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Asthma, symptoms of chronic bronchitis and ventilatory capacity among cobalt and zinc production workers

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Academic dissertation, to be presented with the assent of the Medical faculty of the University of Oulu, for public discussion in the auditorium of the Department of Physiology, Kajaanintie 52, Oulu, on 11 April 1980 at 12 o'clock noon.

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Introduction

Cobalt and zinc plants are examples of metallurgic industries with work-related health problems primarily caused by a complex atmosphere of gases, fumes and dusts. The paucity of cobalt and zinc plants with detailed technical hygienic control surveys has limited possibilities for research on the health effects of exposure in these industries.

The Outokumpu Company's sulfur, cobalt and zinc plants in Northwest Finland provide an occupational health program for workers which is suitable for epidemiologic research. Since the beginning of operations at the cobalt plant in 1966 and the zinc plant in 1970 the workers and their work environment have been monitored.

The environment of the sulfur plant presented a unique opportunity for evaluating the role of background exposure to sulfur dioxide and the iron-containing oxides found in exposure conditions of cobalt workers because the cobalt plant had the same basic background exposure elements as the sulfur plant, but had considerably more cobalt- and nickel-containing dust than the sulfur plant.

There were three reasons for carrying out this study.

1. Since 1966 the plant physician had annually observed one to two new patients with bronchial asthma in a group of 230—240 cobalt workers.

2. Literature on mixtures of sulfur dioxide and dusts indicated that the exposure occurring in the cobalt and sulfur plants, and in some areas of the zinc plant, might impair pulmonary function.

3. There were no available earlier studies of the effects of a cobalt- or zinc-containing atmosphere upon pulmonary function.

The study was designed to have the following separate parts:

- I. A case-referent study aimed at assessing the risk of asthma in workers exposed to cobalt.

- II. A cross-sectional study to determine the occurrence of symptoms of chronic bronchitis and an eventual decrease of pulmonary capacity in workers exposed to cobalt- and zinc-containing air.

The study was carried out in the Outokumpu Kokkola Works between 1 February and 1 November 1977.

Study site and environment

The Outokumpu Kokkola metallurgic works are located on the Ykspihlaja peninsula, 4 km to the west of the city of Kokkola. It is situated on the Gulf of Bothnia

at a latitude of 64° and an east longitude of 23°. The climate tends to be humid and windy. The mean daily temperature ranges from —5 to —10°C between January and

March and +10 to +18°C from June to September.

The Works consists of separate sulfur, cobalt and zinc plants. The plants have a common power plant and maintenance and administrative sections in buildings at a distance of 500 m from the process buildings. With the adjoining sulfuric acid (H_2SO_4) plant of Kemira, Ltd, the Outokumpu Works forms the principal industrialized area of the region. The sulfur plant annually produced 350,000 t of hematite (Fe_2O_3), 120,000 t of elementary sulfur, and 100,000 t of sulfur dioxide (SO_2) before its partial closure in May 1977. The incoming raw material comprised 500,000 t of pyrite (FeS_2). A pyrometallurgic flame smelting process, described in appendix I, was used.

The cobalt plant annually uses 240,000 t of pyrite ore concentrate, which contains 0.5 % cobalt. From this raw material the plant produces 1,000–1,200 t of metallic cobalt (5 % of world production), 140,000 t of hematite, 10,000 t of ammonium sulfate $[(\text{NH}_4)_2\text{SO}_4]$, 500 t of copper sulfide (Cu_2S) and nickel ammonium sulfate

$[\text{Ni}(\text{NH}_4)\text{SO}_4]$, and 40,000 t of sulfur dioxide.

The zinc plant produces 120,000 t of metallic zinc, 190,000 t of sulfur dioxide, 2,300 t of copper residue, 1,000 t of cobalt residue, 500 t of cadmium, 35 t of mercury, and 10 t of selenium annually.

Both the cobalt and zinc plants have pyrometallurgic and hydrometallurgic stages in their processes, and these are described in detail in appendix I. The sulfur plant commenced operations in 1961, the cobalt plant in 1966, and the zinc plant in 1970. Studies on the environmental pollution of the Kokkola region have shown that, until 1967, the main sources of air pollution were traffic and heating (32). In 1971, the effect of industrial emissions of sulfur dioxide was observable in the environment within 2–3 km of the industrial area (33).

Between 1973 and 1977 the annual sulfur dioxide emission of the Outokumpu Works was 40,000 t. Other major pollutants were hydrogen sulfide (H_2S) and carbon disulfide (CS_2).

Exposure information

Quantitatively, the most important impurities found in the areas of the sulfur plant and roasting buildings of the cobalt and zinc plants were aerosols containing metals, sulfur, and sulfur dioxide. The metallic contents of the total dust are given as the percentage of the dry weight of the samples in table 1. The current Finnish threshold limit values (TLVs) of the most common contaminants from the sulfur, cobalt, and zinc plants are given in table 2.

Under normal operating conditions the mean concentration of total dust has been less than 10 mg/m^3 (the Finnish TLV) in all areas of the Outokumpu Kokkola Works except in the cobalt roasting building, where the concentration has fluctuated between 8 and 19 mg/m^3 . Also under normal

conditions the most common work areas have had sulfur dioxide concentrations between 0.2 and 4.5 ppm (cm^3/m^3) [Finnish TLV = 5 ppm (cm^3/m^3)].

Regular monitoring of the total dust and sulfur dioxide concentration was started in the cobalt, zinc, and sulfur plants in 1970. The annual geometric mean concentrations ($\text{SD} = \pm 1$) of these measurements are given in fig 1–8.

The stationary samples were collected on Millipore® filters placed in different work areas of the plants. The sampling procedure was the same as that later adopted by the Finnish Standardization Association (59) as the recommended dust sampling technique.

The dust samples were analyzed gravi-

Table 1. Metallic contents, expressed as percentage of the weight of the total sample, of airborne dust in work areas of the sulfur, cobalt and zinc plants of the Outokumpu Kookola Works.^a

Building	Iron	Zinc	Cobalt	Nickel	Copper	Calcium	Aluminum	Lead
Cobalt roasting	15—20	0.7—1	0.3—0.4	0.2	0.4—0.6	0.3—0.4	0.07	0.015
Zinc roasting	5—7	90	0.03	0.02	0.5—0.7	0.5—0.7	0.3—0.4	0.6—0.8
Sulfur roasting	20—30	0.6—0.8	0.4—0.6	0.025—0.035	0.4—0.6	0.3—0.4	0.1	0.6—0.8
Cobalt leaching	4—6	0.7—1	4—6	1.5—2.5	0.3—0.4	0.1	0.5—0.7	0.015

^a The analyses were carried out with a Hilger and Watts/Littrow quartz prismograph. The dust samples were collected with stationary samplers in September 1977. Concentrations of arsenic, cadmium, antimony, chromium, manganese and magnesium were $\leq 0.5\%$.

Table 2. Finnish threshold limit values (17) of the most common contaminants in the sulfur, cobalt and zinc plants of the Outokumpu Kookola Works.

	ppm (cm ³ /m ³)	mg/m ³
Gases		
Sulfur dioxide	5	13
Ammonia	25	18
Hydrogen sulfide	10	15
Fumes		
Sulfuric acid		1
Dusts		
Total dust		10
Hematite		10
Iron sulfide		10
Metals		
Iron		10
Zinc (oxide fume)		5
Cobalt		0.1
Nickel		1
Copper		1
Arsenic		0.5
Cadmium		0.02

metrically in the laboratory of the Company. About 25 % of the dust from all the areas monitored contained particles of a diameter of less than 3μ . The analyses to determine particle size were carried out in 1977, also in the laboratory of the Company with a celloscope after ultrasound dispersion.

The monitoring of gases was conducted with Dräger® ampuls. Sulfur dioxide, ammonia (NH₃), and hydrogen sulfide were

Fig 1. Annual geometric mean concentration of sulfur dioxide (SO₂) 1.5 m above the floor of the cobalt roasting building. (ppm = cm³/m³)

Fig 2. Annual geometric mean concentration of sulfur dioxide (SO₂) 1.5 m above the floor of the zinc roasting building. (ppm = cm³/m³)

monitored in the process areas where they occur.

Detailed exposure information on each plant follows. Descriptions of the processes are given in appendix I.

Fig 3. Annual geometric mean concentration of total dust 1.5 m above the floor of the cobalt roasting building.

Fig 4. Annual geometric mean concentration of total dust 1.5 m above the floor of the zinc roasting building.

Fig 5. Annual geometric mean concentration of total dust 1.5 m above the floor of the sulfur roasting building.

Fig 6. Annual geometric mean concentration of sulfur dioxide (SO₂) 1.5 m above the floor of the sulfur smelter. (ppm = cm³/m³)

Fig 7. Annual geometric mean concentration of total dust 1.5 m above the floor of the sulfur smelter.

Fig 8. Annual geometric mean concentration of sulfur dioxide (SO₂) 1.5 m above the floor of the sulfur roasting building. (ppm = cm³/m³)

COBALT PLANT

The studied cobalt plant comprised a cobalt roasting building (pyrometallurgic stage of the process) and solution purification/leaching and reduction buildings (hydrometallurgic stage).

The annual mean concentration of the total dust in the roasting building varied between 8 and 19 mg/m³ (fig 3) and that of sulfur dioxide between 1 and 2.5 ppm (cm³/m³) (fig 1). The dust contained 0.5–1.0 % water-soluble cobalt and nickel sulfates (table 3). It did not contain measur-

able amounts of other forms of cobalt. The content of water-soluble cobalt in the air of the roasting building varied between 0.05 and 0.1 mg/m³ (Finnish TLV = 0.1 mg/m³).

The main impurities in the cobalt leaching building were ammonia and hydrogen sulfide. Their annual geometric mean varied between 1 and 4 ppm (cm³/m³) at a height of 1.5 m above the floor of the process areas. Total dust concentration in the leaching building ranged between 0.1 and 0.5 mg/m³ and consisted of sulfides and sulfates. It contained 3.5–5 % cobalt sulfate (CoSO₄). In a limited cobalt packing area metallic cobalt dust in the air ranged between 0.01 and 0.1 mg/m³ during the operations.

ZINC PLANT

The studied zinc plant consisted of three separate process buildings, one for zinc roasting, another for solution purification, and the last for the cell house and casting.

The annual geometric mean concentration of total dust in the zinc roasting building was between 2.5 and 4.5 mg/m³ (TLV 10 mg/m³) (fig 4), and that of sulfur dioxide from 0.2–1.1 ppm (cm³/m³) (fig 2). Its zinc content was 90 %, mainly in the form of zinc oxide (ZnO). The air of the zinc solution purification building did not contain measurable amounts of zinc. In the cell house and casting building the zinc content of the air was not monitored between 1970 and 1977. Information collected later suggests that the zinc concentration in this building has been less than 0.1 mg/m³. The air of the zinc solution purification building contained 10 µg/m³ of metallic cadmium dust (TLV 20 mg/m³) in

the cadmium extracting areas.

The main impurity of the cell house was sulfuric acid (H₂SO₄) fumes. Their concentration was continuously monitored and varied between 0.5 and 1.0 mg/m³ (TLV 1 mg/m³).

SULFUR PLANT

The studied sulfur plant included the sulfur roasting and smelter buildings. Their main impurities were sulfur dioxide, iron sulfide (FeS) and oxide dusts. The annual geometric mean concentration of these impurities are given in fig 5–8.

EVALUATION OF THE EXPOSURE LEVEL OF THE SULFUR, COBALT AND ZINC WORKERS

In both parts of the study the work history of each participant was obtained by means of an interview. Any previous work in companies other than Outokumpu was recorded, along with the work history of their present employment (appendix II).

In the case-referent part of the study a person was considered to be exposed to cobalt if he had worked regularly for at least six months in the cobalt plant.

In the cross-sectional part exposure groups were formed of sulfur, cobalt, and zinc workers. In the analysis the three main groups were also divided according to the process areas with a similar exposure profile. The criteria of exposure data collection, expressed as exposure years, are given in appendix III.

The exposure times of the process workers in all three plants varied between 2 and 4 h/shift under normal processing conditions but increased two to four times a year for periods of one to two weeks during maintenance operations. During the usual processing operations, the workers did not wear protective masks regularly. The exposure time of the workers in the cell house of the zinc plant was usually 6 h/shift.

Extrapolation of the general exposure information to individual exposures is difficult because the work habits of the workers and their tasks vary. Personal monitoring of the exposure of zinc and cobalt workers in 1977 suggested that the 8-h average of the sulfur dioxide exposure

Table 3. Contents, expressed as percentage of the total sample, of water-soluble cobalt, iron, nickel and zinc in dust samples collected with stationary samplers in work areas of the cobalt, sulfur and zinc plants in September 1977.^a

Building	Cobalt	Iron	Nickel	Zinc
Cobalt roasting	0.35	2.58	0.17	0.75
Zinc roasting	0.008	0.0005	0.003	3.64
Sulfur roasting	0.14	1.25	0.044	0.28
Cobalt leaching	3.90	0.001	1.12	0.1

^a Standard atomic absorption method.

level in the cobalt and zinc roasting buildings was between 0.15 and 0.5 ppm (cm^3/m^3). On the average the dust exposure was 20 % lower when assessed on the basis of personal samples, being

2—3.5 mg/m^3 in the zinc roasting building and 6.5—14.5 mg/m^3 in the cobalt roasting building. The daily exposure to water-soluble cobalt sulfate varied between 0.03 and 0.15 mg/m^3 .

Case-referent part of the study

LITERATURE REVIEW

Occupational asthma: Definition and diagnosis

Bronchial asthma is a disorder characterized by reversible bronchospasm with wheezing, the symptoms occurring in short-lived paroxysm (7). Murphy described in detail the variety of definitions proposed for occupational asthma (47). In his review, Brooks (9) defined bronchial asthma of occupational origin as "a respiratory disorder characterized by reversible obstruction of the airways caused by the inhalation of substances or materials which are manufactured or directly used by a worker or are incidentally present at the work site." This definition is in accordance with the current clinical practice of the Finnish Institute of Occupational Health.

The Institute uses the following clinical criteria for occupational asthma (3, 29): (a) a 15 % or more decrease in forced expiratory volume in 1 s (FEV_1) after histamine challenge or after provocation with 1 % methacholine vapor and (b) a 15 % or more decrease in peak flow after challenge with a specific occupational agent and a clear distinction of the normal peak flow from normal circadian variation after a specific challenge test.

Sometimes the work environment of the subject cannot be simulated in a laboratory. In such cases a controlled work exposure test may give confirming results (46). If the mechanism of the bronchial obstruction is immunologic, skin tests may provide additional information. Increased serum levels of immunoglobulin E (IgE) or

specific antibodies to allergens encountered in the patient's work support the diagnosis. Specific provocation tests with an aerosol of a suspected agent seem to be the most accurate method for securing a diagnosis (47, 52). This procedure is time-consuming and requires hospitalization of the subject. Even if the pathogenetic mechanism of the bronchial obstruction is immunologic, specific provocation tests give more information than antibody determination (52). Skin tests with metals are unreliable because of their cross-reactivity (20). Chronic bronchitis is the most common disease to be differentiated. It may occur together with asthma.

Asthma associated with exposure to metals and their salts

Up until now information about occupational asthma in workers of the metallurgical and metal industries has been obtained from case reports. Reversible bronchial obstruction has been reported after exposure to chromium, platinum and nickel salts, metallic cobalt dust, and cobalt salts. The principal information of the reports has been summarized in table 4.

The first two accurate reports of bronchial asthma associated with metal exposure came from the English chrome plating industry in 1930 (11, 27). The probable causal agents were chromic acid and oxide dusts. The symptoms of asthma appeared after the polishing of chrome and nickel plated objects. They disappeared some days after the cessation of exposure. In 1970 McConnel et al (41) described occupational asthma in a 24-year-old nickel plater. The diagnosis was affirmed in a provocation test with nickel sulfate. These three cases

were carefully reported, and with high probability the patients had bronchial asthma.

Of the other metals, platinum causes bronchial obstruction. A syndrome of acute rhinitis, conjunctivitis, and reversible bronchial obstruction occurs in workers of platinum refineries (19, 50).

The largest uniform working population exposed to cobalt containing dusts occurs in the hard metal industry. Hard metal dust usually contains 60 % cobalt and 40 % tungsten carbide. Hard metal is used for tools and engine parts which should endure temperature and corrosion. In several studies (4, 13, 51, 60) chest tightness and wheezing have been reported in workers exposed to hard metal dust. The cobalt in

the dust has been considered the biologically active component because inhalation studies and skin tests have shown tungsten to be inert (13). Some investigators have considered the wheezing and chest tightness as the acute stage of hard metal disease (60), which is a chronic pneumoconiosis type of pulmonary disease, characterized by increased pulmonary fibrosis at a later stage. Dust containing metallic cobalt in concentrations of 0.06—0.1 mg/m³ causes a progressive decrease in the FEV₁ during the workweek (4). The symptoms of bronchial obstruction, such as wheezing, are associated with the decrease, but they disappear during the weekend.

Most of the literature concerning respiratory symptoms caused by cobalt refer to

Table 4. Asthma associated with exposure to metals and their salts.

Country	Reference	Industry	Number of cases	Exposure time	Agent under study	Skin test
England	Joules 1932 (27)	Chrome plating	1	6 months	Potassium dichromate	Potassium dichromate positive intracutaneously
England	Card 1935 (11)	Chrome plating	1	5 months	Chromium oxide	Positive to potassium dichromate
United States	McConnel et al 1973 (41)	Nickel plating	1	2 weeks	Nickel sulfate	Positive cut. reaction to nickel sulfate and circulating antibodies to nickel sulfate
United States	Freedman & Krupey 1968 (19)	Platinum refining	1	10 a	Complex platinum salt	Positive to hexachloro platinate
France	Parrot et al 1969 (50)	Platinum refining	8	2—8 months and 7 a	Chloroplatinic acid and its salts	Chloroplatinic acid 3 positive, 1 negative, 4 not known
France	Tolot et al 1970 (60)	Hard metal tool manufacturing	5	18 months to 17 a	Metallic cobalt	Not reported
United States	Coates et al 1973 (13)	Tungsten carbide manufacturing	9	6—18 months	Metallic cobalt	Not reported
United States	Bruckner 1967 (10)	Tungsten carbide tool	1	15 months	Tungsten carbide and cobalt dust	Negative
United States	Key 1960 (30)	Cobalt refining	7	Not reported	Not reported	Not reported
Belgium	Verhamme 1973 (62)	Cobalt refining	?	?	Cobalt salts	Not reported
Finland	Ahlman 1971 (1)	Cobalt refining	10	10—14 months	Cobalt sulfate, sulfides and oxides	4 positive to cobalt, 5 not done

wheezing and transient bronchial obstruction. Therefore the few reports referring to asthma are interesting and require careful evaluation. Key (30) described an outbreak of asthma in a cobalt refinery in the United States in 1958. The population at risk was 120 persons. No definite relationship to any particular job category was observed. Neither the time in which the cases were accrued nor the diagnostic criteria were mentioned. Conceptually the author spoke of a prevalence figure of 5 % but used the word incidence in his report. If the patients had asthma and the evident change of employment due to asthma was not controlled, the prevalence figure underestimated the incidence rate. The company doctor of a Belgian cobalt-producing plant reported various types of respiratory difficulties in workers exposed to cobalt oxide dust (62). He did not mention the diagnostic criteria or risk estimations of the diseased in his report.

Bruckner (10) described a case of asthma in a 45-year-old grinder who had been exposed to dry tungsten carbide dust for 2 a before he contracted clinical asthma. The symptoms required bronchodilator therapy and hospital admission. Though carefully documented, differential diagnostic information was missing in the description of the diagnostic procedure.

During the first 4 a of operation of the Outokumpu Kokkola cobalt plant Ahlman (1) reported 10 cases of "asthma or asthmatic bronchitis." Three of the patients worked in the cobalt roasting building and seven in the leaching building. The symptoms disappeared or diminished on free days but reappeared when the employee returned to work. All of the patients remained symptom-free after removal from cobalt exposure. From the data of this report it is, however, impossible to distinguish those who probably had only nonspecific bronchial irritation from the rest of the patients.

In the light of the literature review, the basic question as to whether cobalt or its compounds cause bronchial asthma or whether the symptoms described are only a reflection of bronchial irritation is still definitely unanswered.

According to the statistics of the Finnish Institute of Occupational Health, the number of new cases of occupational asthma

diagnosed increased steadily up until 1974, when 88 new cases were found. In 1975, the number of new cases was 64. According to provocation tests two cases from the latter group were caused by cobalt. In 1976, 17 new cases of occupational asthma were reported from the Finnish metal products and machine manufacturing industries, where the population at risk was about 140,000 (29). Former morbidity rates for asthma from the Finnish metallurgic industry are not known. Among pulpmill workers the prevalence of asthma is less than 1 % (24). Due to the selection which occurs in the population, the estimate is probably low because in the general working age population the prevalence is between 2 and 3 % (2).

PURPOSE

The purpose of the case-referent part of the present study was to determine whether occupational exposure to aerosols containing cobalt was associated with an increased risk of asthma.

SUBJECTS AND METHODS

The frequency of cobalt exposure of 21 persons having clinically diagnosed asthma was compared with the frequency of cobalt exposure of 55 randomly selected workers without asthma from the Outokumpu Kokkola Works.

Methacholine tests were performed for the assessment of the frequency of methacholine hyperreactivity in cobalt workers and in the working population of the Outokumpu Kokkola Works.

Selection criteria for the case-referent population

All of the workers with a diagnosis of bronchial asthma in their health records from 1969 on were included as potential cases. After the diagnoses of 26 persons were checked, 21 satisfied the criteria (page 14) required in order to be accepted as a case for this study. The 26 persons with probable asthma were also interviewed according to the method used for the participants of the cross-sectional part

of the study. One person met the criteria for chronic bronchitis (page 23). He was one of the five persons excluded. Four of the excluded subjects had been exposed to cobalt.

Every 60th male was selected as a referent from the alphabetic roster of the Company. Fifty-five referents were drawn.

The characteristics of the working population of the Outokumpu Kokkola Works are given on pages 20 & 21.

Methacholine, histamine and cobalt provocation tests

One hundred and forty-seven cobalt workers and 60 men who had never worked in the cobalt plant voluntarily participated in the methacholine test. The two groups were of similar ages and had similar smoking habits. They were tested one or more days earlier with a bronchodilator (salbutamol). The same eligibility criteria as for other pulmonary capacity measurements were used for the methacholine test. The subjects inhaled a 1 % methacholine vapor through a DeVilbiss® 40 nebulizer, making 1, 5 and 15 inhalations at intervals of 2 min. If the FEV₁ decreased more than 15 % before all the inhalations had been performed, the test was interrupted. The methacholine test was considered positive if the FEV₁ of a subject decreased more than 15 % after a maximum of 21 inhalations.

The histamine provocation tests were carried out at the Institute of Occupational Health according to an application of the method published by Laitinen (34). The test solution contained 1 % histamine di-phosphate in physiological saline.

The cobalt provocation test was performed with 0.1 and 1.0 % cobalt chloride solutions vaporized in a DeVilbiss 40 nebulizer. The subject was asked first to inhale 2 ml of the 0.1 % solution. If his bronchi did not react within 1 h with a decrease in FEV₁ of more than 15 %, he then inhaled 2 ml of the 1.0 % cobalt chloride solution. The cobalt chloride provocation was considered positive if the FEV₁ of the subject decreased by more than 15 % within 1 d after the test. Cobalt provocation tests have been made at the pulmonary function laboratory of the Institute of Occupational Health in Helsinki since 1977.

Health records

Written records of preemployment examinations, periodic health examinations, and other health screenings were available for use in this study. Sickness absenteeism and morbidity have been followed since 1973 with a computerized health information system, operated by the health center of the Company (53). Each employee who, due to an illness, was absent from work for 3 d or more had to report to the health center with a doctor's certificate. The date, place, and International Classification of Diseases (ICD) number, as found on the doctor's certificate, have been recorded systematically by the same medical assistant since 1973.

The health records of the nearby central hospital and of the Institute of Occupational Health were also available for this study.

Operational definitions

Case

All of the subjects who met the following diagnostic criteria for bronchial asthma were included as cases: expiratory wheezing observed through auscultation by any physician and documented in health records, documented relieving effect of bronchodilator drugs, and a 15 % or more decrease in the FEV₁ or the peak expiratory flow rate (PEFR) in the asymptomatic respiratory status after methacholine or histamine challenge.

Occupational asthma

The subjects with asthma and a positive cobalt provocation test had occupational asthma. If a previously healthy person becomes sensitized to agents encountered in his work environment and the outcome is asthma, the person is usually eligible for compensation for an occupational disease. A positive specific provocation test is normally required (29).

Exposure to cobalt: Grades 0—2

The following scale was used to rate the subjects' exposure to cobalt: 0, no exposure; 1, worked intermittently in the cobalt plant; 2, worked regularly in the cobalt plant (see appendix IV).

Atopy

In the present study the following criteria were established for atopy: A person who reported in the interview that he had had hay fever, asthma, infantile eczema, urticaria, or an allergic type of dermatitis, as diagnosed by a physician, was considered to be atopic.

Positive skin test

A skin test was considered positive if patch test erythema was present after patches retaining the suspected allergen had been kept on the arm and back for 48 h.

The prick test was not available for cobalt. Instead the test was done with the standard hay, hair, and chemical pattern used at the Institute of Occupational Health. The test was considered positive when the reaction was at the same level as the control reaction caused by a 1 % histamine solution. The zero control solution was glycerol saline (Dome).

Data analysis

Cases

The diagnostic information obtained from the company health records for all of the asthma cases was checked with the hospital records of the patients. Also, all of the subjects with asthma were interviewed according to the same method used with the subjects in the cross-sectional study.

Control of confounding factors

A confounding factor has been defined as an attribute associated both with the exposure and the illness in question. Confounding factors do not cause illness or increase the risk of it but may cause spurious association between the illness and suspected etiologic agent. If the distribution of confounding factors is dissimilar in the case and referent groups, their misleading effect can be controlled in the data analysis of the study.

The possible confounding factors considered were age, length of employment, exposure to sulfur dioxide (working in the sulfur plant or in the zinc roasting building) and former respiratory illnesses; also height and smoking were considered. These factors were controlled with a multiple re-

gression analysis. The basic information on the confounding factors was obtained from the interview of the workers. Because only age was associated with asthma and cobalt exposure, its effect was controlled in the analysis by stratification by age.

Risk estimation

The Mantel-Haenszel risk estimate for relative risk was calculated as the odds ratio (EOR) from the age strata (table 5) according to the following formula (40):

$$\text{Incidence density ratio (IDR)} = \frac{\sum_j a_j d_j / T_j}{\sum_j b_j c_j / T_j},$$

where a_j = number of exposed cases within the j^{th} stratum, b_j = number of nonexposed referents within the j^{th} stratum, c_j = number of exposed referents within the j^{th} stratum, d_j = number of nonexposed cases within the j^{th} stratum, and T_j = total number of subjects within the strata.

Table 5. History of exposure to cobalt among the cases and referents.

Age stratum (a)	Exposed		Total
	Yes	No	
29—33			
Cases	3	0	3
Referents	3	22	25
Total	6	22	28
34—38			
Cases	4	2	6
Referents	7	7	14
Total	11	9	20
39—43			
Cases	3	1	4
Referents	2	3	5
Total	5	4	9
44—48			
Cases	2	2	4
Referents	2	7	9
Total	4	9	13
49—53			
Cases	3	1	4
Referents	0	2	2
Total	3	3	6

Mantel-Haenszel risk estimate (EOR) = 4.80
 $\chi^2_1 = 11.7$; two-tailed p -value = 0.0008
95 % confidence interval for the risk estimate:
2.0—11.7

For hypothesis testing a normal distribution was assumed. Chi-square with one degree of freedom was obtained from the formula:

$$\chi^2_1 = \frac{(\sum a_j - \sum E_{oj})^2}{\sum V_{oj}},$$

where E_{oj} = expected number of cases within the j^{th} stratum and V_{oj} = variance of the mean of the expected cases.

The 95 % confidence interval for the Mantel-Haenszel estimate was calculated with the formula:

$$\text{EOR}, \overline{\text{EOR}} = \hat{\text{EOR}} \pm \chi_\alpha / \chi_p,$$

where $\chi_\alpha = (\chi^2_{0.05})^{1/2} = 1.96$ and $\chi_p = \chi$ and is the square root of the χ^2 obtained in the analysis (45).

The risk ratio was also estimated from the application of Bayes' theorem as given by Neutra & Drolette (48).

The statistical significance was expressed as $0.01 \leq p < 0.05$ almost significant, $0.001 \leq p \leq 0.01$ significant, and $p < 0.001$ highly significant.

RESULTS

Increased risk of asthma in cobalt workers

Of the 21 men with clinically confirmed asthma, 15 worked in the cobalt plant when they fell ill, one in the sulfur plant, one in the power plant, and four in the maintenance section. The work history and diagnostic information on the subjects with asthma are given in appendix IV.

The approximated relative risk of asthma, as calculated from unstratified data, was 7.3 for the cobalt workers on the basis of the odds ratio shown in table 6. The ex-

Table 6. History of exposure to cobalt among the cases and referents.

	Cases	Referents	Total
Exposed	15	14	29
Nonexposed	6	41	47
Total	21	55	76
Relative risk	4.1		
Odds ratio	7.3	(an approximation to true relative risk)	

posure specific risk estimate obtained with Bayes' theorem was 6.8 on the assumption that the overall rate of asthma in the general population is 3 %. The Mantel-Haenszel risk estimate was 4.8, the 95 % confidence interval of the estimate being 2.0—11.7. The chi-square value was 11.7, and the p-value 0.0008. The basic data utilized in the Mantel-Haenszel test are given in table 5.

Seventeen of the 21 patients with asthma were examined at the Institute of Occupational Health in Helsinki, two at the nearby central hospital, and two at the Oulu University Central Hospital. Altogether five of the 15 cobalt workers with asthma had a positive respiratory challenge with cobalt chloride and one with the dust of the cobalt roasting building. They met the criteria of occupational asthma given on page 14. The 17 patients examined at the Institute of Occupational Health were tested with a patch test in which cobalt and nickel were used, and eight were also given the prick test with various test substances. Only one cobalt worker with asthma had a positive reaction in both skin tests.

When the workers developed asthma, or symptoms of it, they were examined by the plant physician, remitted to further medical examinations, and transferred to another job where they were no longer exposed to cobalt. The symptoms of asthma disappeared in all but three persons after removal from exposure. Of the cases other than cobalt workers, one sulfur worker and one power plant worker remained asthmatic. Two of the asthmatic cobalt workers were reexposed to cobalt accidentally in 1977, 7 and 8 a, respectively, after removal from cobalt exposure. One was exposed to water-soluble cobalt dust in maintenance operations and the other to metallic cobalt dust while grinding a piece of metallic cobalt. After the first exposure day both workers experienced typical clinical symptoms of asthma. They were examined at the Institute of Occupational Health in 1977 and had a positive result in the cobalt chloride provocation test.

Methacholine tests

As shown in table 7, the cobalt workers did not have more bronchial hyperreactiv-

ity from methacholine than workers who had not been exposed to cobalt. The workers who had not been exposed to cobalt had somewhat more positive reactions to methacholine; however the difference was not statistically significant.

The average increase in FEV₁ after salbutamol inhalation and before the methacholine test was less than 1 % in both groups. In no case did a testee have a higher than 5 % increase in FEV₁ after the salbutamol challenge.

Two cobalt workers had an increased sensitivity to methacholine immediately after a work shift, but this sensitivity had disappeared when the test was reproduced after a weekend. Two of the nine persons with increased bronchial reactivity to methacholine were atopic.

DISCUSSION

The elevated risk of asthma among the cobalt workers of the Outokumpu Kokkola Works was highly significantly associated with former exposure in the cobalt plant.

Of the metals encountered in amounts above the analytical detection limit in the dust of the cobalt, zinc and sulfur plants, chromium, nickel and cobalt have been identified to cause reversible bronchial obstruction (9, 10, 11, 12, 41). The chromium concentration of the dust was very low and similar in all plants (table 1). In addition the referents and the asthmatics were similarly exposed to chromium. Therefore it was unlikely that chromium would have caused the elevated asthma risk. Nickel and cobalt occurred in water-soluble form in the cobalt plant and mainly as a water insoluble form in the sulfur plant. In the zinc plant there were only very limited

areas with exposure to cobalt and nickel. The concentrations of water-soluble cobalt and nickel salts were the highest in the cobalt roasting and leaching buildings. In light of the exposure information, it is very likely that nickel, cobalt, or both have caused asthma among the cobalt workers.

The literature and the results of the case-referent part of the present study suggest that cobalt was more probable to cause occupational asthma than nickel. Hard metal disease, which has been documented to be caused by metallic cobalt dust, has an acute form which resembles clinical bronchial asthma (12, 60). Observations from the American and, probably, from the Belgian cobalt industry suggest an elevated risk of asthma among cobalt-producing workers (30, 62).

Observations from the early years of production at the Outokumpu Kokkola Works also suggest an elevated risk of asthma among cobalt workers (1). There were four cobalt workers who had a specific bronchial reaction to cobalt chloride and one with a specific reaction to the dust of the cobalt roasting building. Two of the four were also tested with nickel sulfate with negative results. One patient with a positive reaction in the cobalt provocation test also had positive reactions to hay pollens. Despite their light nickel exposure, the sulfur and zinc workers had no higher risk of asthma than the referent subjects. So far, there have been no reports from the nickel-producing industry indicating an elevated risk of asthma among nickel workers, although their number exceeds the number of cobalt workers by several times in the world (14).

The diagnostic information of the present study was collected retrospectively,

Table 7. Findings from the methacholine tests. (FEV₁ = forced expiratory volume in 1 s)

	Cobalt workers (N = 147)		Workers not exposed to cobalt (N = 60)	
	Decrease in FEV ₁ 7—14 % (N)	Decrease in FEV ₁ ≥ 15 % (N)	Decrease in FEV ₁ 7—14 % (N)	Decrease in FEV ₁ ≥ 15 % (N)
Smokers	7	2	1	1
Exsmokers	4	1	3	2
Nonsmokers	4	2	4	1
Total	15 (10 %)	5 (3 %)	8 (13 %)	4 (8 %)

and strict criteria were used so that false positive cases would not be included. Among the excluded "cases" recorded as asthma in the computerized health register of the Company, at least five persons had acute bronchitis or bronchial irritation which might have been associated with infection or exposure to sulfur dioxide. None of these persons had had to change work later because of respiratory difficulties.

The possibility was checked of whether asthmatic workers not listed in company health records had quit the sulfur and zinc plants or other areas of the Outokumpu Kokkola Works. The hospital records of the workers who had quit their job between 1973 and 1977 did not yield any additional cases of asthma.

It was unlikely that the employment selection process would have concentrated persons with asthma in the cobalt plant. A check of the preemployment examination forms did not indicate that any of the cobalt workers or the reference subjects had asthma before their current employment. The differential diagnosis of the cases was completed with an interview of the same type as was used in the cross-sectional part of this investigation. In addition the chest radiographs of the subjects were examined. There were no indications that some of the persons included as asthmatics would have had prominent signs of earlier chronic bronchitis or pulmonary emphysema. The differential diagnostic procedure also took place at the Institute of Occupational Health.

The cobalt workers considered to be asthmatic had clinically demonstrated bronchial asthma. Their disease caused subjective symptoms requiring bronchodilator therapy and removal from cobalt exposure. Although there was evidence that cobalt sulfate caused asthma, a definite confirmation must be obtained in additional studies of the biological properties of this compound.

Although the cobalt exposure of the workers did not exceed the current Finnish TLV (0.1 mg/m^3), their risk of asthma was increased. This finding indicates that the present TLV for cobalt is not safe for the prevention of asthma.

The risk of asthma among cobalt workers was increased without a doubt. However, only 6 of the 15 workers tested had a positive reaction to cobalt. There are at least two plausible reasons for this. First 15 of the 21 workers with asthma had been tested with the cobalt chloride challenge. Second, according to experience obtained in the pulmonary function laboratory of the Institute of Occupational Health, the bronchial reactivity to specific testing substances might be diluted as a function of time. All of the tested cobalt workers had stopped working in the cobalt plant at least two months before the test.

Unexpectedly, there was no indication of increased sensitivity to methacholine among the cobalt workers. The workers who had not been exposed to cobalt had slightly more positive reactions to methacholine, probably as a result of irritation. Some of these nonexposed workers were from the sulfur and zinc plants, where they had been exposed to sulfur dioxide and other irritant air impurities. The finding that two cobalt workers had transient sensitivity about 1 h after exposure to sulfur dioxide and cobalt-containing dust presumably means that many respiratory irritants encountered in the work conditions of the plants may transiently increase sensitivity to methacholine.

The mechanism of the asthma encountered in connection with cobalt exposure may be evaluated with immunologic studies as a prospective study. Development of a specific IgE antibody to cobalt would further clarify the picture of the respiratory effects of cobalt.

Cross-sectional part of the study

LITERATURE REVIEW

Studies on chronic bronchitis and ventilatory capacity in the mining and metallurgic industries

Few studies have been made concerning ventilatory capacity and respiratory diseases in the nonferrous metals-producing industry (23). Except for the presence of zinc and cobalt compounds the impurities in the work environment of cobalt and zinc plants, eg, ferrous metals containing sulfates, sulfides and sulfur dioxide, are also common in the mining and steel industries (16, 37, 38, 39). The most important information of studies on the mining, foundry and steel industries is summarized in table 8 as background for the present study. The lack of control groups (38, 39, 28, 57) and methodological differences limit the direct comparison and generalization of the results of these studies. All of the larger studies except that of Smith et al (57) were cross-sectional investigations

with no adequate report of the controlling of the selectivity of the study population. Therefore, evaluation of the accuracy of the risk estimations of chronic bronchitis is difficult.

In foundries and the steel industry the prevalence of chronic bronchitis, as defined by the British Medical Research Council, varies between 2 and 13 % for exposed nonsmokers, and 4 and 30 % for smokers (28, 37, 38). Among males in the Finnish nonsmoking population, the prevalence varies from 0 to 2 % (21, 25).

Smoking and a dusty work environment seemed to increase the frequency of symptoms of chronic bronchitis and decrease FEV₁ in all the reviewed studies. Age and smoking combined were associated with a greater increase in the risk of chronic bronchitis than either alone.

For the medical prevention of the pulmonary impairment of industrial workers one should know the safe level of exposure and susceptible persons. Smith et al (57) approached this problem with a 1-a follow-

Table 8. Studies of chronic bronchitis and ventilatory capacity in the metal mining and metallurgic industries.

Country	Reference	Industry	Ex- posed (N)	Control (N)	Age (a)	Prevalence of chronic bronchitis (%)			
						Exposed ^a		Control ^a	
						Nsm	Smk	Nsm	Smk
Italy	Sartorelli et al 1969 (55)	Pyrites mining	983	345	18—35	7	32	0	4
England	Lloyd Davies 1971 (37)	Ferrous and nonferrous foundries	1,780	1,730	35—64	2	4—6	1	3—6
England	Lowe et al 1970 (38)	Steel pro- duction	10,449	None	20—69	13	117		
United States	Smith et al 1976 (57)	Copper smelter	113	None	19—64	Not investigated			
Finland	Kärävä et al 1976 (28)	Ferrous and nonferrous foundries	931	None	44 (mean)	2—9	19—30		

^a Nsm = nonsmokers; Smk = smokers.

up study of 113 workers in an American copper smelter. They suggested that exposure to 1.0–2.5 ppm (cm^3/m^3) of sulfur dioxide caused a significant loss of FEV_1 (79 ml/a) in a susceptible subgroup. In the normal US male population the yearly decrease in FEV_1 is 25–35 ml between the ages of 30–50 a. They also concluded that there was no significant interaction between copper sulfate containing particulates and sulfur dioxide. Again, for this study, the brief description of the methods made the evaluation of the practical importance of the results difficult. For instance, eligibility criteria, standardization of the spirometry and BTPS¹ correction were not reported. Alexandersson (4) recently reported a significantly higher frequency of chest tightness and cough with phlegm among 291 Swedish hard metal workers in comparison with 126 matched referents. He also demonstrated a significant decrease in FEV_1 during the work week. The FEV_1 improved after a night's sleep and the weekend. Alexandersson & Hedenstierna (5) measured closing volume in relation to vital capacity (VC %) in 155 hard metal workers and 74 matched referents. According to the authors cobalt caused small airway obstruction that still persisted even after four weeks in the group with the highest cobalt exposure.

There is evidence from controlled laboratory studies that sulfur dioxide concentrations of 3–5 ppm (cm^3/m^3) decrease bronchial air flow already after 3–5 min of exposure (31). It also causes throat irritation and a cough at these concentrations. The symptoms do not seem to be correlated with changes in air flow.

Zinc sulfate and zinc ammonium sulfate particles of 0.3 μ in diameter, together with sulfur dioxide at a concentration of 2.5 ppm (cm^3/m^3), have been shown to increase airway resistance in guinea pigs (6).

Extrapolation of laboratory investigations of a single chemical to conditions in metallurgic plants is difficult because the plant environment consists of a complex atmosphere of dusts and gases. The possible interaction of different chemicals, climate, humidity, and ventilation may great-

ly influence the effect of a single compound on bronchi and affect the results of technical hygiene measurements (56). Whether metal-containing sulfates, with sulfur dioxide or separately, cause bronchial impairment which may progress to deleterious pulmonary disease is yet unknown. Parkes (49), for instance, concluded, mainly on the basis of the studies referred to in the present review, that there is little evidence that chronic obstructive bronchitis is causally related to past exposure to dusts or sulfur dioxide. However, on the basis of the fragmentary observations of earlier studies, categorical views are not warranted because of the variety of the methods employed in them. One part of the puzzle seems to be somewhat clearer than the others, ie, smoking is more harmful in dusty occupations than in an uncontaminated environment.

PURPOSE

The purpose of the cross-sectional part of the present study was to determine whether cobalt- or zinc-containing aerosols increase the occurrence of symptoms of chronic bronchitis or decrease ventilatory capacity.

SUBJECTS AND METHODS

The occurrence of symptoms of chronic bronchitis in exposed and nonexposed persons was assessed with the aid of a structured interview. Ventilatory capacity was measured from expiratory-flow-volume loop curves made immediately after the interview.

The cross-sectional part of the study included 224 cobalt workers, 234 zinc workers, and 158 sulfur workers, employed for more than 1 a in the Company. One hundred and fifty-one laboratory, office, and power plant workers comprised the nonexposed reference group.

The exposure information was obtained from the Company's records of technical hygienic measurements. The exposure levels of the main pollutants were checked with personal samplers in 1977 and from the standard sampling survey of the Company since 1970. The length of exposure was assessed on the basis of interviews with the subjects.

¹ BTPS = temperature of 37°C, ambient pressure, saturated with water vapor at 37°C.

Subjects

The permanent working population of the Outokumpu Kokkola Works varied in number between 1973 and 1977 from 1,650 to 1,750 persons, 10 % of whom were females. The turnover rate varied between 1973 and 1977 from 2.5 to 7.0 %, being 2.5 % in 1977. Turnover occurred mainly among young workers under 25 a of age. Ninety-five percent of the workers were first generation industrial workers from nearby rural areas, mainly with farming backgrounds. Three percent of the workers had been employed by other industries before their current employment. In 1977, 1,546 men worked in the Outokumpu Kokkola Works. Their mean age was 34 a, and their average length of employment 7.5 a.

Age and height

The cobalt workers and referents were similar with respect to age and height. Their mean age was 33.6 a. The age of the zinc workers averaged 1.5 a less. The height distributions were similar in all groups (table 9).

Smoking

The smoking habits were different in all groups. Thirty percent of the subjects smoked, and 38 % had never smoked. There was a general trend that the younger men in the exposed groups smoked more than the older ones. Details are given in table 10.

Selection of the cross-sectional population

The selection process is described in table 11. Three exposed groups were formed from the roster of the periodic health examinations of 1,385 workers, and one reference group from the group of 313 non-exposed workers who had not worked in the process areas of the plants.

Selection criteria

Those workers who had worked for more than 1 a in the Company and had spent at least two-thirds of their employ-

Table 9. General characteristics in the cross-sectional population.

	Cobalt workers (N = 224)	Zinc workers (N = 234)	Sulfur workers (N = 158)	Referents (N = 161)
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Age (a)	33.6 $\pm$ 6.6	32.0 $\pm$ 5.9	36.7 $\pm$ 5.7	33.7 $\pm$ 7.7
Height (cm)	175.2 $\pm$ 5.4	174.4 $\pm$ 6.1	174.5 $\pm$ 5.7	175.5 $\pm$ 5.6
Length of exposure (a)	7.3 $\pm$ 3.4	5.5 $\pm$ 2.7	8.6 $\pm$ 4.8	8.7 $\pm$ 3.9 ^a

^a Years of employment.

Table 10. Smoking habits in the cross-sectional population.

	Cobalt workers		Zinc workers		Sulfur workers		Referents	
	N	%	N	%	N	%	N	%
Smokers	71	(32)	114	(49)	43	(27)	48	(30)
Exsmokers	101	(45)	69	(29)	75	(48)	52	(32)
Nonsmokers	52	(23)	51	(22)	40	(25)	61	(38)
Length (a) of smoking (mean $\pm$ SD)	9.5 $\pm$ 7.7		8.3 $\pm$ 6.3		10.9 $\pm$ 9.6		7.2 $\pm$ 7.8	

ment in either the cobalt, zinc or sulfur plant were included as eligible subjects for the three respective exposed groups. Workers who were employed for a year or less were included if they had been in either of the three plants for six months or more. Two hundred and forty-three cobalt workers, 285 zinc workers, and 166 sulfur workers satisfied these criteria. Two hundred and nine workers who had been employed for more than 1 a in the Company were the eligible referents.

Exclusion criteria

Women, maintenance workers, and men who had worked less than 1 a in the Company before 1 February 1977 were excluded. Fifty workers who had changed from one process plant to another were also excluded because of their heterogeneous exposure history. Asthmatic persons were excluded because the results of their ventilatory capacity measurements would reflect more status of the disease than the effect of exposure. Before the statistical analyses ten exposed men and two referents were excluded due to their unsatisfactory performance in the ventilatory capacity measurements.

Study population

Ninety-two percent of the eligible cobalt workers (224 men), 82 % of the eligible zinc workers (234 men), and 95 % of the eligible sulfur workers (158 men) formed the three exposed groups, whose interview and expiratory flow volume data were analyzed in this study. Seventy-seven percent of the eligible referents (161 men) were included in the analysis.

Unreached population

The average absentee rate due to work accidents and disease was between 5 and 8 % of the total working population of the Company from 1973 to 1977. The exposed persons who were not reached belonged mainly to this category. Of the workers, 2 to 5 % have extra days off because of shift work.

Twenty-three percent of the eligible referents did not participate because of the following reasons: 4—5 % were on sick leave; 2—4 % were on holiday because of shift work; 10 % were on business trips; and the rest would not participate.

Table 11. Selection of the cross-sectional population. (1,698 persons worked in the Outokumpu Kookola Works in 1977)

<i>Exposed groups</i>		<i>Reference group</i>	
Number of persons		Number of persons	
1,385	in periodic health examination roster	313	not in periodic health examination roster
<i>Excluded</i>		<i>Excluded</i>	
475	maintenance workers		
67	worked less than one year before 1 February 1977	23	worked less than one year before 1 February 1977
17	subjects with asthma	1	subject with asthma
72	women	80	women
50	heterogeneous exposure		
78	unreached population	46	unreached population
10	unsatisfactory tracing in ventilatory capacity measurement	2	unsatisfactory tracing in ventilatory capacity measurement
<i>Included (616)</i>		<i>Included (161)</i>	
224	cobalt workers	161	laboratory, office and power plant workers
234	zinc workers		
158	sulfur workers		

Health information

Interview

The frequency of respiratory symptoms was obtained from a Finnish translation of a Harvard questionnaire for respiratory symptoms, which is based on the British Medical Research Council's questionnaire (44).

The subjects of both the case-referent and cross-sectional studies were interviewed by two nurses who were specially trained to use standardized interview methods (44). The subjects were randomly allocated for interviewing to either of the nurses. The interview took place in the same place and at the same time as the periodic health examinations of the occupational health program of the Kokkola Works.

The distributions obtained by the two nurses were similar for the yes/no answers to the questions concerning chronic production of phlegm and wheezing.

Ventilatory capacity measurement

The maximal expiratory flow volume (MEFV) loop was the main index of ventilatory capacity. The characteristics of flow volume curves have been described by Cotes (15). The indices of the analyzed expiratory flow volumes were the following: forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), $(FEV_1/FVC) \times 100$ ($FEV_1\%$), and the instantaneous flow rate at 50 % of FVC ($\dot{V}_{max\ 50}$).

The ventilatory capacity measurements were performed with a "Pumolab 220" drolling seal spirometer (Cardio Pulmonary Instruments Co). It had an x-y recorder, BTPS correction and digital reading of FEV_1 , FVC, PEF, FEF_{25-75} (forced midexpiratory flow) and $\dot{V}_{max\ 50}$. The spirometer and x-y recorder were calibrated weekly.

The measurements were performed by two nurses specially trained by the staff of the pulmonary function laboratories of the Institute of Occupational Health and the Helsinki University Central Hospital. The mean values of the FEV_1 and FVC measured by each nurse varied less than 1 % when evaluated from 60 randomly selected flow-volume loop curves.

Before the spirometry the eligibility of each subject was determined in a brief interview and examination. The subject's weight, height without shoes, and blood pressure were recorded. The MEFV curves were recorded from the subject as he stood wearing a nose clip. Each subject practiced one or more times, and then three tracings were recorded for the analyses. The interval between tracings was 30–60 s.

The following steps were taken to improve the accuracy of the ventilatory capacity measurements:

1. The subject had to be free from minor respiratory illnesses for two weeks before the test day.
2. Smoking was not allowed for 1 h before the test.
3. The difference between the three test tracings was not allowed to be more than 5 %, measured from the FEV_1 in the curve.
4. The flow-volume curve with maximal FEV_1 was analyzed (18).

Hall & Gandevia (22) introduced the so-called loose cough or "objective cough" sign in screening for chronic bronchitis. The subject is asked to cough. If he produces phlegm or gives the sound of having loose phlegm, he has a loose cough, which implies bronchial hypersecretion. The test was performed in connection with the ventilatory capacity measurements of each subject.

Operational definitions

Chronic cough

A subject was considered to have a chronic cough if he coughed daily for at least three months a year.

Chronic production of phlegm

The production of phlegm daily for at least three months a year was the criterion to be met for the chronic production of phlegm.

Chronic bronchitis

Chronic bronchitis was the production of phlegm and chronic cough together for at least three months a year during the 2 a preceding the examination with no other local or specific pulmonary disease present (43).

Smoker

A subject was considered a smoker if he regularly smoked more than one cigarette a day and had smoked for at least six months before the examination.

Exsmoker

Those subjects who had smoked at least 20 packs of cigarettes during their lifetime or had smoked at least one cigarette a day and had stopped smoking six months before the examination were classified as exsmokers.

Nonsmoker

Any subject who had never smoked more than 20 packs of cigarettes during his lifetime was listed as a nonsmoker.

Data analysis

Exposure

The goal in the collection of exposure information was to describe the different exposure patterns of the cobalt, sulfur, and zinc plants. This procedure was described in the chapter called Exposure Information.

The geometric mean concentration was used in the description of the exposure level of the ambient air. This model provides a better reflection of the real exposure level than does the arithmetic mean, on which momentary peaks of high gas or dust concentrations have a greater effect (36).

Fig 9. Frequency of symptoms of chronic bronchitis in participants of the cross-sectional part of the study.

Health data

The nurses who interviewed the subjects recorded the results of the interviews on a coding form (IBM form 24-6436-4 5/0123). Before the final data analyses, the coded data were edited with a special program which revealed all of the impossible answers and measurement values that could be caused by coding errors. Errors were corrected before the final analyses. The chi-square test was applied in the evaluation of the statistical significance of the differences in the frequencies of respiratory symptoms between the exposed and nonexposed groups. In the significance testing of the results of the ventilatory capacity measurements the t-test was used.

A stepwise multiple linear regression analysis was used in the determination of possible effects of various industrial exposures upon the ventilatory capacity of sulfur, cobalt, and zinc workers. An IBM application of the step-up multiple regression was used (26).

In the step-up method the regressions of Y on $X_1 \dots X_n$ are determined as follows: the variable giving the greatest increase in the proportion of Y variance accounted for by the addition of the corresponding X variable to the equation estimating Y is selected. This variable can be called X_1 . Then all the bivariate regressions in which X_1 appears are worked out. The variable giving the greatest increase in the squared multiple correlation after the fitting of X_1 is selected. It can be called X_2 . With the same procedure used for the bivariate, all the trivariate that include X_1 and X_2 are worked out (58). The exposure years of the subjects in the sulfur, cobalt, and zinc plants were used as the X variables in the analysis.

RESULTS

The results of the cross-sectional part of the study indicated that exposure to less than the current Finnish TLVs of gases, fumes and dusts given in table 2 did not cause serious persistent bronchial impairment in less than 10 a of employment in the cobalt, zinc or sulfur plant. It was possible, however, that exposure to sulfur dioxide in concentrations of less than 5 ppm (cm^3/m^3) in combination with sulfide

and/or sulfate dusts and smoking had a detrimental effect on small bronchi before 10 a had elapsed.

Respiratory symptoms

Fifteen percent of the cobalt workers, 11 % of the sulfur workers, and 11 % of the zinc workers reported chronic production of phlegm, as shown in fig 9. Twenty-eight percent of the cobalt workers, 28 % of the sulfur workers, and 21 % of the zinc workers reported wheezing. Compared with the referents, the exposed groups had a highly significantly greater chronic production of phlegm and wheezing, except for the zinc workers whose frequency of wheezing did not differ significantly from that of the referents.

The workers of the cell house did not differ from the referents with regard to respiratory symptoms. They had been exposed to 0.5–1.0 mg/m³ of sulfuric acid fumes for an average of 5–6 h a day for 5–6 a.

When the cobalt workers were divided, according to length of exposure, into groups of more or less than 5 a, the frequencies of respiratory symptoms did not differ.

The reported respiratory symptoms were neither associated with lower ventilatory capacity or higher absenteeism due to respiratory illnesses nor with the different exposure entities in the cobalt, sulfur, and zinc plants.

Smoking and respiratory symptoms

The chronic production of phlegm and wheezing were clearly associated with smoking among cobalt and sulfur workers. Fig 10 shows that, in the cobalt group, 25 % of the smokers reported chronic production of phlegm, and 34 % wheezing. The nonsmoking cobalt workers and referents did not differ with regard to respiratory symptoms. Smoking cobalt workers had more wheezing than the smoking referents, but the difference was not significant. The association between respiratory symptoms and smoking habits was similar among the sulfur workers. This finding indicates that, under exposure levels of 10 mg/m³ of iron sulfide/sulfate and 5 ppm

(cm³/m³) of sulfur dioxide, the effect of exposure was probably a nonspecific irritation enhanced by the inhalation of tobacco smoke. Sulfur dioxide and dusts seemed to be more harmful to smokers at the present Finnish TLV than to nonsmokers.

Bronchial hypersecretion

Bronchial secretion was not increased in any of the exposed groups. Seventeen cobalt workers (8 %), 22 zinc workers (10 %), 15 sulfur workers (9 %), and 13 referents (8 %) were found to have a loose cough. The sign was not associated with the production of phlegm reported in the interview. More than two-thirds of the persons with a loose cough in each group were smokers.

Chronic bronchitis

The prevalence of chronic bronchitis among cobalt and zinc workers was 2 % (5 cases in both groups) and 0 % for the sulfur workers and referents. All of the five zinc workers smoked. Three of the cobalt workers were smokers, one was a nonsmoker, and one an exsmoker.

Ventilatory capacity

Table 12 shows the mean levels of the indices of the ventilatory capacity measure-

Fig 10. Frequency of symptoms of chronic bronchitis in the cobalt workers (71 smokers and 52 nonsmokers) and referents (48 smokers and 61 nonsmokers).

Table 12. Ventilatory capacity in the cross-sectional population.

Parameter ^a	Cobalt workers (N = 224)	Zinc workers (N = 234)	Sulfur workers (N = 158)	Referents (N = 161)
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
FEV ₁ (l)	4.32 $\pm$ 0.66	4.34 $\pm$ 0.65	4.19 $\pm$ 0.63	4.35 $\pm$ 0.66
FVC (l)	5.39 $\pm$ 0.63	5.39 $\pm$ 0.79	5.24 $\pm$ 0.69	5.38 $\pm$ 0.75
FEV %	80.6 $\pm$ 6.3	81.1 $\pm$ 5.7	78.8 $\pm$ 7.7	81.6 $\pm$ 6.6
$\dot{V}_{\max 50}$	5.30 $\pm$ 1.46	5.45 $\pm$ 1.78	4.98 $\pm$ 2.11	5.46 $\pm$ 1.55

^a An explanation of the abbreviations of the ventilatory capacity indices can be found on page 23 of the text.

Table 13. Age, height, length of exposure and results of the ventilatory capacity measurements of the nonsmoking subjects aged 30–45 a in the three exposed groups and the reference group.

Parameter ^a	Cobalt workers		Sulfur workers (N = 21)	Zinc workers (N = 28)	Referents (N = 30)
	Roasting (N = 11)	Leaching (N = 20)			
	Mean $\pm$ SD	Mean $\pm$ SD			
Age (a)	37 $\pm$ 3	35 $\pm$ 5	37 $\pm$ 5	35 $\pm$ 4	36 $\pm$ 4
Height (cm)	177 $\pm$ 6	177 $\pm$ 6	173 $\pm$ 7	174 $\pm$ 7	177 $\pm$ 6
Length of exposure (a)	8 $\pm$ 2	9 $\pm$ 2	11 $\pm$ 5	5 $\pm$ 3	9 $\pm$ 2 ^b
FEV ₁ (l)	4.2 $\pm$ 0.4	4.6 $\pm$ 0.8	4.1 $\pm$ 0.6	4.3 $\pm$ 0.6	4.5 $\pm$ 0.7
FVC (l)	5.2 $\pm$ 1.4	5.9 $\pm$ 1.3	5.1 $\pm$ 0.7	5.4 $\pm$ 0.8	5.5 $\pm$ 0.8
FEV %	82 $\pm$ 7	81 $\pm$ 6	77 $\pm$ 4	80 $\pm$ 4	82 $\pm$ 6
$\dot{V}_{\max 50}$ (l/s)	5.2 $\pm$ 0.5	5.7 $\pm$ 0.8	4.7 $\pm$ 1.4	5.3 $\pm$ 1.1	5.6 $\pm$ 1.7

^a An explanation of the abbreviations of the ventilatory capacity indices can be found on page 23 of the text.

^b Years of employment.

Table 14. Age, height, length of exposure and results of the ventilatory capacity measurements of the smokers aged 30–45 a in the three exposed groups and the reference group.

Parameter ^a	Cobalt workers		Sulfur workers		Zinc workers			Referents (N = 41)
	Roasting (N = 17)	Leaching (N = 28)	Roasting (N = 11)	Smelter (N = 21)	Roasting (N = 5)	Leaching and casting (N = 22)	Cell house (N = 32)	
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
Age (a)	34 $\pm$ 5	35 $\pm$ 4	37 $\pm$ 4	37 $\pm$ 5	36 $\pm$ 5	35 $\pm$ 4	35 $\pm$ 4	34 $\pm$ 4
Height (cm)	175 $\pm$ 5	176 $\pm$ 5	174 $\pm$ 5	175 $\pm$ 5	173 $\pm$ 5	175 $\pm$ 7	173 $\pm$ 6	176 $\pm$ 5
Length of exposure (a)	8 $\pm$ 3	8 $\pm$ 2	8 $\pm$ 3	9 $\pm$ 4	5 $\pm$ 3	5 $\pm$ 2	5 $\pm$ 2	9 $\pm$ 2 ^b
FEV ₁ (l)	4.2 $\pm$ 0.5	4.3 $\pm$ 0.6	4.0 $\pm$ 0.5	4.1 $\pm$ 0.6	4.0 $\pm$ 0.6	4.3 $\pm$ 0.8	4.1 $\pm$ 0.6	4.3 $\pm$ 0.5
FVC (l)	5.2 $\pm$ 0.5	5.5 $\pm$ 0.7	5.1 $\pm$ 0.5	5.3 $\pm$ 0.6	5.4 $\pm$ 0.9	5.5 $\pm$ 1.0	5.1 $\pm$ 0.7	5.4 $\pm$ 0.7
FEV %	80 $\pm$ 6	79 $\pm$ 6	78 $\pm$ 7	77 $\pm$ 8	76 $\pm$ 3	79 $\pm$ 6	81 $\pm$ 5	79 $\pm$ 6
$\dot{V}_{\max 50}$ (l/s)	5.1 $\pm$ 1.7	5.1 $\pm$ 1.3	4.5 $\pm$ 1.5	4.7 $\pm$ 1.7	4.3 $\pm$ 1.8	5.2 $\pm$ 1.5	5.4 $\pm$ 2.0	5.0 $\pm$ 1.2

^a An explanation of the abbreviations of the ventilatory capacity indices can be found on page 23 of the text.

^b Years of employment.

Table 15. Age, height and results of the ventilatory capacity measurements of the cobalt leaching and roasting workers who were ex-smokers.

Parameter ^a	Roasting workers (N = 22)	Leaching workers (N = 34)
	Mean $\pm$ SD	Mean $\pm$ SD
Age (a)	34.5 $\pm$ 4.4	34.4 $\pm$ 4.3
Height (cm)	175.1 $\pm$ 3.9	175.4 $\pm$ 4.9
FEV ₁ (l)	4.13 $\pm$ 0.53	4.33 $\pm$ 0.48
FVC (l)	5.50 $\pm$ 0.57	5.50 $\pm$ 0.66
FVC %	81.1 $\pm$ 4.8	79.7 $\pm$ 6.6
$\dot{V}_{\max 50}$ (l/s)	5.46 $\pm$ 1.20	5.24 $\pm$ 1.36

^a An explanation of the abbreviations of the ventilatory capacity indices can be found on page 23 of the text.

ments of the exposed and reference groups. The differences between the groups were not great. Stratification according to smoking and exposure (tables 12—15) or by length of exposure (tables 16 and 17) did not change the results. The means of the FEV₁ and $\dot{V}_{\max 50}$ were the lowest for the sulfur workers. They had been exposed longer and were older than the subjects in the other study groups.

A comparison of the frequency distributions of different values of FEV₁ and $\dot{V}_{\max 50}$ showed that cobalt and sulfur workers who smoked had lower values than the referents (see fig 11—14). In addition it also indicated that a few study subjects had a seriously decreased FEV₁ or FVC.

Table 16. Age, height, length of exposure and results of the ventilatory capacity measurements of the nonsmoking cobalt and zinc workers exposed for more than 5 a and the corresponding parameters of the nonsmoking referents.

Parameter ^a	Cobalt workers (N = 40)	Zinc workers (N = 30)	Referents (N = 47)
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Age (a)	36.1 $\pm$ 6.1	35.1 $\pm$ 6.0	35.2 $\pm$ 7.7
Height (cm)	176.3 $\pm$ 5.8	174.5 $\pm$ 5.5	175.3 $\pm$ 5.8
Length of exposure (a)	8.6 $\pm$ 1.9	7.6 $\pm$ 1.5	10.5 $\pm$ 3.1 ^b
FEV ₁ (l)	4.34 $\pm$ 0.72	4.28 $\pm$ 0.65	4.26 $\pm$ 0.64
FVC (l)	5.36 $\pm$ 0.81	5.29 $\pm$ 0.74	5.25 $\pm$ 0.68
FEV %	81.5 $\pm$ 6.1	81.6 $\pm$ 6.4	82.0 $\pm$ 7.0
$\dot{V}_{\max 50}$ (l/s)	5.53 $\pm$ 1.69	5.58 $\pm$ 1.62	5.66 $\pm$ 1.58

^a An explanation of the abbreviations of the ventilatory capacity indices can be found on page 23 of the text.

^b Years of employment.

Table 17. Age, height, length of exposure and results of the ventilatory capacity measurements of the smokers and exsmokers, combined, who had been exposed in the cobalt and zinc plants for more than 5 a and the corresponding parameters of the smokers and exsmokers, combined, in the reference group.

Parameter ^a	Cobalt workers (N = 122)	Zinc workers (N = 96)	Referents (N = 84)
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD
Age (a)	35.0 $\pm$ 6.1	33.4 $\pm$ 4.6	34.0 $\pm$ 7.6
Height (cm)	174.9 $\pm$ 4.9	173.9 $\pm$ 6.0	175.3 $\pm$ 5.8
Length of exposure (a)	9.0 $\pm$ 2.3	7.5 $\pm$ 1.4	9.8 $\pm$ 2.9 ^b
FEV ₁ (l)	4.22 $\pm$ 0.58	4.27 $\pm$ 0.64	4.31 $\pm$ 0.67
FVC (l)	5.34 $\pm$ 0.66	5.39 $\pm$ 0.81	5.40 $\pm$ 0.80
FEV %	79.6 $\pm$ 6.0	80.0 $\pm$ 6.0	80.5 $\pm$ 6.3
$\dot{V}_{\max 50}$ (l/s)	5.06 $\pm$ 1.34	5.25 $\pm$ 1.43	5.34 $\pm$ 1.51

^a An explanation of the abbreviations of the ventilatory capacity indices can be found on page 23 of the text.

^b Years of employment.

Regression of forced expiratory volume in one second and forced vital capacity

The results of the multiple regression analyses (appendix V) indicated that exposure to the air of the cobalt, sulfur or zinc plant did not significantly decrease the FEV₁ or FVC of workers when the exposure level was below the present Finnish TLVs for cobalt, zinc and sulfur dioxide. Table V-1 shows that smoking highly significantly decreased the FEV₁ of the cobalt workers. Smoking, age and height contributed the most to the

decreases in FEV₁ and FVC in all of the exposed groups. On the basis of the results of the multiple regression analysis, the effect of exposure cannot be evaluated independently without the underlying age and height distributions of the analyzed groups being taken into consideration. These distributions are discussed further on page 31.

The yearly decrease in FEV₁ was 12–37 ml in the nonsmoking study subjects and 15–24 ml in the smoking subjects. The sulfur workers who smoked had the highest yearly decrease in FEV₁ (54 ml),

COBALT WORKERS

ZINC WORKERS

SULFUR WORKERS

REFERENTS

Fig 11. Frequency distribution of the FEV₁ (forced expiratory volume in 1 s) values of the nonsmokers in the three exposed groups and the reference group.

as is shown in table V-9. The FVC annually decreased 11–33 ml in the nonsmokers and 11–51 ml in the smokers. Detailed results of the multiple regression analyses are given in the tables in appendix V. The β regression coefficients for age represent the annual decreases in FEV₁ and FVC in centiliters.

Fig V-2 shows that the sulfur workers who smoked had the deepest decline in FEV₁ of all the study groups. Otherwise the declines in FEV₁ and FVC of the exposed groups seemed to be similar to those of the referents and the normal Finnish

population, as shown in the figures of appendix V.

A log-linear model was also fitted in the comparison between the exposed and reference groups as to the simultaneous effects of exposure and smoking. Smoking had a decreasing effect on the $\dot{V}_{\max 50}$ of the cobalt and zinc workers, but the effect in connection with exposure was neither synergistic nor additive. Neither smoking nor exposure to cobalt or zinc had any effect on FEV₁ in this model.

The zinc workers and the referents had similar ventilatory capacities.

COBALT WORKERS

ZINC WORKERS

SULFUR WORKERS

REFERENTS

Fig 12. Frequency distribution of the FEV₁ (forced expiratory volume in 1 s) values of the smokers in the three exposed groups and the reference group.

DISCUSSION

The cross-sectional approach for estimating the respiratory effects of cobalt- and zinc-containing air was chosen so that an overview of the respiratory status of the exposed population would be obtained within a short time period. Extensive exposure information with detailed health records and accurate spirometric methods (expiratory flow volume measurement) also supported the choice of the method.

The results indicated that there was no evident respiratory impairment in non-

smoking cobalt and zinc workers. The number of workers exposed to zinc oxide was low and therefore limited any definite inferences. Although the results were "negative," the study provides valuable information about the respiratory health effects of an aerosol containing sulfur dioxide, cobalt and nickel on a young homogeneous population that has been exposed for less than 10 a. The study also confirmed that the TLV of sulfuric acid fumes (1 mg/m³) seems to be sufficient to prevent respiratory damage, even after 5 a of exposure. The fact that sulfur workers

COBALT WORKERS

ZINC WORKERS

SULFUR WORKERS

REFERENTS

Fig 13. Frequency distribution of the $\dot{V}_{\max 50}$ (instantaneous flow rate at 50 % of the forced vital capacity) of the nonsmokers in the three exposed groups and the reference group.

who smoked had a faster decline in FEV_1 than the other groups probably reflected altered bronchial sensitivity to sulfur dioxide. It is possible that the water-insoluble cobalt sulfide encountered in small quantities in the sulfur plant might have contributed to this alteration in the smokers.

The obstruction of small airways is probably an early sign of chronic bronchitis (35, 42). The sulfur workers and the workers in the cobalt roasting building had the lowest $\dot{V}_{max\ 50}$ values and the highest sulfur dioxide exposure. This may

indicate that sulfur dioxide exposure with cofactors such as cobalt, iron sulfide, or hematite may lead to the development of chronic bronchitis after 8 or 9 a of exposure. No elevated $FEV_0\%$ values indicating restrictive lung status were observed.

The small yearly decrease in FEV_1 and FVC among cobalt workers, as shown in the multiple regression analysis, was the reflection of a later culmination point than the age of 28 a which was suggested in an earlier study (8). A control analysis of the cobalt workers showed that for those over 32 a of age the yearly decrease

COBALT WORKERS

ZINC WORKERS

SULFUR WORKERS

REFERENTS

Fig 14. Frequency distribution of the $\dot{V}_{max\ 50}$ (instantaneous flow rate at 50 % of the forced vital capacity) of the smokers in the three exposed groups and the reference group.

in FEV₁ and FVC was 35 and 33 ml, respectively. Smoking had a significant effect on the mean decrease of ventilatory capacity for the entire group of cobalt workers. Further division of the group into over 32-year-old smoker and non-smoker categories would have caused biased results in the multiple regression analysis because of the small size of the population.

The regression slopes describe the decrease on a group basis. The frequency distributions of FEV₁ and FVC suggest however that there were a few study subjects with a seriously decreased FEV₁ or FVC.

Validity aspects

Exposure information

The validity of occupational hygiene measurements depends on the following three major factors: sampling errors, errors of analytical methods, and variability of the environment with time (61). The first two aspects were checked in a control survey of the technical hygiene measurements taken in 1977. As shown in fig 1—8, the extensive number of gas and dust samples dilute the effect of extreme process conditions. Furthermore the use of the geometric mean in the display of the results (36) corrects them towards a more realistic level. In addition, the control survey showed that the results were similar to those of the standard survey of the Company. Personal monitoring of the dust exposure indicated that the real exposure level was about 20 % lower than the exposure estimate would have been if it had been based only on the measurements of the stationary samplers. Analogously, personal monitoring showed an 80 % lower exposure to sulfur dioxide or hydrogen sulfide than the stationary sampling. The analytical error (sample collection and analysis) was about 5 % in the dust measurements and 10 % in the gas measurements.

In general, excess humidity and hydrogen sulfide interfere with Dräger ampuls in the analysis of sulfur dioxide and tend to lower the readings of these tubes (56). The areas where sulfur dioxide was moni-

tored did not contain hydrogen sulfide in measurable amounts. The relative humidity in these areas was constantly less than 50 %, which did not affect the results of the sulfur dioxide analysis.

Comparability of the study groups

There was no major source of incomparability between the study groups. The same selection process employed in the preemployment examinations and the same ethnic, social and demographic background were the elements which contributed to the exceptional homogeneity of the study population. Furthermore, the exposed workers seemed not to have quit their jobs in any of the plants because of pulmonary diseases other than asthma. A comparison between 90 randomly selected participants and nonparticipants with respect to reasons for sick leave did not suggest an uneven distribution of clinically diagnosed respiratory diseases either in the study population or in the group that could not be contacted.

Interview

When comparisons are made between studies, modifications of the British Medical Research Council's questionnaires may lead to biases (54). Except for the translation, which may affect international comparisons, no modifications were made in the questionnaire employed in the present study. The interview of the study subjects was the first structured interview they had ever experienced, and therefore the effect of training was unlikely. Interobserver variance was controlled as described on page 23. It proved to be insignificant.

Spirometry

Factors affecting the accuracy of the ventilatory capacity measurements have been described on page 23. If some of the exposure entities under study had caused transient irritation and a decrease in FEV₁, like metallic cobalt evidently does, the time between the last exposure and the taking of the measurement would have been important. The tracings made after weekends would have shown higher values

than those made following normal workdays. For practical reasons exact timing of the end of the last exposure was impossible in the ventilatory capacity measurements.

The exposed workers and half of the referents did three-shift work with an irregular frequency of free days, and their workdays began and ended irregularly. There was no indication that the measurements of any of the groups had been concentrated on certain week days or to certain times of the day.

Today cobalt compounds are widely used in both the chemical and metal industries. Earlier literature concentrated on the respiratory effects of metallic cobalt. The present study reports on the health effects of water-soluble cobalt sulfate as part of an exposure mixture of sulfur dioxide, iron sulfide and hematite.

Compared with the findings of former studies carried out on respiratory symptoms and ventilatory capacity in the metal industry, the results of the present study did not differ remarkably once the age differences between studies had been taken into account. The effect of smoking found in the present study was similar to the one reported earlier (28, 37, 38, 57). The FEV₁ and FVC decreases of the referents followed the pattern of the general Finnish male population (63). The frequency of respiratory symptoms and the prevalence of chronic bronchitis were of the same magnitude as reported earlier for the Finnish industrial and general male populations (21, 24, 25).

A selectivity of the cross-sectional population leading to underrepresentation of sick persons was unlikely in the present study because of the young age and

short exposure time of the study subjects. In the case of the sulfur workers who had a prevalence of 0 % for chronic bronchitis, some kind of selectivity might explain the low figure. Such an observation has been made in other studies where there has been no positive correlation between the results of ventilatory capacity measurements and the frequency of reported respiratory symptoms (21).

Conclusion

The results of the cross-sectional part of the present study lead to the following conclusion.

Air containing cobalt sulfate or zinc oxide does not cause chronic bronchitis in less than 6 to 8 a of exposure when at concentrations under the present Finnish TLVs. The use of ventilatory capacity measurements in an occupational health program should be planned carefully so that useless examination activity is avoided. The calibration of the equipment and the validity of the measurements should be controlled if one intends to compare measurements which have been taken in different years. The standardization of measurement time in relation to recent exposure to respiratory irritants is important. It might be possible to use short duration follow-up programs based on cross-sectional ventilatory capacity measurements to reveal persons susceptible to bronchial impairment. In order to diagnose possible small airway obstructions in connection with an occupational health program, spirometers which provide possibilities for flow measurements in small lung volumes (maximal expiratory flow volume curve) should be recommended.

Summary

This epidemiologic study was designed to determine whether occupational exposures to cobalt and zinc in the metallurgical industry increase the risk of asthma and symptoms of chronic bronchitis or decrease ventilatory capacity. The results indicated that, already at concentrations under 0.1 mg/m^3 , cobalt sulfate exposure increased the risk of asthma by about five times in exposed workers. The mechanism of sensitization was not studied further in this project. Neither zinc exposure nor sulfuric acid caused asthma or any other pulmonary impairments.

All of the exposed groups had a highly significant chronic production of phlegm. This symptom was associated with smoking. Cobalt and sulfur workers had significantly more wheezing than the referents. The high frequency of this symptom probably reflected bronchial irri-

tation caused by sulfur dioxide and cobalt sulfate. There was no evidence confirming that cobalt sulfate would have caused persistent bronchial obstruction or increased the risk of chronic bronchitis at the concentrations measured. Cobalt and/or sulfur dioxide exposure probably increased bronchial reactivity to methacholine transiently, but this effect did not last for more than 2 d.

The prevalence of chronic bronchitis was between 0 and 2 % in the exposed groups and 0 % among the referents. There was no evidence that any exposure other than smoking would have caused chronic bronchitis. The $\dot{V}_{\text{max } 50}$ measurements did however indicate that sulfur dioxide and dusts probably increase the risk of chronic bronchitis gradually after more than 5 to 8 a of exposure at concentrations between 1–5 ppm (cm^3/m^3).

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Appendix I

Metallurgic processes

Cobalt plant

The flow sheet of the metallurgic process for cobalt is given in fig I-1 and the letters in parentheses in the text provide a key to the corresponding letters in the figure.

Pyrometallurgic stage: Sulfatizing roasting

The purpose of sulfatizing roasting is to transform the valuable metals into a water-soluble form, leaving the iron as insoluble oxides. The reactions in sulfatizing roasting are:

The sulfatizing roasting takes place in two fluidized bed furnaces (A) at a temperature of 680°C. The roasted ore concentrate is cooled (B) to 120°C and goes on to leaching, where the "purple ore" is separated, and the solution containing the valuable metals goes on to purification. Before transferral to the sulfuric acid plant of Kemira, Ltd, the sulfur dioxide-

containing gas is cooled in a waste heat boiler (C) and purified in cyclones and electrical precipitators (D).

Hydrometallurgical stage: Leaching and solution purification

The roasted ore is fed into a multistage counter current leaching system (E), which produces purple ore and a solution containing cobalt and other metal sulfates. Thereafter copper (F) and zinc (G) ore are

precipitated by hydrogen sulfide gas in two separate reactors. Nickel and cobalt are then precipitated together (H) with hydrogen sulfide. The cobalt sulfide and nickel sulfide are separated (I) from the waste solution and released in autoclaves (J) with pressurized air. In the three subsequent stages (K, L, M) cobalt and nickel are separated according to the so-called "soluble cobaltic penta ammine process" (2), which produces solid nickel ammonium sulfate and a cobalt penta ammine solution.

Fig I-1. Flowsheet of the Outokumpu cobalt plant.

Cobalt reduction

The cobalt-containing solution is converted with cobalt powder to cobalt diamine sulfate (N), which is further reduced to metallic cobalt powder in autoclaves (O) with hydrogen gas. Ammonium sulfate containing the final solution is crystallized (P).

Zinc plant

The flow sheet of the metallurgical process for zinc is given in fig I-2, and the letters in parentheses in the text provide a key to the corresponding letters in the figure.

Pyrometallurgical stage

Roasting

The zinc ore concentrate is burned in two furnaces (A). Roasting transforms the zinc sulfide into acid-soluble zinc oxide and mixed ferrites according to the following primary reaction:

The roasting process is exothermic and takes place at a temperature of 950°C. The roasting gases containing about 10 % sulfur dioxide are cooled in a boiler (B). The dust carried with the gases is separated in cyclones (C) and in electric precipitators (D) prior to the conveying of the gas to the sulfuric acid plant. The calcine is cooled (E) and ground together with dust in a ball mill. The dust from the cyclones and the electric precipitator is combined with the main calcines and transported to storage bins (F).

Leaching and solution purification

The calcine is leached (G) with the acid of the electrowinning process. The zinc sulfate solution obtained is separated in thickeners (H) and fed into the purification step. The zinc sulfate solution contains minor amounts of impurities such as copper, cobalt, cadmium and nickel. These metals are precipitated from the solution in three stages (I, J, K) with metallic zinc dust. The purified solution containing zinc (150 g/l) is fed to the electrowinning process in the cell house.

Fig I-2. Flowsheet of the Outokumpu zinc plant.

Electrowinning and melting

The cell house (L) contains 672 electrolytic cells in four electrical circuits. The zinc is precipitated on aluminum cathodes and stripped automatically. The stripped zinc is fed into induction melting furnaces (M) and cast into ingots (N) (1).

Byprocesses of cadmium, mercury and selenium

Selenium and mercury are part of the sulfur dioxide gas which goes to the washing tower (O), where the metals are precipitated with sulfuric acid. Thereafter selenium and mercury are separated in a distillation oven (P). After separation (Q) from the main process the cadmium precipitate is leached, purified and cemented (R) into cadmium sponge, which is briquetted and cast into cadmium sticks (S). All of the byprocesses are situated in a separate building, except for cadmium cementation, which takes place in the purification building.

Sulfur plant

Because 158 workers of the total study population were employed in the sulfur

plant before its closure in 1977, the sulfur process will be described briefly.

The sulfur plant comprised one roasting and one smelter building. The incoming ferrous sulfide was burned in two reverberatory furnaces into iron sulfide. In the smelter the iron sulfide was burned in a flash smelting furnace into hematite and sulfur dioxide, which was conveyed to the nearby sulfuric acid plant. The sulfur plant annually used 500,000 t of pyrite ore concentrate. It produced 350,000 t of hematite, 120,000 t of elementary sulfur and 100,000 t of sulfur dioxide gas. The sulfur smelter was the main source of environmental pollution in the Outokumpu Kokkola Works.

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Appendix II

Part of the questionnaire, adapted from the Harvard questionnaire for respiratory symptoms, used to determine exposure history

OUTOKUMPU CO.
Kokkola Works
Health service

Interviewer Date

Sex ☐ male ☐ female

Present address and phone

Positions held at Outokumpu

Period	Job title	Main type of work on a year to year basis	Air pollutants to which you were exposed
1960			
1965			
1970			
1975			

In what year did you begin using a respirator at work?

Appendix III

Classification of exposure in the data collection

The exposure information was recorded as exposure years in one of the following 14 qualitative exposure categories:

1. Office, power plant and laboratory (nonexposed)
2. Maintenance, storage and painting
3. Miscellaneous exposure (working throughout the entire area of the Outokumpu Kokkola Works)
4. Sulfur plant, all areas
5. Cobalt plant, all areas
6. Zinc plant, all areas
7. Sulfur roasting building
8. Sulfur smelter
9. Cobalt roasting building
10. Cobalt solution purification and reduction building

11. Zinc roasting building
12. Zinc solution purification building
13. Zinc cell house
14. Zinc casting house

Two through fourteen were automatically considered as exposed categories.

If a person worked less than 1 a but had been six months or more in one exposure category, then the time was recorded as 1 a. Shorter times were not taken into account. This definition of exposure was maintained in both the cross-sectional and case-referent surveys. The limited amount of subjects hindered quantitative classification according to an individual exposure agent.

Appendix IV

New cases of asthma in the Outokumpu Kokkola Works from 1969 to 1977 (two female patients excluded)

Case	Age (a)	Exposure category ^a						Exposure rating ^b	Positive cobalt provocation	Certainty of diagnosis ^c	Exposure time before first symptoms	Atopy	PT/IC ^d	Family history of allergy	Blood eosinophils ^e	IgE ^f (iu/ml)
		Category number	Years	Category number	Years	Category number	Years									
YF	44	4	6	5	2	2	4	2		1	6-8 months	hay fb	IC-nd	no	8.5 %	420
MH	36	12	2	5	2	2	3	2		1	2 a	no	nd	no	1.0 %	
KH	31	9	9					2		1 ?	8 a	no	PT-	no	normal	50
KH	44	4	2	9	13			2		1	9 a	no	nd	no	nd	nd
SI	33	9	3	2	7			2		1 ?	9 a	no	nd	yes	3 %	85
EJ	38	1	14					0		1		yes	+animal +hay	no	8-13 %	nd
OJ	51	8	16					0		1		no	nd	yes	12 %	770
KK	48	5	3	2	6			2		1	2 months	no	IC and PT-	no		
VK	36	10	0.5					2	yes	2	3 a	no	IC-	no	3 %	254
TK	41	8	15	10	0.5			2	yes	2	6 months	yes	IC-	yes	3 %	60
JK	40	9	8	13	4			2		1 ?	5 a	no	IC-	no	1 %	20
RK	44	2	13					1		1		no	nd	no	3 %	65
PM	31	3		5	2	13	2	2	yes	2	16 months	no	IC and PT-	no	2 %	60
AM	41	9	2	3	4	2	6	2		1		yes	+animal +hay	no	14 %	85
PN	37	10	2	12	8			2		1	4 a	no	IC and PT-	no	2 %	10
AP	44	3	12					1		1		no	IC-	no	3 %	nd
KP	29	10	7					2		1	7 a	no	IC-	no		105
AP	48	8	15	10	0.5			2	yes	2	2 months	no	nd	yes	2 %	250
VP	27														6 %	230
JT	27	2	7					1		1 ?		no	nd	no	4 %	630
TV	51	5	7					2		1	2 a	no	IC and PT-	yes	2 %	40
VV	43	9	8					2	yes	2	2 a	no	IC-	yes	2 %	62
KW	41	2	14					1		1		no		no		
VW	33	9	0.5	14	7			2	yes	2	6 months	no	IC-	no	30 %	340
VY	35	2	5	3	7			1		1		no	nd	no	3-5 %	295
PZ	34	5	2	10	2	2	5	2		1	2 a	no	IC—animal—hay	no	2 %	105

^a Explanations for the exposure category numbers have been listed in appendix II.

^b 0 = no exposure, 1 = worked intermittently in the cobalt plant, 2 = worked regularly in the cobalt plant.

^c 1 ? = reported expiratory wheezing, no provocation test, 1 = expiratory wheezing and positive histamine or methacholine test, 2 = as for grade 1 but positive cobalt challenge test.

^d PT = patch test, IC = intracutaneous test, nd = not done.

^e Normal = 1-3 %, nd = not done.

^f IgE = immunoglobulin E, normal < 150, nd = not done.

Appendix V

Results of the multiple regression analyses made in the cross-sectional part of the study

Smoking cobalt workers

Table V-1. Effect of age, height, smoking and exposure on the FEV₁ (forced expiratory volume in 1 s) of 73 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Smoking (pack-years)	-3.04	0.94	-3.22	< 0.001
Height (cm)	4.42	1.12	3.95	< 0.001
Age (a)	-1.45	1.41	-1.02	
Years in cobalt plant	-0.79	2.24	-0.35	
Constant term $\alpha = -256$				
Multiple correlation coefficient = 0.67				

^a SE = standard error of β .

Table V-2. Effect of age, height, smoking and exposure on the FVC (forced vital capacity) of 73 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Height (cm)	6.14	1.27	4.82	< 0.001
Smoking (pack-years)	-2.45	1.07	-2.29	< 0.05
Age (a)	-1.05	1.61	-0.65	
Years in cobalt plant	-0.95	2.55	-0.37	
Constant term $\alpha = -463$				
Multiple correlation coefficient = 0.64				

^a SE = standard error of β .

Nonsmoking cobalt workers

Table V-3. Effect of age, height and exposure on the FEV₁ (forced expiratory volume in 1 s) of 43 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Height (cm)	7.82	1.55	5.06	< 0.001
Years in cobalt plant	-5.51	5.44	-1.01	
Age (a)	-1.19	1.73	-0.69	
Constant term $\alpha = -855$				
Multiple correlation coefficient = 0.69				

^a SE = standard error of β .

Table V-4. Effect of age, height and exposure on the FVC (forced vital capacity) of 43 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Height (cm)	8.64	1.80	4.80	< 0.001
Age (a)	-1.67	2.01	-0.83	
Years in cobalt plant	-4.18	6.32	-0.66	
Constant term $\alpha = -888$				
Multiple correlation coefficient = 0.67				

^a SE = standard error of β .

Smoking zinc workers

Table V-5. Effect of age, height, smoking and exposure on the FEV₁ (forced expiratory volume in 1 s) of 79 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Height (cm)	6.59	0.96	6.83	< 0.001
Age (a)	—3.92	1.33	—2.95	< 0.01
Smoking (pack-years)	—1.40	0.86	—1.62	
Years in zinc plant	2.71	2.55	1.06	
Constant term α = —587				
Multiple correlation coefficient = 0.75				

^a SE = standard error of β .

Table V-6. Effect of age, height, smoking and exposure on the FVC (forced vital capacity) of 79 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Height (cm)	8.77	1.15	7.62	< 0.001
Age (a)	—5.05	1.59	—3.18	< 0.01
Years in zinc plant	4.20	3.04	1.38	
Smoking (pack-years)	—0.63	1.03	—0.61	
Constant term α = —837				
Multiple correlation coefficient = 0.77				

^a SE = standard error of β .

Nonsmoking zinc workers

Table V-7. Effect of age, height and exposure on the FEV₁ (forced expiratory volume in 1 s) of 46 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Height (cm)	5.72	1.18	4.84	< 0.001
Age (a)	—2.78	1.37	—2.03	< 0.05
Years in zinc plant	—0.94	3.40	—0.28	
Constant term α = —466				
Multiple correlation coefficient = 0.66				

^a SE = standard error of β .

Table V-8. Effect of age, height and exposure on the FVC (forced vital capacity) of 46 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Height (cm)	7.90	1.39	5.68	< 0.001
Years in zinc plant	—4.13	4.01	—1.03	
Age (a)	—1.09	1.61	—0.68	
Constant term α = —782				
Multiple correlation coefficient = 0.68				

^a SE = standard error of β .

Smoking sulfur workers

Table V-9. Effect of age, height, smoking and exposure on the FEV₁ (forced expiratory volume in 1 s) of 60 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Age (a)	—5.37	1.01	—5.32	< 0.001
Height (cm)	3.66	1.22	3.00	< 0.01
Years in sulfur plant	—0.42	1.61	—0.26	
Smoking (pack-years)	0.14	0.85	0.16	
Constant term α = —41				
Multiple correlation coefficient = 0.75				

^a SE = standard error of β .

Table V-10. Effect of age, height, smoking and exposure on the FVC (forced vital capacity) of 60 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Age (a)	—3.49	1.08	—3.24	< 0.01
Height (cm)	4.84	1.30	3.72	< 0.01
Years in sulfur plant	0.84	1.72	0.49	
Smoking (pack-years)	—0.20	0.91	—0.21	
Constant term α = —205				
Multiple correlation coefficient = 0.65				

^a SE = standard error of β .

Nonsmoking sulfur workers

Table V-11. Effect of age, height and exposure on the FEV₁ (forced expiratory volume in 1 s) of 32 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Age (a)	-3.49	1.31	-2.66	< 0.02
Height (cm)	3.53	1.37	2.57	< 0.02
Years in sulfur plant	-1.76	2.17	-0.81	
Constant term $\alpha = -50$				
Multiple correlation coefficient = 0.69				

^a SE = standard error of β .

Table V-12. Effect of age, height and exposure on the FVC (forced vital capacity) of 32 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Height (cm)	5.46	1.37	3.97	< 0.001
Age (a)	-2.52	1.31	-1.92	< 0.1
Years in sulfur plant	0.58	2.17	0.27	
Constant term $\alpha = -344$				
Multiple correlation coefficient = 0.70				

^a SE = standard error of β .

Smoking referents

Table V-13. Effect of age, height and smoking on the FEV₁ (forced expiratory volume in 1 s) of 32 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Height (cm)	7.80	1.20	6.48	< 0.001
Age (a)	-4.08	1.17	-3.48	< 0.01
Smoking (pack-years)	-1.22	1.00	-1.21	
Constant term $\alpha = -791$				
Multiple correlation coefficient = 0.83				

^a SE = standard error of β .

Table V-14. Effect of age, height and smoking on the FVC (forced vital capacity) of 32 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Height (cm)	11.61	1.66	6.97	< 0.001
Age (a)	-4.70	1.62	-2.90	< 0.01
Smoking (pack-years)	1.08	1.39	0.78	
Constant term $\alpha = 1,351$				
Multiple correlation coefficient = 0.81				

^a SE = standard error of β .

Nonsmoking referents

Table V-15. Effect of age and height on the FEV₁ (forced expiratory volume in 1 s) of 48 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Height (cm)	5.37	1.14	4.69	< 0.001
Age (a)	-3.69	0.94	-3.91	< 0.001
Constant term $\alpha = -383$				
Multiple correlation coefficient = 0.71				

^a SE = standard error of β .

Table V-16. Effect of age and height on the FVC (forced vital capacity) of 48 men aged 28 a or more.

Variable	β regression coefficient	SE ^a	t	p
Height (cm)	6.16	1.26	4.90	< 0.001
Age (a)	-3.35	1.03	-3.24	< 0.01
Constant term $\alpha = -436$				
Multiple correlation coefficient = 0.69				

^a SE = standard error of β .

Nonsmokers

Fig V-1. Regression of age on FEV₁ (forced expiratory volume in 1 s) according to exposure group, the average height of 175 cm and eight exposure years being used as criteria. [1 = Finnish normal male population (Viljanen A, Leikkauskelpoisuussymposiumi. Ciba-Geigy, Helsinki 1979, pp 18–21), 2 = study population]

Smokers

Fig V-2. Regression of age on FEV₁ (forced expiratory volume in 1 s) according to group, the average height of 175 cm, smoking a pack/d for 8 a and eight exposure years being used as criteria. [1 = Finnish normal male population (Viljanen A, Leikkauskelpoisuussymposiumi. Ciba-Geigy, Helsinki 1979, pp 18—21), 2 = study population]

Nonsmokers

Fig V-3. Regression of age on FVC (forced vital capacity) according to exposure group, the average height of 175 cm and eight exposure years being used as criteria. [1 = Finnish normal male population (Viljanen A, Leikkauskelpoisuussymposiumi. Ciba-Geigy, Helsinki 1979, pp 18—21), 2 = study population]

Smokers

Fig V-4. Regression of age on FVC (forced vital capacity) according to exposure group, the average height of 175 cm, smoking a pack/d for 8 a and eight exposure years being used as criteria. [1 = Finnish normal male population (Viljanen A, Leikkauskelpoisuussymposiumi. Ciba-Geigy, Helsinki 1979, pp 18—21), 2 = study population]