphates. Cobalt and nickel were present as water-soluble sulphates. In the reduction plant and powder production facility, cobalt was mainly in the form of cobalt powder and fine powder. In the chemical department, the cobalt and nickel compounds were mainly sulphates, carbonates, oxides and hydroxides.

Total exposure to dust, cobalt, nickel, sulphur dioxide, hydrogen sulphide and ammonia were regularly monitored several times a year since 1966 both as static measurements and with personal sampling. The mean exposure level of total dust was high in the sulphatizing roasting department, 8.5 mg/m^3. The mean levels of cobalt in the workplace air in 1967–2003 are presented in Figure 2, and the mean levels of different gases in the Results. The methods of measuring workplace exposures have been described in detail before [11,20].

According to biological monitoring surveillance, exposure to cobalt was highest in the reduction and powder production department. The highest urinary content of cobalt was ~16 000 nmol/l (level of unexposed persons being <40 nmol/l). In the solution purification and chemical departments, the urinary cobalt levels were between 200 and 2000 nmol/l. Respirators were available since the plant started operating, and mandatory in the last 10 years in the powder production and chemical departments. Results of the biological monitoring show that a marked exposure still exists regardless of the intensified use of respirators [20].

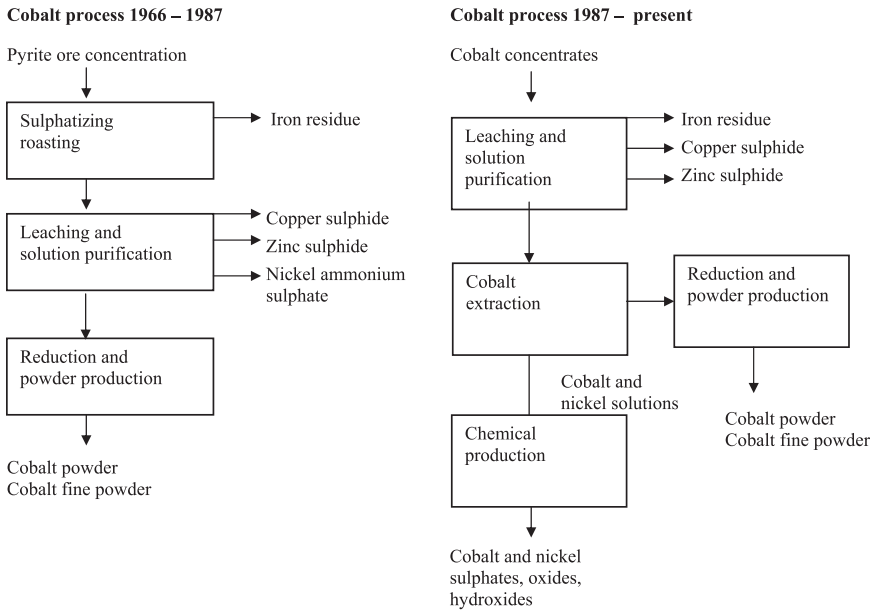

Figure 1. Cobalt production process in the Kokkola cobalt plant in 1966–87 and 1987 to present.

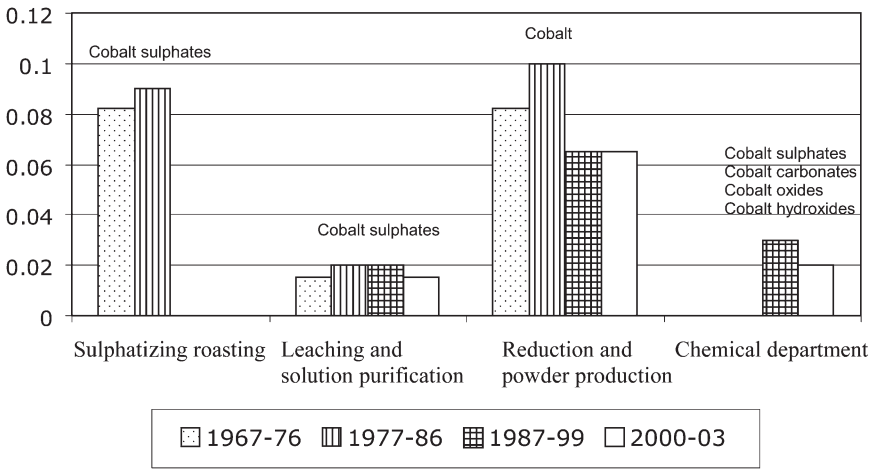

Figure 2. Mean exposure levels in the Kokkola cobalt plant in 1967–2003.

Results

The general characteristics of cobalt asthma patients are described in Table 1. All patients bar one were male. Atopy was only found in four (18%) of the patients, and SPT to cobalt were negative in all patients examined. Work rearrangements had been made quite early after the beginning of symptoms in order to eliminate exposure to cobalt, but the diagnosis of occupational asthma was only made 7.4 years after the onset of symptoms on average. Mostly late or dual asthmatic reactions were observed in specific bronchial challenge tests with cobalt. A total of 31 specific bronchial challenge tests were performed on the 22 patients. Of the reactions, 5 (16%) were of immediate type, 19 (61%) delayed type and 6 (19%) dual reactions. According to the patient history, 11 (50%)

Table 1. General characteristics and allergy testing of study patients

Subjects, number	22
Age at diagnosis, years (range)	45.8 (32–61)
Gender; male, *n* (%)	21 (95)
Family history of asthma, *n* (%)	4 (18)
Duration of symptoms before diagnosis; mean (years) (range)	7.4 (0.1–17)
Smoking habits, *n* (%)	
Non-smoker	7 (33)
Ex-smoker	10 (48)
Current smoker	4 (18)
Allergy testing	
Positive prick tests to one or more common allergens, *n* (%)	4 (18)
Positive prick tests to cobalt, *n* (%)	0 (0)
Elevated total IgE value (>114 kU/l)	4 (18)

of the patients experienced symptoms during working hours, 16 (55%) after the shift and 7 (32%) at night.

The results of lung function examinations at the time of diagnosis of occupational asthma are presented in Table 2. Of the patients, 16 (73%) had bronchodilating medications, 6 (27%) had inhaled corticosteroids and 4 (18%) did not have any asthma medication at that time.

Data on the control visit to the FIOH 6 months after the diagnosis were obtained from 14 patients: one patient was still working in the cobalt plant, but assigned to a different department in order to minimize exposure to cobalt; three patients had retired; two were in vocational rehabilitation and eight had changed jobs within the same industrial area. Eight patients were symptomless or feeling better subjectively, but six patients still had daily asthma symptoms. Bronchial hyperreactivity was retested in 10 of the 14 patients. It had remained at the same level as it was at the time of diagnosis in half the patients, while in four cases, it had increased and only in one case had decreased. The person who continued working in the plant had severe non-specific bronchial hyperreactivity both at the time of diagnosis and at the follow-up 6 months later. At the time of the control visit, forced vital capacity was normal (>80% of the reference values) in all patients tested, but FEV1 was decreased (< 80% of the reference value) in three patients.

Table 2. Symptoms and lung function examinations of study patients at diagnosis of occupational asthma

	Results of lung function tests and symptoms at the time of diagnosis, n = 22 (%)
Pulmonary function tests	
Forced vital capacity < 80%	3 (14)
FEV1 < 80%	4 (18)
Hyperreactivity at diagnosis	
No hyperreactivity	5 (23)
Mild hyperreactivity	7 (32)
Moderate hyperreactivity	6 (27)
Severe hyperreactivity	4 (18)
Symptoms	
Dyspnoea	22 (100)
Wheezing	14 (64)
Rhinitis	10/21 (48)
Cough	9 (41)
Phlegm	3 (14)
Eye irritation	1/18 (6)

Table 3 presents the asthma cases by the departments of the plant during 1967–87. In addition to those included in the table, one case was detected in the plant after the year 1987 and it was in the repair department. The exposure level of cobalt in the repair department is difficult to calculate, because the exposure was mainly caused by dusty machines brought in from other departments and the workers also circulated in other departments. The incidence density of cobalt asthma was highest in the reduction and powder production department, where the cobalt exposure levels were highest. There was significant individual variation in the working time before the onset of symptoms (0.1–17 years). The shortest latencies were in the sulphatizing roasting department, where the total dust concentrations and SO_2 level were high. No cases of cobalt asthma were reported in the chemical department where additional irritant gases like SO_2, H_2S or NH_3 were not present in the ambient air in addition to cobalt.

Discussion

A total of 22 cases of cobalt-induced asthma were reported in the cobalt plant that started operating in 1966 and cases

Table 3. The incidence of cobalt asthma and exposure to cobalt in different departments of the plant 1967–87

Department	Number of cobalt asthma cases	Number of workers in the department, mean	Person-years	Incidence density[a] of cobalt asthma in the department	Working time before onset of symptoms, median (min to max) (years)	Exposure levels of cobalt, median (min to max) (mg/m^3)	Gaseous exposures (p.p.m.)
Sulphatizing roasting	9	77	1550	0.006	0.5 (0.1–6.0)	0.1 (0.006–1.0)	SO_2 (1.4)
Leaching and solution purification	5	55	1100	0.005	7.5 (0.5–17.0)	0.03 (0.01–0.1)	H_2S (1.0) NH_3 (3.5)
Reduction and powder production	7	18	360	0.02	3.0 (0.1–11.0)	0.15 (0.1–0.4)	NH_3 (1.0)
Chemical department	0	34	102	–	–	0.12 (0.02–0.3)	–

[a]Incidence density: number of new cases in each department per person-years.

were collected from 1967 to 2003. Previous studies had shown an increased risk of asthma [12] and increased frequency of symptoms indicating work-related asthma in a questionnaire study [11] in this plant. The strength of our study is that we were able to find all the data pertaining to the cases, as the specific provocation tests for cobalt were centralized at the Finnish Institute of Occupational Health. In 1975–2001, a total of 42 cases of cobalt asthma in the whole country were reported to the Finnish Registry of Occupational Diseases so our 22 cases represent more than half the total number. Another strength of this study lies in the regular occupational exposure measurements performed in the cobalt plant and which describe the exposure levels in different departments. This enabled us to compare the incidence density of cobalt asthma and exposure levels. The weakness of the study is the long time span, during which the methods of specific provocation tests changed, influencing the variety of agents used in the provocation tests. However, the provocation tests were always performed in the FIOH following best practice of the time.

The incidence density of cobalt asthma varied from 0 to 0.01 in different departments and the figures correlated with the mean cobalt exposure levels in corresponding departments. In the departments where the cobalt levels were the highest, the latency before symptoms occurred was the shortest. Some workers developed symptoms already after a couple of months working time. The mean exposure levels in sulphatizing roasting and reduction and powder production departments exceeded the current Finnish occupational exposure limit (0.05 mg/m^3), whereas in the other departments, the exposure levels were slightly under that. A survey on diamond polishers' respiratory health has suggested an exposure limit of 0.0151 mg/m^3 for cobalt to protect the workers from respiratory symptoms [21].

The presence of irritating gases was associated with a higher risk of cobalt asthma. In the sulphatizing roasting department, where the exposure levels of SO_2 were the highest, the mean latency before the first symptoms of asthma was the shortest. On the other hand, in the chemical department, where there was no significant exposure to irritant gases, no cases of cobalt asthma were encountered. These findings are coherent with Andersson's [22] findings that repeated peak exposure to SO_2 increases the incidence of asthma [22] and so it may also enhance the pathologic process of cobalt asthma. This is supported by the finding that only one case of cobalt asthma has been diagnosed in the entire plant since 1987, at which time the process was changed and the workers were no longer exposed to sulphur dioxide.

The pathophysiology of cobalt asthma may involve both immunologic and non-immunologic mechanisms. Japanese researchers were able to show specific IgE antibodies to cobalt-conjugated human serum albumin in some of the cobalt asthma patients [23]. Because no commercial radioallergosorbent tests for cobalt are available, we were not able to use them. None of our patients had positive reactions against cobalt in SPT, indicating a non-immunologic mechanism. The reactions in the challenge test were mostly late or dual, which may also suggest rather a non-immunologic mechanism of asthma [24]. In an Italian study, the challenge test reactions for cobalt were also either late or dual [25].

In this study, the mean duration of symptoms was 7.4 years before the diagnosis of occupational asthma. In a Canadian study, the mean time for diagnosis of occupational asthma was 4.9 years [26]. Other studies have reported delays of 3.2 [27], 4.5 [28] and 3.8 years [29] in the diagnosis of occupational asthma. If a worker complains of work-related asthma symptoms, actions should be undertaken without any delay to study further the work-related aspects further and to minimize or abolish the exposure, because early avoidance of further exposure offers the best chance for complete recovery. Regular health examinations including a questionnaire inquiring work-related respiratory symptoms, spirometry and serial workplace PEF measurements are recommended to shorten the time to diagnosis.

The bronchial hyperresponsiveness had decreased only in one patient at the time of the follow-up visit 6 months after diagnosis when compared to the situation at the time of diagnosis. Our results are in line with the findings of a recent systematic review, in which only 32% of the patients with occupational asthma recovered and were asymptomatic, while in 73%, the non-specific bronchial hyperreactivity was permanent [29]. There is also a report of the outcome of cobalt asthma up to 3 years after the diagnosis [24], where bronchial hyperresponsiveness persisted in asymptomatic subjects.

Current evidence indicates that as the mean exposure levels to inhaled cobalt increase, the risk of occupational asthma induced by cobalt also increases, and the irritating gases seem to contribute to the risk. Although exposure to the causative agent ceases, the symptoms and bronchial hyperreactivity may continue. An early diagnosis and cessation of exposure are important when an occupational asthma induced by cobalt exposure is suspected.

Key points

- The incidence of cobalt asthma correlated with cobalt exposure levels in corresponding departments.
- An irritating effect of gaseous compounds may enhance the risk of cobalt asthma.
- Despite the fact that occupational exposure to cobalt ceases, the symptoms of asthma may continue.

Conflict of interest

None declared.

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