ASKO LINNA

Effects of Cobalt Exposure on the Respiratory System and the Heart Among Cobalt Production Workers

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ACADEMIC DISSERTATION
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To Anne, children Olavi, Kyösti, Nora, and their families

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ABSTRACT

The aim of the study was to investigate the respiratory and possible myocardial effects of mainly long-term exposure in the production of cobalt and its compounds. The study concerning the respiratory system consisted of two parts. In the epidemiological study, the association of exposure and respiratory symptoms, functions, and possible diseases was examined. The study population consisted of current and former cobalt workers who had been working in cobalt production for at least 10 years (110 men). The reference group consisted of 140 unexposed workers. The study methods contained a questionnaire, a chest X-ray, spirometry including diffusion capacity, and measurements of Clara cell protein. The case study characterised 22 occupational cobalt asthma patients whose diagnosis had been confirmed with a specific bronchial challenge by the Finnish Institute of Occupational Health. The cardiac studies were performed in 2000 and 2006. The first cross-sectional study surveyed a study group of workers with at least a year's work history in cobalt production as well as an unexposed reference group. These groups consisted of 203 and 94 men, respectively. The study methods included a questionnaire, laboratory tests, blood pressure measurements, and electrocardiography (ECG). In addition to this, an echocardiograph (ECHO) examination was performed for the 122 men with the highest cumulative cobalt exposure and for an age-matched control group of 60 unexposed men. In the follow-up study, the subjects were workers who had continued working at the cobalt factory after the year 2000 and who had gone through an ECHO examination, and referents who had been examined similarly (93 and 49 men, respectively). The study methods were the same as in 2000 with the addition of using pulsed-wave tissue Doppler imaging and long-term ECG registration (Holter). Therefore, the results in 2006 were analysed as a new cross-sectional study design using similar statistical models as employed in 2000.

In the analyses of the epidemiological studies, the unit used for metal exposures was mg-year. In the respiratory study ppm-year was also used in the case of gas exposures. These parameters were calculated for all the exposed study subjects. In the results, symptoms of asthma based on questionnaire responses were more prevalent among the exposed workers. The respiratory flow rates MEF50 and MEF25, which refer to the smaller airways, were significantly lower among the smoking-exposed workers than among the smoking-unexposed workers. One new case of cobalt asthma but no cases of hard metal disease or fibrosing alveolitis were found. Among the cobalt asthma

patients, on challenge tests mostly late or dual asthmatic reactions were observed. The incidence of cobalt asthma was the highest in the department with the highest cobalt exposure levels. All cases of cobalt asthma were encountered in departments where irritant gases were present in the ambient air in addition to cobalt. At the time of the follow-up examination 6 months after diagnosis, non-specific hyperreactivity had mostly remained at the same level or increased. In the first heart study, two of the ECHO parameters measuring early diastole, the left ventricular isovolumic relaxation time (IVRT), and the deceleration time of the velocity of the early rapid filling wave (DT) were prolonged and associated with cobalt exposure. These findings, indicating altered left ventricular function, could not be repeated in the follow-up study and no significant differences were found between the exposed and unexposed groups for any other ECHO, ECG, or Holter parameters or laboratory values. In conclusion, no chronic respiratory diseases except asthma were found in the study. Smoking and exposure had an interacting negative effect on the respiratory functions. Cobalt asthma had mainly developed in circumstances where exposure to cobalt and irritant gases had been high. The clinical picture and the results of the studies fit an IgE-independent mechanism in the development of asthma. It is possible that minor findings of the first cardiac examination were masked by the changes developed in the common risk and lifestyle factors affecting heart function and its measurement during the 6 years of follow-up. Regardless, as shown in other studies, healthy individuals can tolerate very high blood cobalt levels, so the development of clinical cobalt cardiomyopathy is very unlikely in appropriate working conditions.

TIIVISTELMÄ

Tutkimuksen tavoitteena oli selvittää erityisesti pitkäaikaisen altistumisen vaikutuksia hengityselimistöön ja sydänlihakseen koboltin ja sen yhdisteiden valmistuksessa. Hengityselimistöä koskeva tutkimus oli kaksiosainen. Epidemiologisessa osassa tutkittiin altistumisen vaikutusta hengityselimistön toimintaan, oireistoon ja mahdollisiin sairauksiin. Tutkimuksen kohderyhmänä olivat ne nykyiset ja entiset työntekijät, jotka olivat työskennelleet koboltin tuotannossa vähintään kymmenen vuotta (110 miestä). Vertailuryhmä koostui 140 altistumattomasta työntekijästä. Tutkimusmenetelminä olivat kysely, keuhkojen röntgenkuvaus, spirometria, diffuusiokapasiteetin mittaus ja seerumin Clara cell -proteiinin (CC16) määritys. Hengityselintutkimuksen toisessa osassa analysoitiin 22 kobolttiastmatapausta, joissa diagnoosi oli varmistettu Työterveyslaitoksella tehdyllä spesifisellä altistuskokeella.

Sydäntutkimukset tehtiin vuosina 2000 ja 2006. Ensimmäisen poikkileikkaustutkimuksen kohteena olivat vähintään vuoden kobolttituotannossa työskennelleet nykyiset työntekijät (203 miestä) ja vertailuryhmä, joka muodostui 94 altistumattomasta saman teollisuusalueen työntekijästä. Tutkimusmenetelminä olivat kysely, laboratoriotestit, verenpaineen mittaus ja EKG. Näiden lisäksi tehtiin 122 kobaltille kumulatiivisesti eniten altistuneelle ja 60 iän mukaan kaltaistetulle verrokille sydämen kaikukardiografiatutkimus. Seurantatutkimukseen osallistuivat ne kobaltille altistuneet työntekijät, jotka olivat jatkaneet työskentelyä kobolttitehtaalla vuoden 2000 jälkeen ja jotka olivat kuuluneet kaikukardiografialla tutkittujen ryhmään. Vertailuryhmään kuuluneista tutkittiin ne, jotka niin ikään olivat osallistuneet mainittuun tutkimukseen. Ryhmien koot olivat 93 ja 49 miestä. Tutkimusmenetelmät olivat samat kuin vuoden 2000 tutkimuksessa, täydennettynä kudosdopplerilla ja EKG:n pitkäaikaisrekisteröinnillä (Holter). Koska tutkimusmenetelmät olivat osittain erilaiset, vuoden 2006 tulokset käsiteltiin uutena poikkileikkaustutkimuksena käyttäen samoja tilastollisia menetelmiä kuin vuonna 2000.

Epidemiologisten tutkimustulosten analyyseissä käytettiin metallialtistumisen mittayksikkönä mg-vuotta, hengityselintutkimuksessa kaasualtistumisen yksikkö oli vastaavasti ppm-vuosi. Kumulatiivinen altistuminen oli määritetty kaikille altistuneille tutkituille.

Hengityselintutkimuksen kyselyosiossa ilmoittivat kobaltin tuotannossa altistuneet työntekijät astman kaltaisia oireita huomattavasti useammin kuin altistumattomat verrokit. Pienten hengitysteiden toimintaa kuvaavat virtausarvot, MEF50 ja MEF25, olivat merkitsevästi huonommat tupakoivilla altistuneilla kuin tupakoivilla altistumattomilla työntekijöllä. Altistuneista yhdellä todettiin uusi kobaltin aiheuttama ammattiastma, sen sijaan kovametallitautia tai fibrosoivaa alveoliittia ei todettu. Ammattiastmapotilaille tehdyissä altistustesteissä olivat astmaattiset reaktiot valtaosin viivästyneitä tai kaksivaiheisia reaktioita. Kobolttiastman ilmaantuvuus oli korkein osastolla, jossa oli korkein kobaltille altistumisen taso. Kobolttiastmat olivat kehittyneet osastoilla, joilla oli altistuttu kobaltin lisäksi myös hengitysteitä ärsyttäville kaasuille. Astmapotilaiden seurantatutkimuksessa Työterveyslaitoksella, kuuden kuukauden kuluttua diagnoosin tekemisestä, oli keuhkoputkien epäspesifinen supistumisherkkyys (hyperreaktiviteetti) useimmiten pysynyt ennallaan tai lisääntynyt.

Ensimmäisen sydäntutkimuksen kaikukardiografiatuloksissa olivat kaksi alkudiastolea kuvaavaa muuttujaa (isovolyyminen relaksaatioaika, IVRT, ja E-aallon hidastumisaika, DT) pidentyneet altistuneiden ryhmässä ja pidentyminen näytti olevan yhteydessä altistumisen tasoon. Näitä muuttuneeseen diastoleen viittaavia havaintoja ei tehty seurantatutkimuksessa eikä siinä todettu tutkimusryhmien välillä merkiseviä eroja myöskään muissa kaikukardiografia-arvoissa eikä EKG-, Holter- tai laboratoriotuloksissa.

Yhteenvetona voidaan todeta, että astman lisäksi tässä tutkimuksessa ei todettu muita kroonisia hengityselinsairauksia. Tupakoinnilla ja altistumisella oli negatiivinen vuorovaikutus keuhkojen toimintaan. Kobolttiastma oli kehittynyt pääasiassa olosuhteissa, joissa altistuminen sekä kobaltille että ärsyttäville kaasuille oli ollut voimakasta. Astman kliininen kuva tukee käsitystä, että kobolttiastman syntymekanismi oli IgE-riippumaton. On mahdollista, että ensimmäisessä sydäntutkimuksessa todetut vähäiset muutokset peittyivät kehitykseen, joka tutkittavissa oli tapahtunut kuuden vuoden seuranta-aikana sydämeen ja sen toiminnan mittaamiseen vaikuttavissa yleisissä riski- ja elämäntapatekijöissä. Joka tapauksessa, kuten on havaittu muissa tutkimuksissa, terveet henkilöt kestävät erittäin korkeita veren kobolttipitoisuuksia, joten on hyvin epätodennäköistä, että työntekijälle kehittyisi asianmukaisissa työskentelyolosuhteissa kobaltin aiheuttama kliininen kardiomyopatia.

CONTENTS

ABBREVIATIONS

A	peak atrial filling velocity
ACD	allergic contact dermatitis
AES	atrial extrasystolic beats
Am	diastolic myocardial tissue velocity after atrial contraction
ANCOVA	analysis of covariance
ANP-N	N-terminal atrial natriuretic peptide
ATP	adenosine triphosphate
B1-vit	thiamine
BMI	body mass index
bw	body weight
Ca2+	divalent calcium
CBD	chronic beryllium disease
CC16	Clara cell protein
CDT	carbohydrate deficient transferrin
CI	confidence interval
Co2+	divalent cobalt
Co3+	trivalent cobalt
CoCl	cobalt chloride
CoCr	cobalt-chromium
CoSO4	cobalt sulphate
Cr3+	trivalent chromium
CS2	carbon disulphide
DLCO	diffusing capacity of the lungs for carbon monoxide
DT	E-wave deceleration time
E	early diastolic filling velocity
ECG	electrocardiography
ECHO	echocardiography
EF	(left) ventricular ejection fraction

Em	early diastolic myocardial tissue velocity
Fe2+	bivalent iron
FENO	fraction of nitric oxide in exhaled air
FEV1	forced expiratory volume in 1 second
FIOH	Finnish Institute of Occupational Health
FS	fractional shortening
FVC	forced vital capacity
GI	gastro intestinal
GIP	giant cell interstitial pneumonitis
GT	gamma-glutamyl transferase
Holter	long-term ECG registration
HMW	high-molecular-weight
HP	hypersensitivity pneumonitis
HRCT	high-resolution computed tomography
HTP	haitalliseksi tunnettu pitoisuus
H2S	hydrogen sulphide
H2SO4	sulphuric acid
IARC	The International Agency for Research on Cancer
IDLH	immediately dangerous to life or health
IgE	immunoglobulin E
IIA	irritant-induced occupational asthma
ILD	interstitial lung disease
ILO	International Labour Organization
IQR	interquartile range
IVRT	isovolumic relaxation time
(IVSD+LVPWD)/LVEDD	ratio between the wall thickness and the left ventricular diameter measured at end diastole
LDL	low-density lipoprotein
LIB	lithium-ion battery
LMW	low-molecular-weight
LVMASS	left ventricular mass
LVPWD	left ventricular posterior wall thickness at diastole
MEF25	flow rate at 25% of the vital capacity

MEF50	flow rate at 50% of the vital capacity
MMEF	mean flow
MoM	metal-on-metal
NH3	ammonia
NIOSH	National Institute for Occupational Safety and Health
OA	occupational asthma
OEL	occupational exposure limit
OSHA	Occupational Safety and Health Administration
PEF	peak expiratory flow
ppm	parts per million
ROS	reactive oxygen species
SIC	specific bronchial challenge test
SIR	standardised incidence ratio
SO2	sulphur dioxide
SPT	skin prick test
T3	triiodothyronine
T4	thyroxine
TDI	pulsed-wave tissue Doppler imaging
TSH	thyroid-stimulating hormone
UCo	urine cobalt concentration
VA	alveolar volume
VES	ventricular extrasystolic beats
W	tungsten
WC	tungsten carbide

ORIGINAL PUBLICATIONS

Publication I   Linna A, Oksa P, Palmroos P, Roto P, Laippala P, Uitti J. Respiratory health of cobalt production workers. Am J Ind Med 2003;44:124-132.

Publication II   Sauni R, Linna A, Oksa P, Nordman H, Tuppurainen M, Uitti J. Cobalt asthma—a case series from a cobalt plant. Occup Med 2010; 60:301-306.

Publication III   Linna A, Oksa P, Groundstroem K, Halkosaari M, Palmroos P, Huikko S, Uitti J. Exposure to cobalt in the production of cobalt and cobalt compounds and its effect on the heart. Occup Environ Med 2004;61:877-885.

Publication IV   Linna A, Uitti J, Oksa P, Toivio P, Virtanen V, Lindholm H, Halkosaari M, Sauni R. Effects of occupational cobalt exposure on the heart in the production of cobalt and cobalt compounds: a 6-year follow-up. Int Arch Occup Environ Health 2020;93:365-374.

Author's contribution in the original publications

In the research plan phase, I wrote applications to The Finnish Work Environment Fund for research funding for studies I, III, and IV. For these applications, I described the basis, background, and aims of the study, gave a description of the subjects, material, and methods, outlined the benefits and applicability of the results, and detailed the informing and utilization of the information received, as well as further plans. I prepared, oversaw, and reported the research budgets. After the studies, I compiled and wrote the research reports for The Finnish Work Environment Fund.

Detailed roles

1. In the planning phase of all studies (including study II), I closely co-operated with the professionals of the Finnish Institute of Occupational Health (FIOH) and Tampere University Hospital. The study methods were agreed on with these collaborators. In addition to this, my responsibility was to maintain contact with the

other collaborating parties, such as employers, the City of Kokkola, and the Central Hospital of Central Ostrobothnia.

2. From 1983 to 2006, I examined all employees of the cobalt factory who had suspected asthma or suspected occupational asthma and organised the necessary further examinations either at the Central Hospital of Central Ostrobothnia or the FIOH. I also examined the patients during/after study I if a suspicion of some form of lung disease had been detected.

3. In all studies, I was responsible for the selection of subjects belonging to the exposed groups and the comparison groups, the compilation of exposure data, and the calculation of the workers' individual cumulative exposure numbers. For publication II, I reviewed patient documents concerning cobalt asthma, and the patients who met the study criteria were selected on this basis. I categorised the work and exposure history of these patients.

4. Clinical examinations, including laboratory examinations, were mainly carried out at the mobile research unit of the FIOH. Clara cell protein determinations were performed in a laboratory in Belgium, and the echocardiography examinations were performed at the Central Hospital of Central Ostrobothnia.

5. The research groups included an expert in statistics, except in the asthma study, in which no actual statistical processing was performed. The content of the statistical analyses was determined in the groups of which I was a member.

6. Analysing and interpreting the results together with experts were my central tasks in all sub-studies. In these meetings, we also decided on possible additional analyses and their content.

7. I was the responsible author of all publications, including the early stages of the asthma study (II). Before the asthma study was completed, however, there was a change in my personal career. I moved on to other, more time-consuming tasks as both the director and medical director of a municipal co-operative. For practical reasons, Riitta Sauni's role was more significant than mine during the finalisation of the article.

1 INTRODUCTION

The Kokkola cobalt plant used as the basis for this study began its operations in the late 1960s. It currently accounts for about 10% of the world's cobalt and cobalt compound production and is the largest in Europe (1). The factory area, which also has e.g. a zinc plant, has had its own occupational safety and health organisation since the beginning of its operations until recent years. Computer systems were used early in the collection and storage of data, and sickness absence files based on these were introduced to the health centre in 1973.

Regular health examinations have been performed from the very founding of the cobalt plant. By 2008, 22 cases of cobalt asthma had been detected at the cobalt plant and the diagnoses were certified by the Finnish Institute of Occupational Health (FIOH). The first of these were reported internationally in 1971 (2) and then more comprehensively in 1980 (3). Other respiratory issues have also been central, especially during the first two decades of the plant's existence, when in addition to metal exposure, exposure to various gases, especially sulphur dioxide (SO_2), had also been possible.

Cobalt exposure has been linked to heart health, mainly cardiomyopathy, since the 1960s. Occupational exposure and cardiomyopathy were the subject of several case reports in the 1970s and 1990s, and epidemiological studies were published in the 1980s and 1990s showing indications of altered cardiac working capacity. Modern research methods, particularly echocardiography (ECHO), have significantly improved the chances of elucidating these potential cardiac effects of cobalt exposure.

Cobalt is essential for humans only as a part of vitamin B12; other cobalt intake is unnecessary and, as stated above, often harmful. The effects of occupational exposure have been studied to a great extent, but published studies have been performed in only a few cobalt refineries. To obtain a reliable picture of the health risks of the exposure, different exposure combinations and toxicological mechanisms have to be taken into account.

Kokkola cobalt plant, its employees, and its occupational health care data offer a fruitful source of information on occupational exposure to cobalt over decades and the possible

work-related health effects. There are industrial hygiene measurements available from ambient workplace air as well as the biomonitoring data of the employees. As a company occupational physician, I had an opportunity to follow up the health of the employees from 1983 to 2006 and in connection with some projects also after that. During this time, the processes and techniques of the plant have changed and improved, which can be seen in the diminishing exposure levels. However, previously the exposures have been significantly higher, and it is a very relevant question whether working at a cobalt plant may have had any adverse health effects. This academic dissertation tries to give an answer to this question in terms of the respiratory and myocardial effects of cobalt.

2 REVIEW OF THE LITERATURE

2.1 Cobalt and cobalt compounds

Cobalt is a greyish-silver, very hard transition metal. It is widely dispersed, and the Earth's crust has a cobalt concentration of 0.0015-0.0030% (4). It keeps its strength at high temperatures and has a high melting point. Cobalt is ferromagnetic and maintains magnetic properties even up to 1121°C. Other important properties include its ability to form alloys with other metals, e.g. tungsten, chromium, molybdenum, and nickel. Pure cobalt is not found in nature, and in minerals it is preferentially bound to iron, nickel, copper, and sulphur rather than to oxygen, forming various sulphide and sulpharsenide compounds. At elevated temperatures, cobalt combines with oxygen, which results in cobalt oxide. Cobalt metal is soluble in dilute acids but almost insoluble in water. Cobalt compounds are mainly in a +2 or +3 oxidation state (5).

Today the largest application of cobalt is in materials for rechargeable lithium-ion batteries (LIBs) (1). In 2017, almost 50% of total consumption was in LIBs, and nearly 20% was used in high-temperature materials (superalloys). Hard metals, magnets, special steels, catalysts, and pigments are other important application areas. In 2018, the global mining production of cobalt was nearly 168,000 tonnes, about 65% coming from the Democratic Republic of Congo, where it is a by-product of copper mines. Other big producers are New Caledonia, China, Canada, and Australia, where cobalt is produced mainly as a co-product of nickel extraction. Globally, China is the largest producer of refined cobalt; its production was more than 60% of the world total in 2018, with Finland (10%) and Belgium (5%) having the largest production after China.

2.2 Toxicokinetics of cobalt

2.2.1 Absorption

Unice et al. (6) found in their work that the human body burden becomes much higher via cobalt ingestion compared to the burden associated with cobalt inhalation. Long-term ingestion of cobalt at a reference dose of 0.03 mg/kg-day gave predicted levels of

22-54 µg/l (blood), 0.05-0.1 µg/g (heart), 0.01-0.02 µg/g (testes), and 0.2-0.5 µg/g (liver), the levels being at least five times higher than the burdens from various cobalt inhalation occupational exposure limits (OELs) of 0.1 mg/m³ or less (for 8 h/d and 5 d/w).

Ingestion

The human gastro-intestinal (GI) absorption of cobalt is about 25-35% of the administered dose (from different sources), but the variation between individuals is wide (5-95%). The absorption level depends on different factors, such as the dose, the solubility of the compound, and the nutritional status (e.g. iron deficiency) (7,8). GI absorption rates are similar with two ionic forms of cobalt (Co^{2+} and Co^{3+}) (9). A study of GI uptake showed 60-70 times higher average urinary cobalt levels from a soluble compound (chloride) compared to those of a relatively insoluble cobalt compound (oxide) (10). GI cobalt absorption occurs from the jejunum. There are similarities in the mechanisms between cobalt GI absorption and Fe^{2+}, as can be seen in people with iron deficiency, who can have an increased cobalt absorption (11).

Inhalation

Cobalt in its soluble compounds (chloride, sulphate, and nitrate) is after inhalation rapidly absorbed into the blood, but about 5% is absorbed over several months (12,13,14). The presence of tungsten carbide (WC) enhances the pulmonary absorption of cobalt (15). Cobalt metal is very or moderately soluble in some biological fluids like plasma and intracellular lysosomal fluid. Therefore, a strong correlation was seen between airborne cobalt concentration and cobalt in the blood and urine among workers exposed to cobalt metal or salt and hard metals (16). No similar correlation was found with workers who had been exposed to poorly soluble cobalt oxide. The route from the respiratory system via the oesophagus into the stomach can be significant, as proven in animal studies (17).

Dermal absorption

Dermal absorption of cobalt was studied in a test, where five non-smoking volunteers kept their hands for 1 h in a used cobalt-containing coolant solution and then washed their hands thoroughly (18). Urinary excretion of cobalt increased up to nearly 40 nmol/l on average from a start level of 18 nmol/l during the 24 hours after the exposure. The individual variability was wide; in one subject there was no clear increase in urinary cobalt following exposure. As the concentrations of cobalt e.g. in grinding

coolants can be high, measures to diminish transcutaneous metal absorption is of practical importance (19).

After a wide burn injury from a cobalt material, high cobalt levels were detected in the blood and urine of a metal refinery worker (20).

2.2.2 Distribution

The control of the biokinetics of inorganic cobalt is poorly understood (21). After intake, cobalt mainly spreads into the blood, liver, kidneys, heart, and spleen. Smaller concentrations are found in the skeleton, lymphatic circulation, brain, and pancreas (22). In the adult human body, nearly 85% of cobalt is in the vitamin B12, and the total cobalt burden has been estimated to be about 1.1 mg (23). Vitamin B12 is metabolised in cells, stored in the liver, and excreted via urine or faeces (24).

2.2.3 Excretion

Absorbed cobalt is mainly excreted via the kidneys (25). Swallowed, insoluble cobalt is predominantly excreted via faeces, and the absorbed part via the kidneys. In two studies (26,27) where whole body cobalt concentrations were monitored, 36-44% of the administered dose was cleared within 6-12 hours, and most of the dose was eliminated within 7 days. The half-life for cobalt tended to become longer with the length of the observation time: 600 days for observations over 305-386 days and 800 days for observations over 1000 days. It is possible that some part of the load may have a half-life of many years. The excretion of cobalt seems to be independent of the exposure level (21). The renal reabsorption pathway for cobalt becomes saturated already when blood concentrations exceed 1-2 µg/l (28).

2.3 Human essentiality of cobalt

Although inorganic cobalt as such is not a necessity in the human diet, cobalt is essential as a part of vitamin B12 (cobalamin). Cobalt deficiency has never been reported in humans (29). Foods such as dairy products and meat contain vitamin B12, and the recommended daily supply of B12 for adults is 2.4 µg /d, which contains 0.1 µg of cobalt (30). Both differences and similarities can be found in the biokinetics of inorganic cobalt

and cobalt as vitamin B12. In terms of similarities, both accumulate in the liver and the half-life becomes longer with the observation period in both cases (21).

2.4   Human toxicity of cobalt

The chemical form of cobalt has a major role in toxic reactions due to cobalt exposure. Occupationally, workers are mainly exposed to cobalt metal particles (cobalt metal, WC-cobalt, and cobalt alloys) (31). The immune-mediated particle responses cause local tissue reactions, and they are divided into "metal reactivity" – an innate immunity response that comes as a nonspecific foreign-body reaction – and "metal allergy" – an adaptive immunity response, occurring in people with a genetic allergic predisposition. Contact dermatitis is a typical example of metal allergy (32,33).

Biological fluids can cause surface corrosion of metal-based compounds that, along with the solubilisation of Co^{2+} ions, may lead to the production of reactive oxygen species (ROS), oxidative stress, and e.g. enhanced inflammatory pulmonary effects (34).

Exposure to cobalt (nano)particles and cobalt ions are possible e.g. through metal-on-metal (MoM) hip implants. Cobalt ions that disseminate to the blood and the lymphatic circulation, and later spread to various organs, can lead to systemic toxic reactions. For systemic toxicity, ionised cobalt (Co^{2+}) is the primary toxic form (31), specifically the more bioavailable unbound Co^{2+} ions that, contrary to the albumin bound forms, interact with different cellular receptors, ion channels, and biomolecules (22).

Approximately 8.5% of cobalt is estimated to occur as free ionic cobalt in the serum in concentrations from 0.1 µg/l up to 3000 µg/l, and the rest of the cobalt is bound to serum proteins, mainly albumin (22). A larger proportion of free Co^{2+} ions increases the risk of toxic effects. Potential mechanisms of action for free Co^{2+} ions involve the induction of ROS production and lipid peroxidation, the obstruction of mitochondrial function, the changed homeostasis of calcium (Ca) and iron (Fe), altered erythropoiesis, the obstruction of thyroid iodine uptake, the induction of genotoxic effects, and the disturbance of DNA repair processes (22). The cobalt-binding capacity of albumin can be altered by different pathologies, such as diabetes, infections, severe renal disease, alcoholism, liver cirrhosis, arterial disease, and cancer (28).

The size of cobalt particles is a major factor in the toxicity of cobalt (32). In the lungs, ultrafine particles (0.01-0.10 µm) are associated with longer retention compared to larger particles. Smaller particles diffuse deeper into the lungs and stay in the lower airways and

alveoli. When these particles accumulate, macrophage-mediated clearance is disturbed depending on the chemical and physical presence and activity of the particles. Ultrafine particles made of the same material are more inflammatory than fine particles (0.10-10.0 µm) (35). For example, cobalt-chromium (CoCr) nanoparticles generate more ROS than micrometre-sized CoCr particles, since a higher number of chemical reactions is possible on the larger surface area (32).

Cobalt is a divalent cation similar to Ca^{2+} and has known to interfere with the transport of Ca^{2+} into cardiac myocytes (36). Cobalt may decrease ATP production through the prevention of the citric acid cycle. The cobalt $^{2+}$ ion can react with hydrogen peroxide under physiological conditions to form ROS (37).

Although cobalt oxide particles are poorly soluble, a Trojan-horse type mechanism could explain their toxicity (38). This mechanism may result in a partial solubilisation of cobalt particles within cells, especially within the lysosomes. These cobalt oxide particles can cause long-term damaging effects on the lungs, since their retention times are long.

2.5   Exposure to cobalt

Sources of human exposure to inorganic cobalt are diet, environment, some medical devices, and occupational exposures.

2.5.1   Dietary exposure

The general population is exposed to cobalt mainly through the diet. High cobalt concentrations have been found especially in chocolate, butter, coffee, fish, green leafy vegetables, and fresh cereals (30). In addition, people may purposely take cobalt in the form of cobalt- or vitamin B12-containing supplements. Many energy drinks contain vitamin B12, as well. The mean daily dietary cobalt supply has been reported ranging between 0.13 to 0.48 µg/kg bw (bw=body weight) in adults and between 0.27 to 0.31 µg/kg bw in children.

In the general population, 95% of individuals were found to have a serum cobalt concentration below 0.41 µg/l (39). Big differences between the urinary cobalt concentrations of men and women (median values of 0.22 and 0.39 µg/l, respectively) have been reported (40). Different iron uptake, as cobalt is similar to iron and shares the

same absorptive routes in the small intestine, is thought to be a possible reason for this finding (41).

2.5.2 Environmental exposure

Atmospheric cobalt levels in unpolluted areas are normally under 2.0 ng/m³. Environmental exposure can be of importance in certain circumstances, e.g. for people living near mining areas. In the Katanga Copperbelt (Congo) mining zone, a biomonitoring study among a non-occupationally exposed population revealed urine cobalt concentrations 4.5 times (adults) and 6.6 times (children) higher in the polluted than in the control area (42,43). In environmental samples, the differences in average cobalt concentrations between the areas were 6-40-fold. The authors concluded that dietary cobalt was the main source of high cobalt exposure. In a Chinese study, people living near an e-waste dismantling area had higher blood concentrations of Pb, Ni, Hg, and Co compared to the referents (cobalt 0.42 and 0.33 ng/ml, respectively) (44). Cobalt was associated with the bio-markers of myofibroblast activation and oxidative stress. The researchers speculated that cobalt exposure could increase the risk of tissue fibrosis in people living in such an environment. However, this suggestion contradicts the findings of many other studies (45).

2.5.3 Metal-on-metal hip prostheses

Patients with a MoM hip implant are thought to be the most important cobalt exposure group outside those with occupational exposure (28). Cobalt and chromium are the main metal components of MoM hip prostheses, but prostheses can also contain other metals, e.g. nickel, molybdenum, aluminium, iron, and manganese (46). Metal ions are formed and released by two processes: via friction of the two surfaces resulting in nano-sized wear particles, and via corrosion of the metals (47,48). The wear particles are mainly insoluble oxidised Cr^{3+} with practically no cobalt. In damaged implants, the volumetric destruction and the product of wear are larger, with the result of larger particles that contain more cobalt (49). Cobalt $^{2+}$ ions bind with the synovial fluid proteins and tissue surfaces and disseminate into the blood (50).

Patients with normally functioning MoM prostheses have cobalt concentrations ranging from 0.2 to 10 μg/l (blood) (50), whereas with malfunctioning implants, levels up to 6500 μg/l (blood) have been reported (51).

2.5.4   Occupational exposure

Occupational exposure to cobalt metal and cobalt compounds may occur e.g. during the refining of cobalt, the production of alloys and hard metals, and in the manufacture and use of hard metal and diamond tools containing cobalt. Workers are often also exposed to other substances co-occurring in the cobalt industry, like nickel, tungsten, chromium, iron, silica, and different gases. The real levels of exposures are often hard to interpret, because the scale of the measurements can be huge. For example, the range of cobalt was 0.000028-0.056 mg/m³ in the study presented in the next chapter (52).

Hard metal industry

The hard metal industry is assumed to be the main source of occupational cobalt exposure (52). Powder metallurgy is used both in the hard metal industry and in the bonded diamond tool industry. In hard metals, WC and cobalt form a metal matrix, and in the bonded diamond tool industry, cobalt is used as a matrix for diamonds (53,54). Cobalt, tungsten (W), and WC are the main constituents of hard metal alloys. WC is the main component of the alloy mixture (≥ 90%), while cobalt represents only ≤ 10% and is used as a binder (55). The matrix is called a hard metal because it is 90-95% as strong as diamond.

In a hard metal plant, exposures typically differ between departments. The highest cobalt levels were measured in the powder production, sintering, and pressing departments (56). Exposure to cobalt and tungsten has significantly decreased in recent years with improved technology and protection. For example, Hutter et al. (57) reported cobalt levels as high as 8 mg/m³ in 1985-2012 in an Austrian hard metal plant, while the highest value found by Klasson et al. (52), between 2007 and 2009 in a Swedish hard metal plant was 0.056 mg/m³. During the use of hard metal tools, the levels of exposure to hard metal dust and cobalt are much lower than those found during their manufacture. However, the grinding of stone and wood with hard-metal tools and the maintenance and sharpening of these tools may release cobalt into the air at concentrations clearly over 0.2 mg/m³ (58). Cobalt in coolants can contaminate the hands and cobalt can be absorbed through the skin (18,19,56).

Cobalt-containing diamond tooling

Diamond tools are used to cut stone, marble, glass, wood, and other materials and to grind or polish for example diamonds. The amount of cobalt in bonded diamond tools is high, up to 90%. Diamond polishers may inhale metallic cobalt, iron, and silica during

the polishing of diamond jewels. In a study by Nemery et al. (54) (135 exposed workers), the highest cobalt exposures were below 0.05 mg/m³. In an Italian factory where diamond wheels were used, mean cobalt concentrations in the air were 0.690 mg/m³, but 0.115 mg/m³ after a new ventilation system was installed (59).

Exposure from alloys containing cobalt

For a cohort of nearly 224,000 jet engine manufacturing workers, a historic exposure reconstruction (from 1952 to 2001) was conducted for cobalt, nickel, chromium, metalworking fluids, and solvents (60). The calculated exposures for metals were 0.001-0.005 mg/m³ or less throughout the period. In a factory producing stellite tools, the highest levels of cobalt in the air were over 0.20 mg/m³. Installation of ventilation systems diminished the cobalt concentrations to 0.05 mg/m³ or lower at nearly all workstations (61).

Production of cobalt metal and cobalt salts

Data on exposure levels in the production of cobalt or its various compounds have been reported only in a few industries. One exception is a cobalt plant in Belgium, which has been very active and versatile in research into cobalt and its health effects. The factory is part of a large metallurgical concern, and it uses a broad spectrum of raw materials, including cobalt metal cathodes, intermediate products, and residues. In a 1993 study, among 82 men exposed to cobalt, the exposure levels were high (62). About 70% of the men were exposed to levels higher than 0.050 mg/m³ and about a quarter had values over 0.500 mg/m³. Blood cobalt levels increased somewhat during the work week (median 9.5 vs 12.0 µg/l), urine cobalt concentrations (UCo) significantly (median 22.9 vs 72.4 µg/gcreat; µg adjusted for creatine concentration). In the 1990s and early 2000s, the plant underwent technical reforms that significantly reduced exposure to cobalt (63). Additionally, obligatory use of protective masks since 2002 has lowered urinary cobalt values among the workers even more: in 1993, at the end of the work shift of 82 men, the median UCo (µg/gcreat) was 72.4 (range 1.56-2038) and in 2008-2009, the corresponding value of 256 men was 3.9 (0.3-204). Blood cobalt levels decreased over 15 years from a median of 12 µg/l (range 2.0-120) to 1.0 µg/l (range <0.05-32).

2.6 Occupational exposure limit values

In Finland, like many other European countries, the regulatory occupational exposure limit value (OEL–eight hours; in Finland HTP value), indicating level of exposure that

is considered to be safe for cobalt in the air of a workplace, is 0.02 mg/m³ (64). In the United Kingdom and USA (OSHA), the corresponding values are 0.1 mg/m³ (65). In the USA (NIOSH), the level of immediately dangerous to life or health (IDLH) is 20 mg/m³ for cobalt).

2.7   Biomonitoring of exposure to cobalt in Finland

Occupational hygiene measurements do not consider working methods, clothing or other protection, smoking, washing, gastro-intestinal and dermal absorption, etc. (18,19). Hence, individual exposure is monitored by biomonitoring (urinary cobalt). Urine cobalt analyses are performed at the FIOH. Biomonitoring action limits are concentrations which the FIOH recommends not to be exceeded in occupational exposure. The biomonitoring action limit for cobalt is 130 nmol/l, based on the relationship between airborne and urinary cobalt concentrations. The upper reference limit in the non-exposed population is 25 nmol/l.

The European Union has classified cobalt chloride and sulphate as carcinogenic (Cat 2; R49, H350i). Finnish Government Decree 1335/2004 stipulates that chemicals in this category may be hazardous to the foetus or pregnant women. Thus, exposure to these chemicals is not acceptable during pregnancy: the urine cobalt concentration must not exceed the reference (25 nmol/l).

2.8   Health effects of cobalt exposure

Knowledge of the relationships between the levels of cobalt exposure and adverse health effects has increased remarkably during the past two decades (22). New biokinetic models can be used to assess tissue concentrations associated with exposure from various sources. For example, in the model of Unice et al. (6,66), oral ingestion of 1 mg cobalt a day for 365 days (assuming a 70 kg male and 35% absorption in the GI tract) gave the steady state of 12.5 µg/l (blood). Finley et al. (45) used this model to evaluate human blood cobalt concentrations at which health effects can and cannot be expected to occur. Their analyses meant that blood cobalt levels of 300 µg/l and under have not been connected with adverse effects of any type (excluding respiratory and dermal responses). Concentrations of over 300 µg/l were connected with some haematological and endocrine responses. Blood cobalt levels of 700 µg/l and higher were estimated to be a risk for even serious neurological and cardiac effects.

2.8.1 Haematological and endocrine responses

Finley et al. (45) reported that polycythaemia and thyroidal effects were the most sensitive (systemic) responses to cobalt exposure. Co^{2+} ions at high enough blood concentrations cause a hypoxia-like effect that promotes erythropoiesis and angiogenesis (22). This explains why oral cobalt was often used as a treatment of anaemic patients, including even children and pregnant women, at doses as high as 150 mg/d (45). However, as Co^{2+} ions prevent thyroidal iodine uptake, cases of goitres and other thyroidal effects were also noted in some of these patients (67).

Some occupational studies have assessed correlations between blood cobalt concentrations and haematological and thyroidal effects in cobalt exposed workers (62,63). No haematological effects or changes in triiodothyronine (T3) uptake, thyroxine (T4), or thyroid-stimulating hormone (TSH) were noted in these cohorts at the blood cobalt levels of 1-26 μg/l.

2.8.2 Neurological effects

Some neurological symptoms, for example hearing and vision impairment have been reported in patients with cobalt therapy for anaemia associated with severe kidney disease. Most often the effects appeared to be reversible after ceasing the therapy. The serum cobalt concentrations were often very high (22). For example, peak serum concentrations for three patients, reported by Bowie & Hurley (1975), were 820, 1620, and 2100 μg/l (68). As there is no indication for any use of cobalt in modern medicine, seeing such levels of cobalt today is highly unlikely.

2.8.3 Cardiovascular effects

Beer drinkers cardiomyopathy

In the 1960s, cobalt-related subacute cardiomyopathy was found in heavy beer drinkers as a result of cobalt being added to beer as a foam stabiliser (69,70). Cases of cardiomyopathy were discovered in North America and Europe. In Nebraska (USA), 11 out of 28 patients died, and in Quebec (Canada) 20 out of 48 died, whereas in Belgium only one severely ill patient out of 24 perished. All of the deseased were alcoholics with an average intake of 11 litres of beer per day (71).

Due to suspected causation, adding cobalt to beer was discontinued and the emergence of new cases of cardiomyopathy ended rapidly. Kesteloot et al. (69) examined and followed an all-male group of 24 patients in Belgium with an average follow-up time of 3 years. A group of 12 heavy-drinking male brewery workers, without heart complaints, was studied as a control group. All the men of this group had worked in breweries that added cobalt to their beer. In most breweries, cobalt had been added to the beer in the form of cobalt chloride at a dosage of about 1mg/l, meaning that the daily dose of cobalt among these alcoholics was 6 mg on average (current mean dietary cobalt intake in adults being 10-50 µg/day). It was noticed that the diseased had been anorectic in the first stages of the illness because of poor nutrition and low caloric intake from sources other than beer. Pericardial effusion was found in 18 cases. In the whole group, the mean cardiothoracic ratio (the ratio of maximal horizontal cardiac diameter to maximal horizontal thoracic diameter; a normal measurement is 42-50%) was 64.1 ± 7.8%. At follow-up, after adding cobalt to the beer had been discontinued, the heart volume had diminished and in most patients it normalised fully (to 48 ± 5.7%). In addition, the effusion cleared spontaneously in most cases. The haemoglobin value diminished from a mean of 18.6 ± 1.9 g% to 15.15 ± 1.3 g% (p<0.001). In the control group, it turned out that the caloric intake from non-alcoholic sources had been at an adequate level (69).

In as early as 1966, the link between the effects of cobalt exposure on thyroid function and its possible significance on heart findings was discussed in Canada (72). In 1972, it was suggested that cardiomyopathy in heavy beer drinkers was a multifactorial disease (73). The disease developed when an already significantly impaired heart (from alcoholic intake and severe coexisting protein and thiamine deficiency) was exposed to the toxic action due to the short-term cobalt intake. Because only a few of the exposed population developed the disease, also other factors (e.g. genetics) were to be taken into consideration as a cause of cardiomyopathy (69).

Hip implant patients

Already since 1938, cobalt alloys have been used in hip arthroplastic materials, and since 1967 there have been reports of increased concentrations of cobalt in the blood and other biological specimens of patients with these implants (74). High serum levels of cobalt and their long-term effects have raised concerns, but it has nevertheless been shown that higher concentrations do not increase toxicity in most patients. The kidneys' ability to intensify the renal clearance of cobalt could be the cause for the rarity of toxicity reports in these patients (75).

Despite the long-term exposure to cobalt from prosthetic sources (up to 30 years for some patients), it was not until 2009 that cardiac disorders were connected to cobalt implants (74). In 2016, a comprehensive review of medical literature revealed 15 patients with cardiac findings linked to cobalt alloy prostheses. Eight of these cases had cardiomyopathy (often nondilated), pericardial effusion, weight loss, polycythaemia, and hypothyroidism, with very high serum or blood concentrations of cobalt (>300 µg/l). Cardiac toxicity could not be linked to lower levels of cobalt (22,50,76).

A small case-control study (77) (ECHO; 35 MoM hip implant patients +35 controls) found slightly larger left ventricles with somewhat lower ejection fractions in patients with a well-functioning MoM hip resurfacing (mean plasma cobalt 1.48 ug/l; range 0.90-5.62 ug/l) compared to corresponding findings in the controls. However, the results of the study are difficult to evaluate because cardiovascular confounders (e.g. blood pressure levels) were not reported completely (76).

Cardiovascular effects of occupational exposure

Despite cobalt exposure in a large number of industrial workers, there have only been a few reports of cardiomyopathy cases (76). The first reported case was from 1966 when a 41-year-old man, "who had been exposed for four years to cobalt", was taken to the hospital because of general weakness, dry cough, and pain below the left costal margin (78). There was no history of excessive beer intake or poor diet. Rales over the chest were heard and enlargement of the heart on both sides was seen in an X-ray. The haemoglobin level was 20 g/100 ml and the patient had proteinuria. An electrocardiogram (ECG) showed low voltage in extremity leads. The patient died three days after hospitalisation. The autopsy revealed that both atria and ventricles were dilated, effusions were found in both pleural cavities as well as in the pericardial sac, and the thyroid gland was also enlarged. The content of cobalt in the myocardium was very high, 140 µg/100 g dry tissue weight (repeated workday exposure at the NIOSH IDLH level, Co 20 mg/m³, gave in the model of Unice et al., a cobalt level of 1.3-2.5 µg/g in the heart muscle) (6). The authors saw the case as an example of cardiomyopathy caused by industrial exposure to cobalt.

Jarvis et al. (79) described a cardiomyopathy in two young male employees (19 and 27 years) who had been exposed to cobalt but also to many other metals when analysing e.g. ore samples in mineral assay laboratories. The younger man had only been at the job in question for a month, the other one for two years. For the younger man, the disease resulted in a heart transplant. Cobalt exposure values were estimated to have been high, 0.1-5 mg/m³, and the use of protective masks had never been required. The older patient

had consumed three cans of beer every other day, the younger man did not report alcohol or drug use. The older man returned to work after recovery. Packer (76) assumed that factors other than cobalt had been underlying the diseases in this report: the pathology of the heart differed from that seen in cobalt-related cardiomyopathy, and the patients had no indications of polycythaemia or hypothyroidism that usually develop earlier than cobalt-related cardiac effects (45).

A radionuclide ventriculography was performed on a group of 30 cemented tungsten workers in order to measure ventricular ejection fractions at rest and exercise (controls were not included in this study) (71). The average duration of exposure to cobalt was 9.9 ($\pm$5.3) years. A weak but significant correlation with duration of exposure and left ventricular function at rest was found ($p<0.03$). Employees with some chest X-ray findings (9/30) had a lower exercise right ventricular ejection fraction (45% $\pm$6 vs 52% $\pm$7, $p<0.02$). Although no clear left ventricular dysfunction was found, the researchers estimated that long-term exposure may have had an effect on the myocardium, but the significance of the findings was unclear. It was speculated that the changes in the right ventricle could have been explained by early cor pulmonale.

In a cross-sectional survey from a Belgian refinery (80), the workers (256 male, no unexposed controls) had been exposed to various water-soluble cobalt salts, fine metal powders, and water-insoluble oxides. The exposure to cobalt was expressed as a urinary cobalt concentration (μg/gcreat) reflecting recent exposure, and an integrated exposure index (μg/gcreat$\times$years) reflecting long-term exposure. ECHO and ECG were used to examine the effects on the myocardium. In workers characterised by a median recent cobalturia of 4 μg/gcreat and a median long-term cobalturia of 100 μg/gcreat$\times$years, no correlation between cobalt exposure and findings indicating dilated cardiomyopathy was found. Reduction in the dimensions of the left ventricular internal cavity seemed to reflect recent exposure to cobalt.

2.8.4 Respiratory effects of occupational exposure

Cobalt exposure is known to cause occupational asthma (OA) and interstitial lung disease (ILD). Our knowledge especially of asthma is mainly based on case reports. Epidemiological studies are few, possibly because of the rareness of the disease. By contrast, even large epidemiological studies have been conducted on the effects of cobalt exposure on the airway functions and symptoms, especially in the hard metal industry, but also e.g. in the production of cobalt and its compounds: see Table 1 (81,82,83).

Respiratory symptoms and lung functions in workers exposed to cobalt

In a study by Swennen et al. (62), the subjects were employees exposed to pure cobalt powder and different cobalt salts, but not other metals. In this cross-sectional study of 82 exposed workers and 82 unexposed referents, the cobalt exposure levels were high: at the time of the study, the geometric mean of the air measurements (breathing zone samples) was 0.125 mg/m^3, and 25% of the results were over 0.500 mg/m^3. The exposure time had been 8 years on average. Wheezing and dyspnoea both at rest and exercise were reported more often in the exposed group than in the control group, and wheezing was heard in the lung auscultation in 16% and 6% (p<0.05), respectively. For other respiratory symptoms, there were no significant differences between the groups. Within the exposed group, the connection between the prevalence of dyspnoea and current levels of cobalt in the air was statistically significant in logistic regression, and similarly, a dose-response relation was seen between the decrease of the forced expiratory volume in the 1 second (FEV1) /vital capacity (VC) ratio and the current level of cobalt exposure. There were no differences in findings on lung functions or diffusing capacity between the exposed and the control group, and there were no signs of abnormalities in the chest radiographs

The prevalence of asthma and other respiratory symptoms was low in the studies presented in Table 1. For example, in Sweden approximately 40% of the general population suffers from symptoms due to allergy or other hypersensitivities, with about 8% being diagnosed with asthma by a physician (84). In all three companies presented in the table, there had been a practice of not employing people with pre-existing asthma or allergy. For example, in Rehfisch et al. (82) the prevalence of diagnosed asthma did not reach the prevalence of that in the general population. On the other hand, in this same study, ex-workers were not included, so reasons for leaving the work remained unclear. It may be possible that in this study both healthy worker selection and survivor bias were seen (85).

Two studies (81,82, Table 1) showed an effect of cobalt exposure on the FEV1 levels, the other only in smoking workers. It could be assumed that both exposures were interacting. This phenomenon could be seen in a survey conducted among workers who had been exposed to respiratory irritants: respiratory symptoms were more strongly associated with exposure in smokers than in ex-smokers or non-smokers (86).

Clara cell protein (CC16) is produced into the epithelial lining fluid of the lungs by club cells (87). These cells are sensitive to the effects of toxic factors, and altered levels of blood or serum CC16 can be seen as a marker of possible damage in the lungs.

Table 1. Studies on cobalt exposure and respiratory symptoms and lung functions.

Study protocol	Exposure to Co	Symptoms and asthma	Functions	Reference
Follow-up 1988–2001, 122 cobalt production workers; Characteristics of workers in 2001: Mean age 43.7 yrs (29.9–60.7) Employment duration, mean mo 205.8 Still active at the plant, n 93 Current smokers and ex-smokers, n 86, never-smokers, n, 36 Glu 69 β present, n 54	Average cobalturia* in workers from the different job areas 1992–2001: Co-U (µg/gcreatinine) Dry-stage area A 275-60 Mixed exposure B 30-10 Wet-stage area C 25-15 A cobalturia of 10, 20, or 40 µg/g creatinine was estimated to be roughly equivalent to an average exposure at 0.01, 0.02, or 0.04 mg/m³	14% of the workers reported respiratory symptoms, mainly chronic bronchitis and asthma; Only two (retired) workers were treated for asthma, and cobalt was not implicated as the causal agent.	Cobalturia contributed significantly to the deterioration of FEV1, but only in association with smoking (p<0.05); No significant differences were found in the lung-function values of the three patterns of exposure (A, B, C)[1]	Verougstraete et al. (81) 2004 Belgium
Follow-up 1982–2009, 582 hard metal workers (retired workers were excluded from the analyses); 40% had worked at the company for more than 20 yrs; 19% daily smokers, 57% never smokers	96% of the workers had exposure levels<0.022 mg/m³; For analyses, a cumulative exposure measure was calculated for each participant; Personal protective equipment had not been used	At employment , 5% reported respiratory symptoms; In 2008–2009, 5% stated persistent cough, 7% diagnosed asthma	Dose-response effect[2] between increasing cobalt exposure and decline in FEV1 among both smokers and non-smokers without asthma diagnosis; FEV1 in smokers declined 10 mL more per year than for non-smokers	Rehfisch et al. (82) 2012 Sweden
Cross-sectional, 72 hard metal workers from two plants; Mean age 42 yrs (20–65); Work in the same place for 11 yrs on average; 2 current smokers, 12 ex-smokers	Personal sampling, an average 0.0034 mg/m³ (0.00016–0.019 mg/m³); Adjusted for the use of respirators, an average 0.0017 mg/m³	Non-significant[2] exposure-response relationships between cross-shift inhalable dust or cobalt exposures and asthma, nose dripping, and bronchitis	No statistically significant[3] changes for FEV1 and FVC	Andersson et al (83) 2020 Sweden

*Estimated from the original article
[1] "Workers have transited during the survey period from one exposure pattern to another"
[2,3] Statistically non-significant, 95% CI

In their study, Andersson et al. (83) found statistically significant ($p<0.05$) differences in the serum levels of CC16 when the high and low cumulative exposures to cobalt were compared, and they concluded that an exposure-response relationship between inhalable cumulative cobalt and CC16 levels in the blood might be a sign of injury or recovery process in the lungs. Instead, the fraction of nitric oxide in exhaled air (FENO) had no correlation with inhalable cobalt.

Contrary to what was reported on the effects of hard metals by Potolicchio et al. (88), the presence of glutamate 69 in the HLA-DP chain had no effect on respiratory functions in the study by Verougstraete et al. (81), where exposure to cobalt was not associated with exposure to other components of hard metal, such as tungsten.

Cobalt-related interstitial lung disease

In the medical literature, cobalt-related ILD is also named cobalt lung, giant cell interstitial pneumonitis (GIP), hard metal pneumoconiosis, and hard metal lung disease (89). The association between hard metal and ILD was first addressed by Abraham and Spragg in a patient who had been exposed in the hard metal tool industry (90). Initially, it was unclear whether tungsten or cobalt in the hard metal caused ILD, but through animal models and case reports of ILD occurring in bonded diamond tool manufacturing without tungsten, cobalt was confirmed as the causative agent (89,91,92).

Exposure to cobalt through the manufacture or use of tools created by the process of powder metallurgy is required for ILD to develop in workers (53,89,91,92). However, a significant number of occupational exposures to cobalt does not involve powder metallurgy and thus is not connected to ILD. Exposures not known to cause ILD include e.g. cobalt mining and refining (89).

The latency required for the development of cobalt-related ILD, its pathology, and risk factors, which resemble those of chronic beryllium disease (CBD) and hypersensitivity pneumonitis (HP), support the theory that cobalt-related ILD is an immunological disease. CBD and HP are known to develop as an immune response against an inhaled antigen (93,94). Individual susceptibility contributes to the development of these diseases, as exposure level, for duration or severity, is not known to be critical as to whether or not the diseases will develop (53,95). Another theory suggests that cobalt-related ILD can develop from varying receptivity to oxidant injury (53). Cobalt alone can enhance the production of activated oxygen species, but animal models have shown that the combination of WC and cobalt has a greater effect on lung parenchyma than cobalt alone (96).

Cobalt-related ILD can be subacute or chronic (53). The subacute form manifests itself with dyspnoea, cough, and systemic symptoms like fever, chills, and weight loss within months or years of exposure (53,97). Symptoms and respiratory functions may improve after ending the exposure (98). The chronic form of ILD manifests with a gradual onset of dyspnoea and cough. There are no systemic symptoms, and the illness does not show improvement after removal from the exposure (53). Chronic ILD is usually more common in older patients, and the condition may progress to severe fibrosis and death (95,99).

Even though GIP is the typical pathology of cobalt-related ILD, other histopathologic findings, such as HP, usual interstitial pneumonia, organising pneumonia, and desquamative interstitial pneumonia may be present in this disease (100,101).

Cobalt-related ILD cannot usually be diagnosed through normal radiography due to its non-specific findings. The findings can be either completely normal or demonstrate e.g. a nodular or reticulonodular form (102). Instead, a high-resolution CT scan (HRCT) is essential and superior in the evaluation of diffuse lung diseases (103).

Occupational asthma as a concept

OA can develop due to a sensitiser, either a high-molecular-weight (HMW) allergen (>10kd), usually a protein source such as flour or animals, or a low-molecular-weight (LMW) sensitiser that often is a chemical (e.g. metal salts, including cobalt) (104). After exposure, there is a latency period before the onset of OA symptoms. Furthermore, a subset of OA, irritant-induced occupational asthma (IIA), can arise even from a single exposure to a high-level irritant in the workplace.

Atopy, rhinitis, and bronchial hyperreactivity are strong risk factors for the development of OA induced by HMW agents via IgE-hypersensitivity (105) and in cases of asthma caused by LMW agents that act via the same pathways of hypersensitivity (such as platinum salts), as well. The risk of OA caused by such LMW compounds as isocyanates and red cedar, however, does not appear to be increased because of atopy (106).

An isolated early asthmatic response is common among patients with OA from a HMW agent; only 13% of them had an isolated late asthmatic response in a large survey by Vandenplas et al. (107). On the other hand, OA from LMW, IgE-independent immunologic sensitisers manifests typically as a late asthmatic response 4-6 hours after exposure. Higher blood eosinophils and exhaled nitric oxide (fractional exhaled nitric oxide) could also be found in the HMW group. Atopy (based on a skin test to common

allergens) and preceding rhinitis were also more common in the HMW group. In one study, patients with higher levels of sputum eosinophilia had a better outcome in the follow-up, possibly because of a better response to the corticosteroid treatment (108). The T cell subset and cytokine profile may differ between atopic asthma and asthma caused by LMW sensitisers (109).

In a large Cochrane Database study involving 1,695 OA patients, both removal from exposure and reduction of exposure improved asthma symptoms compared with continued exposure (110). In a similar comparison, only total removal from exposure could improve lung function. When comparing removal from exposure directly with a reduction in exposure, the former improved symptoms and lung function more among patients exposed to LMW agents.

Patients with IIA from one high level exposure (acute) or from several exposures (subacute) seldom show improvement in asthma symptoms, peak flow measurements, and bronchial hyperreactivity when off work (104). Leisure improvement can be seen if the patient has airway hyperreactivity and ongoing exposure to low-level irritants at work. There are no typical pathological changes useful for diagnosis with the exception that patients with IIA more rarely have eosinophilic airway inflammatory markers compared to patients with OA from an HMW sensitiser. In the material of a comprehensive Finnish study, sulphuric acid (H_2SO_4) was the most common single causative factor for both forms of IIA (111) In another study concerning the same material, the prognosis of IIA patients appeared poorer compared to that of patients with an OA induced by HMW or LMW sensitiser (112). The IIA may be associated with long lasting eosinophilic and neutrophilic inflammation resulting in remodelling, a thickened basement membrane, and, with time, even an irreversible deterioration of respiratory function (113).

A Finnish study found that occupational exposures to vapours, gases, dusts, or fumes have a contributing factor to the development of chronic obstructive pulmonary disease (COPD) in patients with asthma (114).

Cobalt-related asthma

During the first five years (1966-1970) of the Kokkola cobalt plant's operation, Ahlman reported 10 cases of "asthma or asthmatic bronchitis"(2). Three of these patients had worked in the cobalt roasting building (pyrometallurgic stage of the process) and seven in the solution purification/leaching and reduction buildings (hydrometallurgic stage). The workers' symptoms ceased when off work, and disappeared when the workers were

moved out of cobalt production. However, based on the case report, it was not possible to distinguish those who probably had only non-specific bronchial irritation and those who really had cobalt-induced OA. By 1977, 15 cases of asthma had been reported at the cobalt plant (3). Altogether five of these workers had a positive respiratory challenge with cobalt chloride and one with the dust of the cobalt roasting building. They met the criteria for OA. The symptoms of asthma disappeared in all but three persons after removal from the exposure. Two of the asthmatic cobalt workers were re-exposed to cobalt accidentally in 1977, 7 and 8 years after removal from cobalt exposure. After the first exposure day, both workers experienced the typical clinical symptoms of asthma. They were examined at the FIOH in 1977 and had a positive result in the cobalt chloride provocation test. Most of these early OA patients are a part of our asthma study, so information related also to them is presented in more detail in sections 4.1, 4.2, 4.3, 5.2, 6.1, and 6.4.

The definition of "asthmatic symptoms" used in the study from the hard metal industry (115) (Table 2) does not give the same result for the incidence or prevalence of asthma as clinically defined asthma. Additionally, making comparisons with the results of other questionnaire-based studies depends on what symptoms the diagnostic algorithm contains. Within the study, however, the importance of different factors can be well assessed. According to the multilogistic analysis, age, atopy, and exposure to metals were clearly linked to asthmatic symptoms (115). Nonallergic asthma occurs most often in middle-aged people, but further clarification is needed if being 40 or older is a risk factor for hard metal (cobalt) asthma. No association between smoking and asthmatic symptoms was found among the subjects, which supports the assumption that although many studies show that smoking may enhance the risk of IgE-mediated sensitisation to some HMW and LMW agents, there is still little evidence for a correlation between smoking and the development of clinical OA (116). A surprising finding was that only a low cobalt exposure (<0.05 mg/m³) was a risk for hard metal asthma. This protective effect (of high exposure) has not been found in other studies on cobalt. In fact, a positive dose effect correlation between concentrations of airborne cobalt and respiratory symptoms was seen in cross-sectional studies at hard metal plants (117,118) and a cobalt refinery plant (62). However, the details of the studies, such as testing atopy and the diagnostic algorithms used, have been different, so a direct comparison of the results is problematic. Exposure level to sensitising agents is interpreted as the most significant environmental risk factor for OA (118).

Table 2. Epidemiological study on hard metal asthma.

Study protocol	Definition of asthma	Results	Reference
Epidemiological, cross sectional, 703 hard metal workers; Characteristics of subjects: Sex Age,mean Men 583, yrs 38.4 Women 120 yrs 34.0 Atopy was defined by immunoglobulin E (IgE) antibody against mite allergen	Attacks of reversible dyspnoea with wheeze were used as a health effect indicator (asthmatic symptoms) **Exposure to cobalt** was measured by personal sampling for all of the workers	Significant independent variables from multilogistic analysis of asthmatic symptoms on sex, age, smoking, atopy, and concentration of airborne cobalt Factor Odds ratio (95% CI) Age 40<50 1.73 (1.05-2.83) Age 50<60 3.01 (1.73-5.24) Atopy 1.60 (1.11-2.31) Concentration of airborne cobalt 0–0.05 mg/m^3 1.61 (1.11-2.31)	Kusaka et al. (115) 1996 Japan

The patient of the case study by Krakowiak et al. (119) (Table 3) had been working in the hard metal industry for 10 years (exposure levels were not reported). He was considered to be atopic. A late allergic reaction after a nasal cobalt chloride provocation was compatible with OA induced by LMW substances. The clinical symptoms combined with his work history could mean that the patient had OA with a hypersensitivity to cobalt. The patient had persistent difficult asthma even after removal from occupational exposure, and during the second hospitalisation an increased bronchial hyperreactivity to histamine was seen. As e.g. Maestralli et al. (120) point out, a longer exposure and symptom time may have a negative effect on the recovery of patients.

In the case series study among stellite (containing i.a. CoCr) workers (121) (Table 3), exposure to cobalt was tested for 10 workers in connection with clinical investigations of asthma. The exposure levels were low, the median value of urinary cobalt, 2.6 µg/l (IQR = 1.7-8.5) being slightly over that of general population. The authors estimated that the exposure may have been higher from time to time, e.g. when ventilation systems were not running at night due to noise reduction. Of the workers, 64% were atopic, 75% had positive skin prick tests (SPT) to cobalt chloride, and six of seven positive specific bronchial challenge tests (SIC) to cobalt chloride were immediate (including dual) asthmatic reactions. This is an indication of a predominant IgE-mediated response. As mentioned earlier, atopy increases the risk for OA due to HMW allergens, but also due to some LMW substances such as nickel salts, trimellitic anhydride, and wood dust; however, cobalt is not usually mentioned in this list (122,123)

Table 3. Studies on cobalt asthma as an occupational disease.

Study protocol	Symptoms	Diagnosis of OA	Other findings	Reference
A case study; A 35-year-old male diamond polishing disc former. He had to quit his job (8 months earlier) because of respiratory symptoms; Ex-smoker, no history of asthma or allergic disorders in family	A 2-year history of worsening dyspnoea with wheezing, cough, and rhinitis; After diagnosis still persistent, difficult symptoms. During his second hospitalisation increased bronchial hyperreactivity was noticed	SPT with cobalt chloride was positive, SPT with nickel chloride was negative; Nasal challenge (cobalt chloride) positive, late reaction (peak after 24 h); After challenge an increase in the proportion of (nasal) eosinophils after 4 and 24 h	On admission FEV1 was 3.15 (63%), no abnormalities in chest X-ray and CT; Total IgE level was 176 kU/l, therefore the patient was considered to be atopic; SPTs of the most common allergens were negative, no specific IgE to house dust mite	Krakowiak et al. (119) 2005 Poland
A case series of 14 manufacturers of stellite-tipped steel engine valves; asthma confirmed 1996–2005; Characteristics of workers at diagnosis: age, mean yrs 44.9, employment prior to onset of symptoms, median yrs 8; active smokers, n 1 ex-smokers, n 5 never smokers, n 8, symptom latency prior to diagnosis, median mo 30 (IQR=24–48)	Cough,　　　n 13 Wheeze,　　　13 Breathlessness,　12 Chest tightness,　12 Nasal symptoms　6 Eye symptoms,　3 Dermatitis,　　3 Resp. symptoms　14 improve when off work	Bronchial　　n 6/14 hyper-responsiveness; PEF,　　　n 14/14 work effect demonstrated; Positive SPT　n 6/8 to cobalt chloride; Positive SIC to　n 7/7 1–10mg/ml cobalt chloride; There were 3 immediate, 3 dual and 1 late asthmatic reactions to cobalt chloride	Atopy: history of asthma, n 1, positive SPT to one or more common allergen, n 9; 5 workers were diagnosed with cobalt asthma based on positive PEF records, clinical picture, and exposure data	Walters et al. (121) 2014 UK

2.8.5 Skin

Cobalt can have a strong sensitising effect on the skin (124), and it is one of the most common causes of allergic contact dermatitis (ACD). In Europe and North America, it is estimated that 5.9% and 7.4% of tested dermatitis patients are allergic to cobalt, respectively (125,126). On the other hand, only about 25% of positive patch test results have clinical importance, as exposure sources most often are unknown (127).

ACD is a T cell-driven skin disease induced by small non-proteinaceous substances (haptens), and immunologically ACD is a delayed-type hypersensitivity disorder, showing symptoms 48-72 hours after exposure (128). Recent studies have shown that sufficient innate immune reactivity is crucial for the development of ACD (129).

The significance of atopic eczema for solitary cobalt contact dermatitis is not completely clear. For example, in a study of nearly 60,000 ACD patients, atopic dermatitis was only weakly indicative of cobalt sensitisation (130). On the other hand, increasing numbers of positive reactions to other substances (patients were patch-tested with nickel, cobalt, dichromate, and at least 10 additional standard series substances) increased the odds of reactions to cobalt. An Italian study found that allergic rhinitis (at least one positive SPT) was not associated with an increased sensitisation to metals (patch-tested with chromium, cobalt, and nickel) (131).

The general population is exposed to cobalt (via skin contact) mainly through materials such as jewellery, leather, cosmetics, and electronics. The hard metal and construction industries, as well as the pottery and porcelain industry, represent sectors where cobalt allergy has been prevalent (132). In the Finnish Registry of Occupational Diseases (133), there were 64 recognised occupational ACD cases due to cobalt recorded in 2005-2018, and 56% of these were process and foundry workers, engineering and construction workers, and installers.

2.8.6 Carcinogenic activity

IARC has in 2022 classified cobalt as follows: Cobalt metal and soluble cobalt(II) salts are classified as "probably carcinogenic to humans" (Group 2A); Cobalt(II) oxide and weapons-grade tungsten alloy is classified as "possibly carcinogenic to humans" (Group 2B) (134). According to this report, there was "inadequate" evidence of carcinogenicity in humans for the evaluated forms of cobalt. The available studies did not permit a conclusion to be drawn about the presence of a causal association between cobalt exposure and any type of cancer in humans. However, the mechanistic evidence for both cobalt metal and soluble cobalt(II) salts was "strong" in human primary cells and experimental systems for e.g. genotoxicity and the Group 2A classification is based on these studies.

In our retrospective cancer study, the cohort consisted of all males employed for at least one year at the Kokkola cobalt plant in 1968-2004 (135). The follow-up of 995 men (26,083 person-years) ended at the latest on 31 December 2013. The data on cancer in

the cohort and in the reference group (men of the central hospital area of Central Ostrobothnia, around Kokkola), was received through the files of the Finnish Cancer Registry. The cohort was divided into subcohorts by cobalt exposure levels according to the department in which they had started working: low, mean 0.018-0.02 mg/m³; moderate, mean 0.02-0.03 mg/m³; high, mean 0.04-0.10 mg/m³; and variable (maintenance workers), with possible peak exposures to cobalt. Almost 80% of the workers had been exposed to nickel as well: the highest levels were measured in sulphatising roasting (1966-1986, 103-107 men) and in the chemical department (1987-1999, 44 men), in both the mean levels of nickel being 0.06 mg/m³. Otherwise, the exposure had been clearly lower, mainly under 0.02 mg/m³ (136). The exposures are described in greater detail in 4.1.

In the study, a total of 92 cases of cancer were diagnosed among men who had been working at the plant for over one year (the expected number was 91.9), and among men who had been working for over five years, 77 cases were diagnosed. The standardised incidence ratios (SIRs) were 1.00, 95% CI 0.81-1.22 and 1.08, 95% CI 0.85-1.34, respectively. The overall cancer incidence was not significantly elevated in any of the exposure groups. None of the exposure group-specific or the age-specific SIRs for lung cancer differed significantly from those of the reference population. The incidence of tongue cancer was clearly increased (3 cases, expected number 0.41; SIR 7.39; 95% CI 1.52-21.6). All three cases were smokers. In different exposure and age groups, the increase was not statistically significant.

The most significant risk factors for oral cancer are smoking and the use of alcohol (137). In our previous study on respiratory health (136,I), the prevalence of current smokers among the employees of the Kokkola cobalt plant was 31.8%. The prevalence of daily smokers in the male population of Central Ostrobothnia in 1990-2005 varied from 18% in the highest educational class to 25% in the lowest (138). This trend was seen also in our study: the mean number of pack-years of the cobalt group was clearly higher compared to that of the control group consisting both of white-collar workers from the same plant area and blue-collar workers from the city of Kokkola (pack-years 21.2 vs 15.8) (136) The sample sizes were small, but the numbers support the assumption that the smoking prevalence of the study population had not been lower compared to the reference population.

In this cancer study, we could not find an increased overall or lung cancer risk among cobalt production workers during the mean follow-up of 26.2 years. Because of the small number of tongue cancer cases, the excess might be explained by chance.

3 AIMS OF THE STUDY

The aim of this study was to investigate the effect of occupational cobalt exposure on respiratory and cardiovascular health and to assess the results in the light of new research. The detailed goals of the study were:

To determine whether long-term (at least 10 years) exposure to cobalt is associated with an increased occurrence of respiratory symptoms and findings or diseases, other than asthma, among cobalt processing workers (Respiratory study; Original publication I).

To characterise 22 cases of occupational cobalt asthma encountered in the cobalt plant at the time of diagnosis and 6 months later, and to evaluate the incidence of cobalt asthma in different departments on the basis of data on occupational exposures (Asthma study; Original publication II).

To investigate whether exposure to cobalt has any measurable effect on the cardiovascular system, especially on the myocardium, at occupational exposure levels (Cardiovascular studies; Original publications III, IV).

4 SUBJECTS, MATERIALS AND METHODS

4.1 Process and workplace exposures

The Kokkola cobalt refinery was the basis for this study. Between 1966 and 1987, cobalt powder was produced at the cobalt plant from pyrite ore concentrate (I,136). After that, cobalt powder, inorganic cobalt, and nickel compounds have been produced using by-products of the metallurgic industry as a raw material. After changes in the process in 1987, exposure to SO_2 diminished significantly. In the sulphatising roasting, 15-20% of the dust in the ambient air was iron, 1% zinc, 0.4% cobalt, and 0.2% nickel. Cobalt and nickel were present as water-soluble sulphates, whereas in the leaching building, the dust consisted of metal sulphides and sulphates. In the reduction department and powder production facility, cobalt is mainly in the form of cobalt powder and fine powder. In the chemical department, the cobalt and nickel compounds have been mainly sulphates, carbonates, oxides, and hydroxides. The flow sheet of the processes is given in Figure 1.

In the industrial area where the cobalt plant is located, a sulphur plant began its operations in 1961 and continued production until 1977. In the sulphur roasting department, workers were exposed to e.g. SO_2, cobalt, and nickel. Exposure to SO_2 was in the same range as in the cobalt roasting building, and exposure to cobalt was at most about half the levels of the cobalt roasting building, with exposure to nickel being clearly lower.

In the industrial area, especially during the three first decades, the SO_2 emissions were high. For example, between 1973 and 1977, the annual emission was 40,000 tonnes (3), which is approximately twice as much as the emission for the whole of Finland in 2020 (139). Other major pollutants at the area were hydrogen sulphide (H_2S) and carbon disulphide (CS_2).

Cobalt process 1966–1987

Pyrite ore concentration

Sulphatising roasting → Iron residue

Leaching and solution purification → Copper sulphide → Zinc sulphide → Nickel ammonium sulphate

Reduction and powder production

Cobalt powder
Cobalt fine powder

Cobalt process 1987–2006

Cobalt concentrates

Leaching and solution purification → Iron residue → Copper sulphide → Zinc sulphide

Cobalt extraction

Reduction and powder production

Cobalt and nickel solutions

Chemical production

Cobalt powder
Cobalt fine powder

Cobalt and nickel (Ni to 2003) sulphates, oxides, hydroxides

Figure 1. Cobalt production process at the Kokkola cobalt plant, 1966–1987 and 1987–2006.

Exposure to most dusts and gases has been regularly monitored in every job task several times a year since 1966. Air samples have been collected both from stationary points and with personal samplers from the workers' breathing zone. Accurate descriptions of hours the workers have been exposed to during their 8-hour workshifts can be found in workplace documents. Therefore, using these documents and a job-exposure matrix based on ambient air measurements, it was possible to calculate cumulative exposure numbers for each worker. In the respiratory study, the mg-years were calculated for total dust, cobalt, and nickel, and the ppm-years for SO_2, H_2S, and ammonia (NH_3). In the heart studies, the mg-years were calculated for cobalt.

In the cobalt plant, average exposure levels measured for cobalt in the air (1966-2006) were at their lowest slightly below the current HTP value (0.02 mg/m³), but mainly above that, even up to almost five times that level. The mean exposure levels to cobalt and its compounds were slightly under the former HTP value (0.05 mg/m³) since the new process was introduced in 1987. As can be seen in Table 11, the individual results of measurements may have been many times higher than the average figures. Corresponding levels of nickel have been at just above or well below the current HTP value. SO_2 concentrations exceeded the current HTP value 2-4-fold, while the levels of

other gases (NH_3, H_2S) were well below the limit values. In the cobalt roasting building, the concentration of total dust was high, fluctuating between 8 and 19 mg/m³.

The exposure data (between 1966 and 1996) collected for the respiratory study (I,136) is presented in Table 4. The arithmetic mean values of exposure (mg/m³, ppm for gases) are counted using personal mg (ppm)-years. The number of workers exposed to different agents is presented as well. Cobalt exposure from 1997 to 2006 was at the same or slightly lower level compared to that of the preceding period: in exposure areas (Table 4) B and C the combined mean is 0.016 mg/m³, in area D the mean is 0.065 mg/m³, and in area E the mean is 0.02 mg/m³. The production of nickel compounds in chemical department (E) ceased in 2003.

Table 4. Industrial hygiene levels in the Kokkola cobalt plant in 1966–1996 (mg/m³; gases ppm).

		1966–1976		1977–1986		1987–1996	
Area		n	Mean	n	Mean	n	Mean
A.	Co	103	0.085	107	0.092		
	Ni*	103	0.057	107	0.061		
	SO_2*	103	1.85	107	1.01		
	H_2SO_4*	33	0.09	33	0,12		
B.	Co	90	0.013	99	0.019	71	0.019
	Ni	90	0.017	99	0.009	71	0.014
	H_2S*	80	1.22	88	1.36	65	0.89
	NH_3*	80	4.38	65	3.36	45	3.43
C.	Co			60	0.018	25	0.011
	Ni			60	0.012	25	0.010
	SO_2			10	0.07	5	0.25
	H_2SO_4			49	0.13		
D.	Co	50	0.084	55	0.10	54	0.065
	NH_3	40	1.05	41	1.05	10	1.0
	H_2S					10	0.20
E.	Co					44	0.03
	Ni					44	0.06

n=number of exposed workers; *Current HTP value-8 hours: Ni-metal 0.01, Ni-compounds 0.05, SO_2 0.5, H_2SO_4 0.05, H_2S 5, NH_3 20
The exposure areas in the table are: A sulphatising roasting; B leaching and solution purification; C solution purification; D reduction and powder production; E chemical department

The biomonitoring results of cobalt exposure are shown in Table 5. Mean or median values have not been calculated for all parameters, because not all individual results were still available. The results from 1986 (Aitio, 140) are not fully representative for all workers, as the aims of the study were primarily to investigate the measurement of exposure by means of biomonitoring as well as the correlation between the results of occupational hygiene and biological measurements. However, the results disclose the

large differences in exposure between individual workers. In later measurements, the correlation between occupational hygiene and biomonitoring results is rather poor, because the use of respirators had become more common in reduction and powder production and in the chemical departments.

Table 5. Biomonitoring results of the urinary cobalt in the Kokkola cobalt plant in 1986–2006 (nmol/l).

	__Area__	__Results__
1986[1]	**B**	range 800–3300
	D	range 1000–16000
	E	range 1000–7000
1990–1998, n. 100	**D E**	25% >1000 75% <1000
1999–2006, n. 142	**B C D E**	median 235, range 11–6280

[1] Results are from the study "Kobolttialtistuminen ja sen biologinen monitoroiminen" (Occupational exposure and biological monitoring of cobalt, 140), conducted by the FIOH
The exposure areas in the table are: B leaching and solution purification; C solution purification; D reduction and powder production; E chemical department

4.2   Subjects

4.2.1   Respiratory study

All the workers who had ever worked at the Kokkola plant in cobalt powder or cobalt-compound production for at least 10 years were invited to participate in the study. Ten years was set as the lower limit of exposure, because that time was found to be sufficient for the development of e.g. chronic bronchitis (141). Eighty-eight of the 142 workers (all men) were still working in the plant. Persons who had worked in other metallurgic industries were excluded. Because welding can affect lung function, those who had regularly welded for 6 months or more were excluded (two persons). Subjects were not excluded based on any symptom or disease.

The reference group consisted of 76 plant employees (8 stockroom/store men and 68 male white-collar workers) who had worked for at least 10 years without exposure in cobalt production or to other irritative agents (e.g. welding fumes) and 64 male blue-collar maintenance workers of the city of Kokkola, who had worked for at least 10 years, but not in the cobalt factory, and who had not been exposed to harmful dusts or fumes.

4.2.2 Asthma study

The subjects of our analysis study were all 22 cases of cobalt asthma found in the Kokkola plant from 1967 to 2003, and the diagnosis was confirmed in the FIOH with SIC tests. The clinical data at the time of diagnosis and during a follow-up visit 6 months later were gathered from the patient files.

4.2.3 Cardiovascular studies

Study in 2000

The employees who were working at the end of 1999 in the cobalt plant and had been exposed to cobalt for at least one year (203 men) were invited to participate in the study. The control group consisted of a stratified random sample of male workers in a zinc plant located in the same industrial area. Age groups of 4 years were used as strata. Since the zinc plant employed fewer workers who had been born in the 1960s and 1970s than the cobalt plant, the number of controls (96) remained smaller than designed. The control group had not been exposed to cobalt, arsenic, or lead. According to the assessment of statistical power, 122 cumulatively most exposed cobalt workers and 60 controls with the same age distribution underwent ECHO.

Study in 2006

After 2000, four employees from the earlier exposed group and one from the unexposed group had died. The cause of death of one of the exposed workers was heart infarction, the deaths of the other deceased were not related to cardiovascular diseases. The rest of the workers who had been examined by ECHO in 2000 and whose results were included in the analyses were invited to participate in this follow-up study. All men in the exposed group had been exposed to cobalt even after 2000. Nineteen workers of the exposure group and 11 workers of the control group had resigned, and 19 persons were unwilling to participate or could not be contacted. Altogether, 93 of the workers exposed to cobalt, and 49 of the workers in the unexposed reference group were re-examined.

4.3 Methods

4.3.1 Respiratory study

Questionnaire

Questions on work history included current and previous tasks in the cobalt plant and also previous occupations, especially those with exposure to hazardous dusts (metal industry, farming, construction work, asbestos exposure, etc.). The reasons for changing work tasks or jobs and workplaces were also asked. All the questions concerning lung diseases and health symptoms were based on the Tuohilampi questionnaire (142). The outcome parameters were defined in groups: *Reported diseases*: allergic rhinitis, asthma, and pneumonia if diagnosed by a physician. *Diseases based on criteria of the questionnaire*: suspected asthma (if a person of adult age had had cough or dyspnoea with wheezing or had had attacks of shortness of breath with wheezing and breathing had been normal between the attacks), suspected work-related asthma (if the person had suspected asthma or reported asthma and reported that the symptoms worsened at work or the symptoms worsened at the beginning or end of the work period or any time during the work period or the person associated the worsening with some particular exposure at work), chronic rhinitis, and chronic bronchitis (143). *Definition of symptoms*: cough and phlegm, cough with wheezing, dyspnoea with wheezing, and breathlessness on exertion, were reported as a direct distribution in the analysis.

Clinical measurements

Spirometry, measurement of diffusing capacity, a chest X-ray, and laboratory tests were carried out by experienced laboratory technicians in the mobile research unit of the FIOH.

Spirometry and diffusing capacity

For spirometry testing, at least three acceptable forced maximal expirations were performed according to the standards of the American Thoracic Society (144). From the maximum expiratory flow volume curves, the highest forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), and flow rates at 50% and 25% of the vital capacity (MEF50, MEF25), and the mean flow (MMEF) were read. All the values were also expressed as percentages of predicted values in Finland (145).

Diffusing capacity of the lungs for carbon monoxide (DLCO) and the specific diffusion capacity DLCO/VA (alveolar volume) were tested (146). The values were adjusted to the real-time haemoglobin measurement (147). The results were expressed as percentages of predicted values for Finland (145).

Chest X-ray

A full-size, posteroanterior chest X-ray was taken if such an X-ray had not been taken within the past year. Only current and former workers from the production departments were examined. The high and low cobalt-exposure groups were compared. The X-rays of each exposed subject were classified according to the modified ILO classification (148).

Clara cell protein

Serum specimens for CC16 analysis were taken from 54 never or ex-smokers of the exposure group and correspondingly from 59 men of the control group (87). The specimens were analysed at the Catholic University of Louvain, Brussels, Belgium.

Statistical methods

Frequency tables in the occurrence of symptoms between the exposed and control groups were analysed with the Chi-squared and Fisher's exact tests. The multivariate analysis was based on a stepwise (forward) logistic regression model. The possible explanatory variables were study group and smoking status as dichotomous variables and age as a continuous variable. In the further analysis of respiratory symptoms in the exposed group instead of the study group, the possible explanatory variables included exposure to total dust, cobalt, nickel, H_2S, SO_2, and NH_3. The effect of exposure on pulmonary function was studied using Student's t-tests and analyses of variance and covariance. In the analysis of variance, the variation in each lung function measurement was explained by the smoking status and the study group to explore the possible interaction in addition to the main effects of these factors. When the effect of different exposure substances on the lung function measurements was studied, the workers were divided into three groups: high, moderate, or no exposure to the substance; for total dust and cobalt, the moderate and no exposure groups were merged. The limit between the high and moderate exposure (as mg-years and ppm-years) was the median of the exposed persons, and in the additional analysis the upper quartile was used. Smoking was included as pack-years in the model as a covariate. The limit for statistical significance was set at 0.05.

4.3.2 Asthma study

At the FIOH in Helsinki, before 1991, a modified method by Laitinen (149) was used in the histamine challenge test. From 1992, the histamine challenge test was performed following the method of Sovijärvi et al. (150). SIC tests were performed according to the international guidelines (151). In the specific test, CoCl (0.1–1 ml/l) was used in 15 cases and $CoSO_4$ powder in two cases. In nine cases, the reaction was confirmed with a provocation test with cobalt powder dust or with the dust from the sulphatising roasting process. In five cases, only cobalt powder or dust from sulphatising roasting was used. In the referent test, lactose powder was used in 17 cases, and dilution fluid was used in 5 cases. The reaction was classified as immediate if there was a decrease of $\geq 20\%$ in the FEV1 or PEF during the first post-challenge hour, a delayed reaction causing a similar decrease in FEV1 or PEF after the first post-challenge hour, and a dual reaction as a combination of these two reactions. Cobalt and 20 common environmental allergens were scratch chamber tested until 1978 and skin prick tested (SPT) from 1979. Histamine hydrochloride (10 mg/ml) was used as a positive control. The concentration of cobalt chloride was 1 mg Co^{2+}/ml.

4.3.3 Cardiovascular studies

Questionnaire

Data on working history in the plant and earlier possible exposure to cobalt, lead, carbon disulphide, and arsenic were requested in the self-administered questionnaire. The reasons for changing work tasks or jobs and workplaces were also asked, as well as history regarding physical exercise, smoking, alcohol consumption, diseases diagnosed by a physician (cardiovascular and pulmonary diseases, diabetes), and medication. The questionnaire in 2006 additionally included questions about shift work and the level of stress.

There were 352 male workers (in 2000) who had been employed and exposed to cobalt for at least one year before leaving the factory. The 321 cobalt factory workers who were still living and the 318 ex-workers with a similar age distribution from the zinc plant were sent the same questionnaire as the workers in study groups, with an additional question regarding reasons for leaving the plant. Some 76% of the former cobalt plant workers and 51% of the former zinc plant workers responded to the questionnaire.

Clinical measurements, (excluding ECHO) were carried out by laboratory technicians in the mobile research unit of the FIOH.

Echocardiography

The transthoracic ECHOs were performed and analysed by a single experienced clinician without knowledge of the status of the examined persons (exposed/referent). Another cardiologist checked the results of the measurements. M-mode dimensions were normalised for body surface area. The left ventricular ejection fraction (EF) was calculated from the fractional shortening (FS). Left ventricular mass (LVMASS) was calculated according to the formula of Devereux et al. (152). Mitral and tricuspid flows were obtained with the pulsed Doppler sampler at the valve tips. Early diastolic filling velocity (E), peak atrial filling velocity (A), E/A ratio, E-wave deceleration time (DT), and slope were measured from the left ventricular filling recordings. Isovolumic relaxation time (IVRT) was measured using the technically better pulsed or continuous wave recording of mitral inflow and left ventricular outflow tract flow. In 2006, ventricular long-axis motion from the lateral and septal myocardium were recorded using pulsed-wave tissue Doppler imaging (TDI). Early diastolic myocardial tissue velocity (Em), diastolic myocardial tissue velocity after atrial contraction (Am), and their ratio (Em/Am) were recorded. Em deceleration time and slope were also measured. The E/Em ratio was calculated (153).

Blood pressure measurement and electrocardiography

Blood pressure was measured after 10 minutes of rest in a sitting position and after two measurements, the lower systolic and diastolic pressure and pulse were noted. A standard 12-lead ECG was recorded. The recordings were analysed independently by two experienced clinicians who both coded the recordings without knowing their origin (exposed/control). Coding was performed according to the Minnesota 1982 method (154).

Long-term ECG registration (in 2006)

Long-term ECG registration (24-h signal sampling) was recorded with Holter technics. The results were interpreted by a physician specialised in clinical physiology. Registrations were started at the beginning of the work shift and continued overnight until the next day. The participants marked their activities and symptoms during the registration period in a diary.

Laboratory tests

The serum lipid and glucose values and (in 2000) thyroid gland function (serum free thyroxine, S-T4-V, and S-TSH) and vitamin B1 deficiency (thiamine, B-B1-vit) were studied as possible confounding factors of cardiomyopathy and ischaemic cardiac disease. Gamma-glutamyl transferase (S-GT) and carbohydrate deficient transferrin (S-CDT) were analysed to study alcohol consumption. N-terminal atrial natriuretic peptide (S-ANP-N) was determined to complement possible findings of cardiac failure (only in 2000).

Statistical methods

The normality of the variables was checked, and logarithmic transformation was applied if the distribution of the variable was skewed. A regression analysis and an analysis of covariance (ANCOVA) were used to study the ECHO data. A forward/backward (2000/2006, respectively) stepwise regression analysis was performed on all the ECHO parameters so that age, exposure, and their interaction were always included in the model. Body mass index was included if the outcome variable had not been divided by body surface area, and heart rate was used if the outcome variable was time related. ANCOVA was also used to study the differences in the ECHO parameters between the various designated exposure groups. In the analyses, high and low exposure was determined based on being above or below the median mg-years of cobalt exposure (0.47 mg-years in 2000 and 0.55 mg-years in 2006). Age was included as a continuous variable in the ANCOVA analyses and categorised above and below 50 years and 56 years in the study in 2000 and in 2006, respectively. Independent factors, such as smoking (non-smoking vs current and ex-smoking), hypertension (as normal vs elevated (>140/90) or as diagnosed hypertension), and competing athlete status (yes or no), were included in the model as dichotomous variables. In some calculations the use of alcohol (weekly consumption over 20 doses of 12 g of alcohol or S-GT>80 or S-CDT>20) was included in the model as a covariate because it was considered a possible confounder. The ECHO values of the cross-sectional study in 2006 with the tissue Doppler device were analysed and adjusted for the 2006 confounders. Those covariates with significant associations with outcome variables remained in the model because they were considered confounders.

Statistical power calculations (requiring the power of at least 0.8 at the significance level of 0.05) were performed (in 2000) to assess the number of ECHO analyses needed in the study. Calculations were carried out in relation to the deceleration time (DT) and the isovolumic relaxation time (IVRT), which were considered to be the most important

outcome variables because of their ability to reflect the earliest changes in cardiac function (155). Calculations showed a need for 186 analyses altogether (62 in each group) when the differences between three groups in DT were studied, and a need for 180 analyses in IVRT, respectively.

The 95% confidence intervals (95% CI) were calculated for the differences between two percentages. The level of significance in ANCOVA was set at equal to 0.05, but exact p-values are reported.

5   RESULTS

5.1   Findings of the respiratory study

There were 140 workers, in total, who were still alive and had worked at least for 10 years at the Kokkola plant in cobalt powder or cobalt-compound production. Thirty-seven of the 54 former workers (69%) answered the questionnaire, and 25 participated in the clinical study. Of the 86 current workers, one did not wish to participate, so in the clinical study the group of exposed workers consisted of 110 men. Most of them were, or had been, process workers; some were or had been maintenance men and foremen. The ex-workers had left their jobs at the plant 0-15 years ago. All the workers in the exposed group had been exposed to cobalt or cobalt compounds, about 80% to nickel and nickel compounds, and about 50% to SO_2, H_2S, and NH_3 (Table 6). Thirty-six per cent of the workers in the exposed group had been slightly exposed to asbestos, mainly in the roasting department. Smoking, reported as the number of pack-years, was greater in the exposed group than in the control group (Table 7).

Table 6. Cumulative exposures of the workers (n=110) in the respiratory study.

Exposure, mg-years	Mean	Range	Exposure, ppm-years	Mean	Range
Total dust	19.4	0.1-38.0	H_2S	7.5	0.0-59.0
Co	1.0	0.1-4.6	SO_2	3.7	0.0-39.7
Ni	0.4	0.0-2.2	NH_3	27.0	0.0-187.4

Exposure time in years, mean 22.1, SD 7.8

Table 7. Characteristics and respiratory diseases and symptoms of the respiratory study groups.

Characteristics	Exposed group n=110	Control group n=140
Age (years)		
Mean (SD)	50.3 (6.0)	48.8 (5.1)
Height (cm)		
Mean (SD)	174.7 (5.7)	176 (5.2)
Work history (years)		
Mean (SD)	22.1 (7.8)	24.7
Agricultural work (%)	22	9
Asbestos exposure (%)	36	21
Smoking status (%)		
Current smoker	31.8	29.3
Ex-smoker	41.8	37.9
Non-smoker	24.5	32.9
Pack-years (smokers and ex-smokers)		
Mean (SD)	21.2 (13.8) $p<0.05$	15.8 (11.4)

Disease or symptom	Exposed group %	Control group %
Prevalence of reported respiratory diseases diagnosed by a physician		
Bronchial asthma	7.3	5.0
Chronic bronchitis	8.1	2.1
Pneumonias during worklife	5	1
Allergic rhinitis	2.8	2.9
Allergic alveolitis	0	1.4
Prevalence of respiratory diseases based on questionnaire criteria		
Suspected asthma	17.3 $p<0.01$	5
Suspected work-related asthma	14 $p<0.008$	3
Chronic bronchitis	8.2	3.6
Allergic rhinitis	8.2	15.8
Prevalence of symptoms		
Cough>3/12 months	9	6
Phlegm>3/12 months	21 $p=0.01$	9
Cough with wheezing	27 $p=0.04$	16
Dyspnoea with wheezing	23 $p<0.01$	8
Breathlessness on exertion*	24 $p<0.01$	9

Fisher's exact two-tailed test
*Shortness of breath when hurrying on level ground

57

5.1.1 Diseases and symptoms

There was no difference in the prevalence of reported asthma between the groups, but asthma based on questionnaire criteria appeared three times more frequently in the exposed group than in the control group (Table 7). Production of phlegm, cough with wheezing, shortness of breath with wheezing, and breathlessness on exertion were significantly more frequent in the exposed group than in the control group. In the analyses, the effect of age and smoking did not explain the differences. In the exposed group, exposure to any single chemical did not have a significant effect on increasing the risk of any of the studied respiratory diseases or symptoms. Ten of the 19 exposed workers with suspected asthma and suspected work-related asthma (4 and 15, respectively) reported chronic rhinitis. One new case of cobalt asthma and one case of allergic asthma were diagnosed in further examinations among all these (19) exposed workers with suspected asthma. Seven persons of the nine with chronic bronchitis in the exposed group were smokers; in the control group four out of five were smokers. There were no cases of allergic alveolitis in the exposed group. In the exposed group, six pneumonias were reported during adult work life; similarly, in the control group, two cases of pneumonia were reported.

5.1.2 Spirometry and diffusing capacity

Among the non-smokers, none of the measured lung function parameters differed between the groups. The FEV1, MEF50, and MEF25 values of the smokers in the exposed group were lower than those of the smokers in the control group (Table 8). In the analysis of variance, the difference in the MEF50 and MEF25 values remained when smoking was included as a covariate in the model. Occupational chemical exposure alone or in a combination had no significant effect on lung function.

Table 8. FEV1, MEF 50, and MEF 25 in the respiratory study, as the percentage of predicted values (Mean and SD).

Lung function variable	Exposed group		Control group	
	Non-smokers	Smokers	Non-smokers	Smokers
FEV1	97.1 (14.6)	88.7 (13.6)[a]	96.4 (14.6)	93.4 (13.0)[a]
MEF 50	93.3 (27.4)	71.7 (25.1)[a]	96.6 (24.2)	81.5 (21.9)[a]
MEF 25	98.7 (36.3)	71.0 (28.5)[a]	102.4 (45.9)	82.8 (31.3)[a]

Student's two-tailed t-test
[a]p<0.05 when comparing smoker groups

5.1.3 Chest X-ray

Only the exposed workers were examined. There was no profusion of small opacities higher than 1/1. Six out of 10 workers with a classification of ILO 0/1 had been exposed to asbestos. In the analyses, smoking and asbestos exposure significantly explained the profusion of small opacities. Three workers with a rating of 0/1 or 1/1 were further studied with HRCT: one of them had a normal finding, one was diagnosed with severe COPD, and one suffered from sarcoidosis.

5.1.4 Clara cell protein

There were no significant differences in the CC16 values between the study groups (Table 9).

Table 9. Serum Clara cell protein in the respiratory study (µg/l), Mean (SD).

Exposed group		Control group	
Non-smokers	Ex-smokers	Non-smokers	Ex-smokers
n=19	n=35	n=30	n=29
15.6 (5.3)	14.7 (5.9)	16.4 (4.7)	14.1 (4.4)

Data from the report to The Finnish Work Environment Fund (136)

5.2 Findings of the asthma study

All cobalt asthma patients except one were male (Table 10). Work rearrangements had been made quite early after the beginning of symptoms, but the time from the symptoms to the diagnosis of OA was 7.4 years, on average. Fifty per cent of the patients had experienced symptoms during working hours, 55% after the shift, and 32% at night. Dyspnoea had been the prominent symptom (in 100% of the patients), while wheezing (64%) and a cough (41%) occurred less frequently.

Table 10. Characteristics, symptoms, and results of the investigations of the occupational asthma patients.

Subjects, number	22	Results of investigations in FIOH n (%)	
Age at diagnosis, years (range)	45.8 (32–61)	Pulmonary function tests	
Gender; male, n (%)	21 (95)	Forced vital capacity<80%	3 (14)
Family history of asthma, n (%)	4 (18)	FEV1<80%	4 (18)
Duration of symptoms before	7.4 (0.1–17)	Hyperreactivity at diagnosis	
diagnosis; mean (years) (range)		No hyperreactivity	5 (23)
Smoking habits, n (%)		Mild hyperreactivity	7 (32)
Non-smoker	7 (33)	Moderate hyperreactivity	6 (27)
Ex-smoker	10 (48)	Severe hyperreactivity	4 (18)
Current smoker	4 (18)	Allergy testing	
Symptoms n (%)		Positive prick tests to one or	4 (18)
Dyspnoea	22 (100)	more common allergens, n (%)	
Wheezing	14 (64)	Positive prick tests to cobalt, n (%)	0 (0)
Rhinitis	10/21 (48)	Elevated total IgE value (>114 kU/l)	4 (18)
Cough	9 (41)		
Phlegm	3 (14)		
Eye irritation	1/18 (6)		

Atopy (SPT) was found in four (18%) of the patients, and SPT to cobalt were negative in all patients examined. Bronchial hyperreactivity was found in 77% of the cases. A total of 31 specific bronchial challenge tests were performed on the 22 patients. Of the reactions, 16% were of the immediate type, 61% delayed type, and 19% dual reactions. Eighteen per cent of the patients did not have any asthma medication at the time of diagnosis.

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

The incidence density of cobalt asthma was highest in the reduction and powder production department, where the cobalt exposure levels were the highest (Table 11). The shortest latencies were in the sulphatising roasting department, where the total dust, cobalt, and SO_2 levels were high. No cases of cobalt asthma were reported in the chemical department where irritant gases like SO_2, H_2S, or NH_3 were not needed or produced in the processes in addition to cobalt and nickel.

Table 11. Number of occupational asthma cases and exposed workers and exposure to cobalt and gases in different departments in 1967–1987.

	Cobalt asthma, n	Exposed* workers, n	Working time before onset of symptoms, years, median (range)	Cobalt exposure, mg/m³, median (range)	Gaseous exposures, ppm, mean
Sulphatising roasting	9	107	0.5 (0.1–6.0)	0.1 (0.006–1.0)	SO_2 1.4
Leaching and solution purification	5	99	7.5 (0.5–17.0)	0.03 (0.01–0.1)	H_2S 1.0 NH_3 3.5
Reduction and powder production	7	55	3.0 (0.1–11.0)	0.15 (0.1–0.4)	NH_3 1.0
Chemical department	0	44	-	0.12 (0.02–0.3)	-

One cobalt asthma diagnosed in 2003 (maintenance worker, variable exposure)

* Report to The Finnish Work Environment Fund (136)

5.3   Findings of the cardiovascular studies

In 2000, all of the 203 invited, exposed men participated in the study. From the control group, two persons did not want to participate. The characteristics of the examined groups and calculated mg-year values are given in Tables 12 and 13. Persons with congenital or acquired cardiac valvular disease (n = 14) and those with a history of myocardial infarction (n=2) were excluded from the ECHO analysis. Thirteen of these persons belonged to the exposed group, and three were controls. In 2006, 93 (85%) of the workers exposed to cobalt and whose ECHO results had been analysed in 2000 (n=109) were re-examined. Nineteen of them had stopped working before 2006, so they represented workers with past exposure in the analyses. Altogether, 49 (86%) of the 57 men who had been in the unexposed reference group and whose ECHO results had been analysed in 2000 were re-examined. One person with a history and echocardiographic signs of myocardial infarction was excluded from ECHO analysis in both groups.

The results are presented in relation to the cumulative amount of exposure only, because it was the most reliable and accurate method of assessing the exposure, and the other measures (recent vs past exposure, the length of exposure time to cobalt) did not show indication of association.

The common characteristics of the groups were very similar. In the original control group, more workers were or had been competing athletes than in the exposed group. When leisure-time sports activities were taken into account, there were no significant

differences in the amount of physical exercise between the workers of the exposed and control groups. Between 2000 and 2006, the participants in the exposed group tended to have increased their leisure-time sport activities, but not statistically significantly (p=0.065). On the contrary, the participants in the unexposed group had decreased their leisure-time sport activities, especially the duration and level of strain (data not shown). The BMI had increased significantly in the exposed group during the follow-up. Consumption of alcohol was more abundant in the control group, but the difference diminished slightly between the two studies. There was no significant difference in reported stress between the exposed and unexposed groups (data not shown). In the exposed group, 71% worked shifts, whereas 50% of the controls worked shifts (2006).

Table 12. Characteristics of the cardiovascular study groups in 2000.

Characteristic	Whole groups		Most exposed workers and age-stratified controls participating in the echocardiographic examination	
	Exposed group n=203	Control group n=94	Exposed group (n=122)	Control group (n=60)
Age (years) Median	45 (23–62)	44 (24–60)	49 (27–62)	49 (28–60)
Height (cm) Median	178 (165–193)	178 (164–196)	178 (165–193)	175 (164–192)
Weight (kg) Median	82 (58–142)	82 (62–133)	84 (59–142)	82 (67–118)
Work history (years) Median	20 (2–34)	25 (3–36)	25 (2–34)	26 (3–36)
Exposure time to cobalt (years)[a] Median	9 (1–34)		24 (1–34)	
Exposure to cobalt (mg-years) Median	0.18 (0.02–2.52)		0.47 (0.03–2.52)	
Non-smokers (%)	33.5	32.6		
Ex-smokers or smokers (%)	66.5	67.4		
Pack-year Median	7 (0–76)	6 (0–51)		
Alcohol, drinks/week Median	3 (0–20)	4 (0–20)		
Competing athlete status (%)				
No	84.7	75.0		
Now or earlier	15.3	25.0		
Leisure time sport activities (%)				
No, never	8.9	8.7		
Yes, two times a week or less	52.0	46.7		
Yes, at least three times a week	39.1	44.6		

[a] Regularly>0.01 mg Co/m^3

63

Table 13. Characteristics of the exposed and unexposed groups in the cardiovascular studies in 2000 and 2006.

	Exposed group (n=93)		Unexposed group (n=49)	
	2000	2006	2000	2006
Age (years) Median	50 (28–63)	56 (34–69)	50 (29–61)	56 (35–67)
Body mass index Median	26.5 (21.6–35.0)	27.2 (20.5–37.9)	26.5 (21.6–35.0)	27.1 (21.2–36.9)
Work history (years) Median	25 (2–34)	31 (8–40)	26 (3–25)	32 (7–41)
Exposure time to cobalt (years)[a] Median	23.0 (0–34)	28.0 (0–39)	–	–
Exposure to cobalt (mg-years) Median	0.45 (0.06–2.5)	0.55 (0.10–4.1)	–	–
Non-smokers (%)	29	33	33	37
Ex-smokers or smokers (%)	71	67	67	63
Alcohol (drinks/week) Median	3.0 (0–20)	4.3 (0–26)	6.0 (0–20)	5.0 (0–25)
Competing athlete status (%) No	91	85	79	88
Now or earlier	9	15	21	12
Leisure-time sport activities (%) No, never	5	3	4	8
Yes, two times a week or less	51	52	46	47
Yes, at least three times a week	44	45	50	45

[a] Regularly>0.01 mg Co/m^3

5.3.1 Diagnosed diseases and medication

There were no significant differences between the exposure group and the control group in the prevalence of reported cardiovascular diseases, diabetes mellitus, or pulmonary diseases, except asthma (and "other pulmonary diseases" in 2006) diagnosed by a physician (Table 14). The increase in physician-diagnosed hypertension was significant during the follow-up period: in the unexposed group, the prevalence of high blood pressure had almost doubled. The proportion of persons using antihypertensive or other heart medication had increased in both groups. The use of beta-blockers was more common in the unexposed group. Complaints of irregular heartbeats (arrhythmia) had increased in the exposed group, but the prevalence was at the same level in both groups in 2006.

Table 14. Prevalence of reported diseases, diagnosed by a physician, in the study groups of the cardiovascular studies in 2000 and 2006.

	Exposed group (n=93)		Unexposed group (n=49)	
	2000 %	2006 %	2000 %	2006 %
Coronary heart disease	2	3	4	4
Heart failure	0	0	0	0
Dilated heart	0	3	2	4
Heart arrhythmias	6	14**	21	16
Cardiomyopathy	0	0	0	0
Any other cardiac disease	1	3	0	0
Hypertension	23	32*	21	37**
Bronchial asthma	1	7	0	0
Chronic bronchitis	2	2	2	0
Other chronic lung disease	4	7	2	2

McNemar test: *$p<0.05$; **$p<0.01$

5.3.2 Electrocardiographic findings and long-term ECG registration

There were no significant differences in the ECG findings or conduction parameters between the exposure group and the control group. Abnormal results in the 24-h Holter registration appeared in 10.4% of the exposed and 9.7% of the unexposed groups. The exposed group had more ventricular extrasystolic (VES) beats than the unexposed group (mean 209, SD 1098 vs mean 114, SD 362, respectively), and the unexposed group had

more atrial extrasystolic beats (AES) than the exposed group (mean 216, SD 1296 vs mean 87, SD 392, respectively). Only one case of severe arrhythmia was found, and it had already been recognised in one of the referents.

5.3.3 Blood pressure and laboratory tests

Table 15 shows the results of the blood pressure measurements and the laboratory tests. Both systolic and diastolic blood pressure had risen in the exposed group in 2006 when the levels were compared to the results from 2000 ($p<0.05$ and $p<0.01$ respectively), but the differences in the changes in 2000-2006 between the two groups were not significant. In an ANCOVA analysis, the S-ANP-N values were the highest in the group with high exposure. The p-value was 0.008 for the exposure group effect and 0.017 for age. The p-value for the interaction of age and group was not significant (p=0.485). In 2006, the S-CDT mean was increased in the exposed group, and the difference in the changes between the groups was significant. The S-LDL-cholesterol mean had decreased significantly in the unexposed group, but the differences between the changes in the two groups between 2000 and 2006 were not significant.

Table 15. Blood pressure, heart rate, and laboratory test results in the study groups of the cardiovascular studies in 2000 and 2006.

		Exposed group (n=93)			Unexposed group (n=49)			
		2000	2006	Difference	2000	2006	Difference	[1]p-value
Systolic blood pressure, mmHg	Mean	135.2	142**	6.8	138.3	140.8	2.5	0.159
	SD	15.5	15.0	16.4	14.9	17.1	17.5	
Diastolic blood pressure, mmHg	Mean	87.7	90.1*	2.3	89.2	89.3	0.02	0.217
	SD	9.7	8.4	9.9	10.4	9.5	11.2	
Pulse/min	Mean	59.1	63.9**	4.8	58.0	60.3	2.3	0.173
	SD	8.2	10.5	10.3	9.6	10.7	9.9	
S-CDT (U/l)	Mean	1.5	1.6	0.09	1.6	1.3	-0.30	0.048
	SD	0.3	0.5	0.4	0.49	0.79	0.9	
S-GT (U/l)	Mean	50.4	52.8	2.40	35.5	41.7	6.2	0.482
	SD	56.4	47.6	29.9	15.5	31.7	27.7	
Serum LDL cholesterol (mmol/l)	Mean	3.6	3.4	-0.24	3.6	3.3*	-0.38	0.578
	SD	1.0	0.9	1.4	0.9	0.7	1.1	

Paired *t* test: *p<0.05; **p<0.001; [1]*t* test between the group differences

5.3.4 Echocardiography

In 2000, the left ventricular isovolumic relaxation time (IVRT) was longer in the highly exposed group than in the less exposed and control groups (Table 16). Both exposure

level and age contributed to the explanation of the variation in the IVRT, the values being shorter for younger people. The ratio of the peak early rapid filling wave to peak filling wave due to atrial contraction (E/A ratio) did not differ between the exposure groups. The E/A ratio was lower for older people. The deceleration time of the velocity of the early rapid filling wave (DT) was longer among the highly exposed subjects than among the less exposed persons or the controls. The left ventricular posterior wall thickness at diastole (LVPWD) was greater among the exposed workers than among the controls, as was the ratio between the wall thickness and the left ventricular diameter measured at end diastole [(IVSD+LVPWD)/LVEDD]. The interaction of age and exposure was not significant (p=0.06), but the effect seemed stronger for younger persons. The systolic parameters of the left ventricular function did not differ between the groups. In 2006, there were no differences in any parameter measuring heart volumes, wall thickness, or muscle mass between the exposed and unexposed groups. There were no differences either in the DT and IVRT values between the study groups. Only Am was lower in the low exposure group than in the control group. There were no differences in any of the ECHO parameters in 2000 between those who participated in 2006 and those who did not (data not shown).

5.3.5   Retired workers

Retired workers did not participate in the clinical examinations, but they were sent a questionnaire. Of these men, twelve workers (5%) had left their work in the cobalt plant due to some form of cardiovascular disease: 10 cases of coronary artery disease or myocardial infarction, one diagnosed case of heart failure, and one diagnosed case of cardiac arrhythmias. In four cases (2.5%), the reason for leaving the zinc plant had been some form of cardiovascular disease: three cases of coronary artery disease and one case of hypertension.

Table 16. Echocardiographic results in 2000 and 2006.

Variable	Exposed to cobalt ≥0.47 mg-year (n=55) Mean (SD)	Exposed to cobalt <0.47 mg-year (n=54) Mean (SD)	Unexposed (n=57) Mean (SD)	p-value Age*	Exposure group	Covariates
2000						
FS (%)	37.6 (5.1)	37.3 (4.2)	36.9 (4.5)	0.124	0.522	–
EF (%)	75.2 (6.2)	74.9 (5.2)	74.5 (5.2)	0.060	0.527	–
(IVSD+LVPWD)/LVEDD ratio	0.45 (0.09)	0.44 (0.06)	0.42 (0.05)	0.263	0.011	0.016 (bp)
IVRT (ms)*	53.3 (7.9)	49.1 (7.2)	49.7 (10.0)	0.022	0.010	0.009 (bmi))
E/A ratio*	1.33 (0.33)	1.41 (0.36)	1.37 (0.34)	0.041	0.398	0.002 (bp))
DT (ms)*	194.3 (32.1)	180.5 (28.2)	171.7 (28.5)	0.179	0.001	<0.001 (hr))

Variable	Exposed to cobalt ≥0.55 mg-year (n=47) Mean (SD)	Exposed to cobalt <0.55 mg-year 1(n=45) Mean (SD)	Unexposed 1(n=48) Mean (SD)	p-value Age*	Exposure group	Covariates
2006						
FS (%)	37.7 (4.1)	37.5 (5.2)	37.8 (5.9)	0.035	0.982	–
EF (%)	66.9 (5.3)	66.7 (6.8)	66.8 (7.1)	0.034	0.991	0.035 (bmi), 0.042 (alc)
(IVSD+LVPWD)/LVEDD ratio	0.40 (0.15)	0.39 (0.07)	0.38 (0.04)	0.018	0.737	–
IVRT (ms)*	66.9 (10.2)	68.5 (12.2)	69.6 (11.7)	0.115	0.545	0.002 (hr)
E/A ratio*	1.26 (0.24)	1.36 (0.33)	1.42 (0.33)	0.001	0.237	<0.001 (hr), 0.035 (bp)
DT (ms)*	187.4 (26.2)	183.4 (24.4)	193.9 (26.9)	0.019	0.278	0.003 (hr)
tissue E_m/A_m ratio	1.03 (0.27)	1.12 (0.34)	1.07 (0.30)	<0.001	0.325	0.017 (bp), <0.001 (hr)
E_mDT (ms)	93.1 (14.9)	90.7 (14.9)	94.2 (19.3)	0.104	0.635	–
E/E_m ratio	8.5 (2.5)	8.6 (2.2)	8.6 (2.1)	0.021	0.83	0.002 (bmi)

*Logarithmic transformation was made for the outcome variable before the analysis.

FS, fractional shortening; EF, ejection fraction; IVSD, interventricular septum (diastolic); LVPWD, left ventricular posterior wall (diastolic); LVEDD, left ventricular end diastolic diameter; IVRT, isovolumic relaxation time; E/A, ratio between velocity of early and atrial filling; DT, deceleration time; E_m, tissue early filling wave velocity; A_m, tissue atrial filling wave velocity; E_mDT, deceleration time. The diameters normalised for body surface area. Covariates in the model: exposure, age, and their interaction are permanently in the model. In addition, the following adjusting covariates have been included in the model (only the significant associations are shown): body mass index (bmi), heart rate in echo (hr), smoking, blood pressure>140/90 or earlier hypertension diagnosed by physician (bp), athlete sports, consumption of alcohol (alc). 1See "Errata" on the page following Publication IV

68

6 DISCUSSION

6.1 The main findings of the study

The respiratory study found that those exposed in the cobalt production had more asthma-like symptoms than those in the control group. The predictability of symptoms for clinical disease was weak even though in the further investigations one new cobalt OA was found. The lung function values of smokers were worse than those of non-smokers in both groups, and the deterioration in smaller airways was accelerated by exposure in cobalt production. No cases of lung fibrosis were found. Of the 22 analysed OA cases, 21 had occurred during the first two decades of the factory's operations, when the exposure to cobalt and gases, especially to SO_2, had been high. The clinical picture and the results of the studies fit an IgE-independent mechanism in the development of asthma, for which simultaneous exposure to gases could be an interacting additional factor. Bronchial hyperreactivity was found in 77% of the cases. For a large part of those affected, the symptoms remained long-lasting even after the end of the exposure. The logical, statistically significant but minor findings of the first cardiac examination, referring to a changed early diastole among the workers of the exposed group, were no longer detectable in the follow-up study. The common risk and lifestyle factors affecting heart function and its measurement had partly developed in different directions in the study groups, which could affect the changes of parameters measured.

6.2 Exposure

In the analyses of the results (in respiratory and heart studies), the unit of exposure is mg-year (or ppm-year) and those exposed are further divided into two groups according to the median exposure. The use of the mg-year (or ppm-year) as a measure of the exposure can accurately take into account the duration of the exposure, as well as working in different departments and short or longer breaks in the exposure. On the other hand, when the exposure is intense, clothing, skin, and hair are quickly dusty, and the exposure continues even during the breaks and after the shifts. Occupational hygiene measurements also do not consider working methods, clothing or other protection, smoking, washing, etc. (18,19).

Although the exposure measurements and the summaries were carefully performed by professionals, it is impossible to obtain accurate retrospective information on the level of exposure of an individual worker over a period of three decades for reasons set out above. So, the numbers are in practice an assessment. The factories were new in the 1960s and 1970s, as were the processes, so surprising leaks leading to exposure peaks must have occurred. Respirators were available, but they were more regularly used only in the powder production department and the chemical department before their use became mandatory in the first decade of this millennium. Biomonitoring was not carried out systematically for cobalt before the 2000s, and the main purpose of the measurements was to obtain additional information on the effectiveness of the occupational hygiene measures. The difficulty in assessing exposure is well illustrated by the wide variation in the urinary cobalt levels; the differences in results between workers working in similar conditions may have been many ten-fold. This phenomenon is not a problem just in biomonitoring the exposure to cobalt, because the systemic (body)uptake of different materials reflects the way the workers live and work (156).

In the statistical analyses, using the exposure group as a unit of the cobalt exposure was justified due to the uncertainties related to the exposure assessment described above. If the analyses had been based solely on individual exposure data, false single results would certainly have been obtained in the dose-response analyses. This would have been a problem especially in the cardiac studies, where exposure data should have specifically described the amount of cobalt absorbed into the body, but we had no such a systematic data available. In addition, especially in the cardiac studies, outcome variables were associated with several covariates/confounders and the variations measured were small, e.g. in the order of milliseconds. At the group level, on the other hand, the exposure magnitudes are obvious because the differences in exposure levels between departments have been clear and information on overall exposure levels from repeated measurements over decades is reliable. The non-exposed control groups ultimately confirmed that the potential effect of exposure could be detected in any case.

6.3   Respiratory study

Symptoms of asthma based on questionnaire responses were statistically more prevalent among the exposed workers. The respiratory flow rates MEF50 and MEF25, which refer to smaller airways, were significantly lower among the smoking exposed workers than among the smoking unexposed workers. There were no significant differences in the CC16 values between the exposed and nonexposed groups. One new case of cobalt

asthma and one case of allergic asthma were diagnosed in the exposed population. No cases of hard metal disease or fibrosing alveolitis were found.

The willingness of the current employees to participate in the study was good (99%). The activity of the ex-workers was lower, but health data was obtained from almost 70%. The number of the ex-workers participating in the clinical trials themselves remained small in the sense that the analyses of the results of the studies did not allow a reliable comparison between the potential effects of recent and old exposure. Reducing the number of required working years would not have significantly increased the number of participants in the study, as the recruitment of new staff had only begun gradually in the 1990s after a break of more than a decade. Cobalt workers have undergone an annual health control, so occupational health personnel have had an idea of the reasons for quitting the factory. On the other hand, symptomless outcomes such as mild lung fibrosis do not cause selection. In connection with the first heart examination, a survey was conducted for all those who had worked for more than a year, which also included a question about the reasons why the person had stopped working at the factory. Respiratory symptoms was the cause or part of the cause among cobalt workers in 6%, while the corresponding figure for zinc plant workers was 5%. Thus, the survivor bias of our study was small (85). Regardless, the healthy worker effect most probably had an influence on some results due to the selection of the workers at the pre-employment phase, as will be noticed in the connection with the results on allergic rhinitis and asthma.

It was not possible to assemble the whole control group from the same industrial area where the cobalt plant is located, because most of the workers in the area were exposed to airborne agents that could have an effect on the respiratory symptoms or functions. For example, the first stage of the zinc production process was roasting, resulting in SO_2 exposure among other things. In the cellhouse (electrolysis), workers were exposed to H_2SO_4 fumes. In the zinc plant, a corresponding respiratory study was performed simultaneously with the cobalt study and with the same group of referents (136). Therefore, the results of the zinc study could be used as supplementary information when evaluating, e.g. in which exposure combinations and at which exposure levels the findings did/did not occur.

The socio-economic distribution between the exposed group and the control group was not ideal. For example, smoking was clearly more common in the exposed group, as was the agricultural background, while leisure-time exercise activity was less frequent. These factors could have a negative effect on the respiratory system, and if the occupational exposure had a negative effect as well, the differences between the groups could increase

due to these confounders. On the other hand, confounders such as differences in pack-years could be taken into account in the statistical analyses.

In a study from a Belgian refinery (62), exposure to cobalt was of the same type as in Kokkola (although without exposure to SO_2), but the exposure levels were higher: at the time of the study, the geometric mean of the air measurements (breathing zone samples) was 0.125 mg/m³ and 25% of the results were over 0.500 mg/m³. The exposure time had been 8 years on average. In this study, the findings concerning symptoms were in line with our results. Asthmatic symptoms, wheezing, and dyspnoea were reported more often in the exposed group than in the control group, and wheezing was heard in the lung auscultation almost three times more often in the exposed group. Within the exposed group, the connection between the prevalence of dyspnoea and current levels of cobalt in the air was statistically significant in the logistic regression. Similarly, a dose-response relation was seen between the decrease of the FEVI/VC ratio and the current level of cobalt exposure. In our study design, this kind of connection between current exposure and respiratory symptoms and functions could not be tested. In another study (82), a weak dose-response effect between exposure and obstruction of the (small) airways was seen in non-smoking hard metal workers at very low levels of cobalt exposure (96% of the workers having exposure levels <0.022 mg/m³). These findings on respiratory functions in non-smoking workers were not noticed in our study. About ten years later in the same Belgian refinery mentioned, the exposure to cobalt had decreased to the level, or lower, of that in Kokkola (<0.1 mg/m³). In a new study (81), the exposure to cobalt (expressed as cobalturia) had a significant lowering effect on FEV1, but only in smokers (p<0.05), and no significant differences were seen in the lung functions at the different levels of exposure. A similar interacting effect of the exposure and smoking on the lung function had been seen earlier also by Roto (3). In addition, it is important to notice that smoking itself can increase exposure to cobalt (18). Contrary to our study, Andersson et al. (83) found with very low exposure levels in the hard metal industry (mean level of inhalable cobalt 0.003 mg/m³; urinary cobalt, median 33-44 nmol/l, range 3.4-220 nmol/l) a statistically significant correlation with blood CC16 and the highest tertile of the cumulative dust exposure compared to the lowest. Such findings emphasise the differences between exposure and its health effects in cobalt production in a plant like the one in Kokkola and, e.g. the hard metal industry.

In our study, symptoms of allergic rhinitis were more common in the control group than in the exposed group, and in the exposed group all asthma cases diagnosed by a physician were cobalt asthma cases. These two findings fit well with the background of the pre-employment selection of the workers, when individuals with a known atopy, in particular associated with respiratory symptoms, were excluded from cobalt production jobs. Thus,

the tendency to develop common allergic asthma or rhinitis was possibly lower in the exposed subjects than in the referent workers. This phenomenon has also been seen in some other studies in workplaces that have used the same recruitment principles (81,82,83). In our case, the practice did not "protect" the cobalt workers from acquiring OA, as there were slightly more cases of asthma than in the reference group. In Kokkola, hay fever was excluded from the exclusion criteria of the workers in the early 1990s.

In the cobalt group, suspicions of asthma, based on questionnaire criteria, were mainly suspicions of work-related asthma. In addition, most of the cobalt-exposed workers with asthmatic symptoms also had symptoms of rhinitis, which may be a risk factor for the development of asthma and is often seen preceding OA, especially if the exposure has been to some HMW agent (158). Already in the 1970s, Roto (3) had found in his study, at the same plant, that compared to the referents, the exposed group of cobalt workers had a significantly greater chronic production of phlegm and wheezing. The reported respiratory symptoms were not associated with lower ventilatory capacity. Additionally, in this aspect our results were similar, as was the fact that no single occupational agent appeared to have an additive effect on symptoms. In principle, it is possible that a poor correlation between abundant symptoms and decreased lung function values could be due to some kind of selectivity, but we did not find any such signs. In the context of the occupational clinical work, it appeared that workers often found the cobalt powder to be very irritating to the respiratory tract, even after the working day. The Tuohilampi survey asked (142), e.g. whether there had ever been a cough associated with wheezing or if there had ever been shortness of breath associated with wheezing. In other words, a one-time experience alone provided a positive answer to these questions, so suspicion of illness in that respect could arise unnecessarily easily. In this study, the predictive value of the survey was quite weak: among the 19 suspected cases of asthma in the cobalt group, two cases of asthma were found upon further investigation, and no new asthma was found in the zinc group (28 suspected asthma cases). Our findings contradict the results from a large Finnish study among young university students (159). Today, it is known that questions about asthmatic symptoms that are better on days away from work have a better sensitivity for validated OA compared to asking about deterioration at work, and the sensitivity is enhanced by asking about symptoms improving on holiday (160). The picture of a large number of possible work-related asthma cases provided by the survey did not materialise after our study either, as to our knowledge, only one case of cobalt asthma has been reported at the cobalt plant since 2003. Regardless, symptom-based questionnaires are suitable for screening also in workplaces like in the Kokkola plant because of their high sensitivity (159).

The fact that serum concentrations of CC16 in non-smoking (including ex-smokers) cobalt-exposed workers and referents were at the same level may suggest that exposure in cobalt production did not cause respiratory damage resulting in dysfunction or the damage of nonciliated bronchial cells, in particular of Clara cells (87). These cells are sensitive to the effects of toxic factors, so the same conclusion may apply to other, more resistant cells.

No cases of lung fibrosis were identified in our study. This result is congruent with the results of Swennen et al. (62). At no point in the process of cobalt production are similar methods used as in the processes of powder metallurgy, so the development of a disease such as hard metal disease is very unlikely in practice (89).

6.4   Asthma study

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

The strength of our study is that we were able to find all the data pertaining to the cases, as the closer investigation of possible OA, including SICs for cobalt, were centralised at the FIOH. Another strength of this study lies in the regular occupational exposure measurements performed in the cobalt plant and which describe the exposure levels in different departments. Also through Roto's research (3), accurate information has been available about the conditions of the 1970s in the entire factory area, the early symptoms and findings of the diseased employees, and the arrangements for examinations and follow-up.

The weakness of the study is the long time-span, during which the methods of SICs changed, influencing the variety of agents used in the provocation tests. However, the provocation tests were always performed at the FIOH following the best practice of the time. The exact incidence density of cobalt asthma in different departments is difficult to calculate, because it is no longer possible to check the exact yearly number of workers

per department, but the magnitude of the differences between the departments is correct.

As far as we know, no OA cases caused by cobalt have been reported from cobalt production in recent years. In a Belgian refinery (62,81), exposure to cobalt induced clear acute responses on the respiratory symptoms, auscultation findings, and lung functions, but not the level of clinical asthma, and no cases of cobalt asthma had been detected at least until 2001. This can highlight the role of SO_2, the exposure to which in Kokkola was high, but which was absent in Belgium. Compared to our study, the picture of cobalt-induced OA has been very different in some studies, where in addition to cobalt, there was also exposure to tungsten (161) and/or chromium in connection with alloys like stellite (containing i.a. cobalt-chromium) and hard metal. In the case series study among stellite workers (Table 3) (121), the median value of urinary cobalt (2.6 μg/l) was just slightly over that of the general population; 75% of the patients had positive SPTs to cobalt chloride (none did in our study) and six of seven asthmatic reactions after positive SICs to cobalt chloride were immediate (including dual). On the other hand, in a study of Shirakawa et al. (162), the findings were very similar compared to the findings of our study: seven of eight hard metal workers with suspected cobalt-induced OA showed non-specific bronchial hyperreactivity, six had late (including dual) reactions in positive bronchial challenges to cobalt chloride, and SPTs with cobalt chloride were negative, but in four patients signs of specific IgE-antibodies to cobalt conjugated human serum albumin (specific RAST) were found. At the FIOH, cobalt IgE-antibodies were not examined due to the lack of reliable specific tests.

In our study, responses after positive SICs to cobalt were predominantly late or dual, and patients often experienced symptoms after the working day and at night. Both of these findings fit well with the clinical picture of OA caused by IgE-independent sensitiser (107), as well as the fact that all cobalt SPTs were negative. According to this, cobalt and its compounds at the Kokkola cobalt plant seem to belong to the group of LMW asthma inducers. Two of the OA patients were tested also with nickel sulphate with negative results.

All but one cobalt asthma case developed during a 20-year period (1966-1986). During these years, there were no major changes in the exposure levels at the cobalt plant. There had been no need to hire new workers in the 1980s. This may be part of the explanation as to why new cases of asthma did not occur after 1986: most workers with a predisposition to asthma had already fallen ill with it, and the remaining workers would not get the disease, especially when the exposure to SO_2 was decreasing. This idea is supported by the observation from the sulphur plant (see section 4.1). When Roto (3)

collected data for his case-referent study on asthma from the period 1969–1977, he found 15 asthma cases that had worked at the cobalt plant at the time of falling ill, and respectively only one case of asthma among the workers of the sulphur factory (the cobalt plant had about 220 employees in 1977 and the sulphur plant about 160). In the early 1960s, the sulphur plant was the only workplace in the area in question, so in case of illness or severe symptoms, the workers had no other option but to resign from the job. No health data are available for those years. It is possible that concerning the remaining workers at the cobalt plant in the 1980s, a similar healthy worker survivor effect was seen as at the sulphur plant in the 1970s.

The operation of the cobalt roasting department ended in 1987. SO_2 exposure decreased in the whole industrial area, but for other gases exposure continued and exposure peaks occurred. The role of gases in the development of asthma is partly unclear. The highest incidence of asthma was in powder production, with exposure to cobalt powder and the highest level of cobalt exposure. The highest number of OA cases occurred in the cobalt roasting department, where the workers were exposed to high levels of SO_2 and cobalt mainly as cobalt sulphate. In this department, the workers had by far the shortest mean exposure time before the onset of asthma symptoms. Especially among the first cases of suspected cobalt asthma, the disease was typical in the way that the symptoms disappeared when off work, but returned when back at work (3). This contradicts the idea that SO_2 had been the real cause of asthma, as IIA is not typically characterised by such a variability (104). In addition, no OA had been reported in zinc roasting (see section 6.3), although the exposure to SO_2 there was at the same level as in cobalt roasting (range 0.2–5 ppm and 0.1–15 ppm, respectively), and exposure peaks occurred. The average number of employees were at the same level in both roasting departments. By 1977, 15 cases of asthma had been reported at the cobalt plant (3), but only six of them had a positive SIC with cobalt. Thus, it is not impossible that among the nine other patients, IIA cases could have occurred, mainly due to the exposure to high levels of SO_2 (163).

In Kokkola, the lowest levels of cobalt exposure have been in the leaching and solution purification department, the mean levels being from 0.013 to 0.019 mg/m³, but peaks up to 0.1 mg/m³ have been measured. These levels have not been low enough to protect the workers from getting cobalt asthma.

Strong evidence has shown that the early diagnosis of OA may lead to an improved outcome (164). In our study, the time from the symptoms to the diagnosis of OA (at the FIOH) was 7.4 years on average and over 80% of the patients used asthma medicines, meaning that many of them had a chronic disease already at the time of OA diagnosis.

From 1966 to 1977, the plant physician observed one or two new patients with bronchial asthma annually (3). Because cobalt was suspected to play a role in the development of symptoms (2), the patients were remitted to further medical examinations and transferred to another job in which they were no longer exposed to cobalt. Only since the study by Roto (3), the practice has been to confirm the diagnosis of OA with examinations, including a SIC test, at the FIOH. Before this, confirming the diagnosis of OA was not considered fundamental, as transferring workers elsewhere seemed to be sufficient. This is one reason for the long delay before the exact diagnosis of OA, at least in the 1960s and 1970s.

If a worker continued to work at the factory site after asthma was diagnosed, he continued to be exposed to gases that spread from the processes and pipelines into the environment, so the risk for further deterioration of the asthma or the development of e.g. chronic obstructive pulmonary disease was increased (114). Exposure to dusts also continued from various raw materials imported into the area as well as from by-product residues stored in the area. It was in practice impossible to completely avoid exposure to cobalt. Cobalt drifted to different parts of the factory area, e.g. via vehicles, equipment, clothing, etc. In the 1970s, two of the asthmatic cobalt workers were re-exposed to cobalt accidentally, 7 and 8 years after removal from cobalt exposure (3). After the exposure, both workers experienced the typical clinical symptoms of asthma. They were examined at the FIOH and had a positive result in the SIC to cobalt chloride. Many of those who had completely stopped working in the factory area ended up in their former jobs in agriculture with exposure to animal epithelium, grain dust, or mouldy hay. Thus, in many ways, the conditions were not optimal for the improvement of asthma symptoms. A follow-up study at the FIOH 6 months after the OA diagnosis found that the symptoms had persisted in about half of the subjects, with hyperreactivity having decreased in only one of the subjects but having increased in four. The first patients who were confirmed as having cobalt asthma in the late 1970s did not participate in a follow-up examination 6 months later. This was understandable, because these workers had been away from direct cobalt exposure for several years at most, so a new study only a few months later would not have described any new situation or the effect of any intervention. After the late 1970s, a 6-month follow-up examination at the FIOH was performed, so in our study data the results of bronchial hyperreactivity testing, for example, represent patients with OA in a more acute phase.

An Italian study found that in cobalt asthma patients, symptoms and lung functions improved faster than methacholine hyperreactivity (165). Asthma symptoms but not lung functions may improve after reducing exposure, but elimination of exposure can improve both symptoms and lung functions in patients with OA induced by LMW

agents (110). The practice of rejecting applicants who had a history of asthmatic symptoms or asthma in the pre-employment health check was well grounded at a time when it was possible to be significantly exposed to SO_2, because asthmatic, non-allergic subjects are known to be much more sensitive to SO_2 than non-asthmatic, non-allergic subjects (166,167). In addition, asthma and associated bronchial hyperreactivity could have been worsened by the irritation of the respiratory tract (168), observed in particular with cobalt powder. As such, the current view on atopy is that it has only a weak positive predictive value for sensitisation to LMW agents and OA (160).

In the Finnish Registry of Occupational Diseases (133), three cases of OA caused by cobalt were registered nationwide in 2005–2018. Only 14% of the urine cobalt analyses performed by the FIOH in 2018 exceeded the current action limit of 130 nmol/l (169), which is estimated to correspond to the current HTP value of 0.02 mg/m³. The changes have been remarkable, compared to e.g. the Kokkola plant's results from the 1990s. Since 2003, one new cobalt asthma case has been found in Kokkola's cobalt production. The cobalt plant now employs a new generation of workers, so the healthy worker survivor effect does not explain the current good situation. The explanation must be the reduction in exposure thanks to technical progress in production processes and more effective protective practices. Exposure to gases has also decreased. According to the information received from the factories, the exposure limit (UCo 130 nmol/l) is adhered to, and if the worker's result exceeds the limit, corrective measures are sought with the occupational health service.

6.5 Cardiovascular studies

Study in 2000

Two of the ECHO parameters, measuring early diastole, were associated with cobalt exposure. In the higher exposure group, the left ventricular isovolumic relaxation time (IVRT) and the deceleration time of the velocity of the early rapid filling wave (DT) were prolonged, indicating altered left ventricular relaxation and early filling. The changes in the left ventricular posterior wall thickness at diastole (LVPWD) seemed to support these findings.

Study in 2006

The results of the study in 2000 could not be repeated in 2006. No differences were found between the exposed and unexposed groups for any of the ECHO parameters in

2006. There were no significant differences in the laboratory values, the ECG parameters, or the results of the Holter registration of the exposed and unexposed workers.

The study in 2000 was the first to have a large, occupationally exposed study population and to use ECHO to assess the possible effects of cobalt on cardiac function. The cobalt plant and the zinc plant, from which the controls were taken, had both been units of the same corporation. Therefore, the employees had been recruited using similar criteria, for example, by using the expertise of the company's occupational health professionals. Some 98% of the controls and all the workers in the exposed group participated in the study. The characteristics of the groups, including the measured confounding factors of cardiomyopathy and ischaemic cardiac disease, were very similar. The health reasons for leaving the job were equally distributed in both groups of retired persons. In our studies, the same observer performed all the ECHO measurements. As the intra-observer errors are lower than those between the two observers (170,171), and because the inter-observer coefficients of variation in our reproducibility study were moderate, the results of the ECHO measurements can be considered reliable. The gathering of a control group of zinc plant workers proved to be a minor problem in the 2006 survey, when the age group was taken as the stratum and when the size of the control group remained at the acceptable minimum in the 2000 survey due to the different age structure of the workers in the two plants. The smaller-than-expected size of the control group in 2006 weakened the strength of the study. There was a surprising increase in the number of reported asthma cases in the exposed group – from one to seven – between 2000 and 2006 (Table 14). It is possible that workers had gotten a false perception of having asthma as they were invited to further examinations after the respiratory study in 1999.

We studied those with recent or past exposure and those with cumulatively high or low exposure separately. Since cumulative exposure becomes higher with age and several ECHO parameters are age-related, we used age limits (i.e. workers under and over 50 years in 2000 and 56 years in 2006, respectively) similar to those used by the European Study Group on Diastolic Heart Failure (172). A stronger basis for exposure assessment, compared to the air measurements, would have been systematically collected biomonitoring data (on urinary cobalt) (80), but we had no such data available.

In both studies, although there were clear differences in the results between the study groups in terms of the type of arrhythmias, the findings were not considered significant by the specialists in cardiology and clinical physiology in assessing myocardial function. The ECHO results in 2000 were consistent in the number of outcome parameters. In IVRT and DT, both of which describe early diastole but a different phase in it, the

workers of the exposed group had worse values than the workers of the control group, and the amount of cumulative exposure was reflected in the differences between the two exposed groups. Similar to this was the left ventricular posterior wall thickness at diastole (LVPWD). This parameter describes the same diastolic phase as the left ventricular diastolic internal diameter in Lantin et al. (80). In this Belgian study, the parameter seemed to reflect the recent exposure to cobalt (estimated by urinary cobalt concentration on the day of ECHO). Since the observed phenomenon is reversible, it must be related to the mechanism of action of cobalt, in which the current amount of cobalt in the body (or in the heart muscle) has a direct effect. Cobalt is a divalent cation similar to calcium and it has been known to compete with the transport of Ca^{2+} into cardiac myocytes (36). This kind of possible acute effect of cobalt could not be tested in our study set-up.

In 2006, all the participants were re-examined (ECHO) by the same cardiologist using the same conventional methods as in 2000, but also tissue Doppler imaging (TDI) was used. Therefore, the results in 2006 have been analysed as a new cross-sectional study design using similar statistical models as employed in 2000. The participation rate was high (85% and 86% in the exposed and unexposed groups, respectively). The weakness of the study was the small size of the control group, and we had no accurate personal health information on those who did not participate in the follow-up. According to the information from the occupational health centre, no clinical cases of cardiomyopathy were found in this factory during the follow-up period. In addition to the health data from the questionnaire, we used the results of the laboratory tests as background variables in assessing the possible changes in the lifestyle profiles of the groups in the follow-up. These test results were in concordance with the questionnaire results. There were no differences in any of the ECHO parameters in 2000 between those who participated in 2006 and those who did not. Thus, there does not seem to be a remarkable selection bias.

Contrary to the previous ECHO findings, in 2006 we found that DT and IVRT were similar in the exposed and unexposed groups. In the 2006 results, the use of the tissue Doppler, when adjusted for confounding variables, did not show any differences between the exposed and unexposed groups. The new results were in good agreement (except for left ventricular posterior wall thickness at diastole/the left ventricular diastolic internal diameter) with those obtained in the Belgian cobalt production plant (80). The researchers there concluded that it is unlikely that exposure below the level of 15 µgCo/l urine (255 nmol/l) could have any significant effect on inducing dilated cardiomyopathy. In our study, no significant differences were found between the exposed and unexposed workers in the laboratory values, ECG parameters, including

heart rate, or Holter registration. These findings support the no-effect results of cobalt exposure found by the ECHO.

In the questionnaire data, background factors, such as lifestyle habits, had changed in both groups during the follow-up. The BMI had increased in both groups, and the use of alcohol was more common among the unexposed participants. The exposed participants had increased their leisure-time sport activities, while unexposed participants had decreased such activities. It seemed that the lifestyle habits of the unexposed group tended to have changed more in an unhealthy direction compared to the exposed group. Possibly the largest effect on heart function was due to hypertension and its medication. The unexposed group used more beta-blockers as antihypertensive medication compared to the exposed group (18% vs 11%). Many of the ECHO variables are dependent on hypertension and heart rate, and, therefore, we adjusted the variables to both factors in the analysis. It seems likely that even if cobalt exposure has a small effect on heart function, it is unlikely that this effect can be demonstrated reliably in a middle-aged male population with many changing risk factors for cardiovascular diseases and medication affecting heart function.

Findings from patients with metal-on-metal hip prostheses and from other sources have shown that healthy individuals can tolerate very high blood cobalt levels (up to 300 μg /l) without falling ill (45). Such levels are impossible to reach in appropriate working conditions. Unice et al. showed that an exposure level of 0.1mg/m³ (five times the current HTP for 8h/d and 5 d/w) raised the blood cobalt level to 5-10 μg/l (6).

In these cardiovascular studies, our aim was not to find illnesses. The clinical appearance of cobalt cardiomyopathy requires the existence of one or more co-factors, especially a low-protein diet, thiamine deficiency, alcoholism, or hypothyroidism (76). The results of our studies cannot confirm that occupational exposure to cobalt has no relevance to cardiovascular health, as the effect of age and other risk factors on it increases. If there is an effect, monitoring of prosthetic patients could be a key in detecting it, as these patients are usually elderly and their exposure to cobalt is continuous.

7   SAFETY AND HEALTH AT WORK

In Finland, the employer has the duty to take care of the health and safety of employees at work, based on the Occupational Safety and Health Act. Employers and employees must work together to maintain and improve occupational safety in the workplace. The basis for the health and safety of employees is risk assessment. The employer must identify the harms and hazards arising from the work, assess the risks, and make improvements as required. The employer also has the duty to submit the necessary information about the workplace and workload factors to the occupational health care service for the workplace survey. The workplace survey includes proposals on how to improve working conditions and promote work capacity. The employer is responsible for implementing the proposals made by the occupational health care service. In addition, the workplace survey includes, for example, an assessment of the need for employees' health examinations in work that presents a special risk of illness. An initial health examination shall be performed in the work that presents a special risk of illness, within one month after the start of the work at the latest. The pre-employment examination is given to establish whether the employee has any deformity, injury, illness or sensitivity which might get worse by the work in question or which prevents the employee from performing that work. Regular health monitoring by the occupational health care service shall be provided for employees exposed to factors causing a special risk of illness in their work. The purpose of regular health surveillance is the early detection of adverse health effects and possible work-related diseases, and the measures needed for prevention of further risks.

Implications and recommendations for prevention of cobalt related occupational health hazards

Occupational cobalt exposure is known to cause asthma, interstitial lung disease, and contact dermatitis. Individual susceptibility contributes to the development of these immunological diseases, therefore, there is no exact exposure level that determines whether the diseases will develop. On the other hand, as a result of diminished levels of exposure, a clear positive development can be seen in the Finnish statistics, especially in the incidence figures for cobalt asthma. The respiratory health effects of cobalt seem to depend largely on the existence of other possible exposures occurring simultaneously, particularly exposures to gases or certain other metals. The impact is very different if the

worker is exposed during the production or use of, for example, hard metals or stellite compared with exposure to cobalt powder or cobalt compounds only.

The methods for exposure-based health examinations concerning cobalt are feasible: individual exposure can be measured accurately by monitoring urinary cobalt concentrations, and the possible respiratory and dermal effects can be found reliably and examined further.

The following recommendations are based on the observations made in our studies and other information that has been discussed in this work. The recommendations only apply to matters related to health and the prevention of factors that may adversely affect it.

1. Cobalt is only necessary for humans as a part of vitamin B12; other cobalt intake is unnecessary and if the exposure causes health effects, the effects are mainly negative. The main goal of occupational health and safety measures must be to prevent or minimise the exposure.

2. Cobalt is absorbed into the body through the respiratory tract, the gastro-intestinal tract, and the skin. Protection from exposure through all these routes is crucial, so the employer must take care that the cleaning of the workspace and other premises, the clothing of the employees, washing practices, and the use of protective equipment is up-to-date with instructions and control.

3. Smoking should not be allowed in the production premises. Employees must be aware that smoking increases exposure and that exposure in cobalt production intensifies the harmful effect of smoking on lung function. Occupational health care should help and encourage employees to stop smoking.

4. Exposure does not only occur in production facilities, but also in break areas and more generally in the factory area, depending on how emissions, e.g. from raw material warehouses, are controlled. A responsible employer recognises and acknowledges its responsibility for the entire production chain, including abroad.

5. Individual exposure should be monitored by biomonitoring (urinary cobalt). In assessing the results, occupational health care needs a good understanding of the complexity of the exposure and the toxicokinetics of cobalt. The subjects are given feedback on the results, which encourages them either to maintain a good standard or to change things that need to be corrected. In an established situation, annual or even

less frequent measurement is sufficient. Proper exposure monitoring also promotes future research projects.

6. In the pre-employment examination, the main focus is on the health of the respiratory system and the skin. The examination should include a sufficient examination of the health history, general examination, and spirometry (always performed using a bronchodilator) for persons with asthmatic symptoms at school age or later. A person with active asthma is poorly suited to the conditions in cobalt production. Atopy in itself is not an obstacle to start working, neither is a history of childhood asthma, but especially in the early stages of career, the monitoring of health should be more frequent.

7. Under normal circumstances, annual periodical health examinations (in addition to biomonitoring) are not necessary. The examination can be replaced by surveys, and employees must have sufficient knowledge of the symptoms (such as improved respiratory symptoms after being away from work or new, long-lasting rhinitis) for which they need to see a doctor. The interval between regular check-ups can be, for example, 3–5 years, and they should include spirometry for workers with symptoms indicating possible asthma or occupational rhinitis. Spirometry should be considered for smokers. Cobalt exposure does not cause a need to perform health checks on the cardiovascular system.

8. Occupational health care must have good capabilities for conducting basic examinations on the respiratory system and organising further investigations. If occupational asthma is suspected, the exposure should be stopped at the latest after workplace peak flow measurements, and an occupational health physician should refer the suspected case to the FIOH or to specialised care for further evaluation without delay.

9. When changing the provider of occupational health care services, the employer must ensure that the health information concerning employees is transferred in an appropriate manner, along with the principles and practices used in the monitoring of the workers.

8 CONCLUSIONS

At the time our epidemiological studies were carried out, the average exposure levels in the air measured for cobalt and its compounds were slightly under the former HTP value of 0.05 mg/m³ and before that, the levels had been mainly somewhat higher.

Exposure in the cobalt refinery caused occupational cobalt asthma but no other chronic respiratory diseases. Among the exposed workers, asthmatic symptoms, especially dyspnoea and cough with wheezing were common, as well as rhinitis, but the predictive value of the symptoms for clinical asthma was weak. Exposure seemed to have an interacting, enhancing role with smoking in the deterioration of respiratory function.

The clinical picture and the results from the examinations of the 22 cobalt asthma patients fit an IgE-independent mechanism in the development of asthma. Irritant gases, especially SO_2, most probably had a central role behind the abundance and severity of asthma cases. For many patients, cobalt-induced asthma appeared to be a chronic disease.

The ECHO findings were minor and variable, and no signs of cardiomyopathy were found either with other cardiovascular examination methods. It seems likely that even if cobalt exposure has a small effect on the myocardium, this effect cannot be demonstrated reliably in a population with many changing risk and lifestyle factors affecting heart function and its measurement. Cardiomyopathy is a severe disease with obvious functional and pathological changes, so it is unlikely that minor, variable findings would be a preceding sign of a serious cardiac illness.

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10 ORIGINAL PUBLICATIONS

PUBLICATION
I

Respiratory health of cobalt production workers

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Respiratory Health of Cobalt Production Workers

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Background *Cobalt production workers are exposed to metallic cobalt and nickel and their compounds and to different irritant gases. The aim of our study was to determine whether long-term exposure is associated with an increased occurrence of respiratory symptoms and findings or diseases, other than asthma, which is a known hazard, among cobalt processing workers.*
Methods *The study population was comprised of 110 current and former cobalt workers who had worked more than 10 years in a cobalt plant. The reference group consisted of 140 unexposed workers. All the participants were men. The analysis was based on exposure history, pulmonary function, chest X-ray findings, and symptom questionnaires.*
Results *Symptoms of asthma based on questionnaire responses were statistically more prevalent among the exposed workers. The respiratory flow rates MEF_{25} and MEF_{50}, which refer to smaller airways, were significantly lower among the smoking exposed workers than among the smoking unexposed workers. The causative factors of these symptoms and pulmonary function changes could not be determined by the study. One new case of cobalt asthma and one case of allergic asthma were diagnosed in the exposed population. No cases of hard metal disease or fibrosing alveolitis were found.*
Conclusions *No chronic respiratory diseases, except asthma, were found among cobalt production workers in this study.* Am. J. Ind. Med. 44:124–132, 2003.
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KEY WORDS: cobalt exposure; cobalt production; respiratory symptoms; respiratory disorders; pulmonary function; chest X-rays; occupational asthma; hard metal disease; fibrosing alveolitis

INTRODUCTION

In different phases of cobalt production, workers are exposed to metallic cobalt and nickel and their compounds and also to sulfur dioxide, hydrogen sulfide, ammonia, and in

some work tasks to asbestos. In addition to the irritant effects of these agents on airways, cobalt and nickel may cause asthma in exposed workers [Roto, 1980; Shirikawa et al., 1989; Taylor, 1994]. The literature indicates that metallic cobalt or cobalt sulfate are the most plausible causes of cobalt asthma [Cirla, 1989]. Cobalt has a role in the development of diffuse interstitial lung disease, hard metal disease, but epidemiological data indicates that pulmonary fibrosis occurs only among hard metal and diamond workers where exposure involves both cobalt dust and other components [Barceloux, 1999].

A cross-sectional study of refinery workers exposed only to cobalt suggests that exposure to other dusts (e.g., tungsten, titanium, iron, silica, diamond) in the hard metal process is necessary to produce the clinical picture of pulmonary fibrosis [Swennen et al., 1993]. In the same study, the workers complained of dyspnea and wheezing more often than

workers in the control group. In Roto [1980] of a Finnish cobalt plant, the risk of asthma was increased. Exposed workers had wheezing as an indicator of bronchial irritation more frequently than controls, but there were no differences in the prevalence of chronic bronchitis.

Cobalt production is a known risk for asthma. Whether cobalt and other exposures in cobalt production cause other long-term changes in the lungs such as decreased lung function, restriction, decreased diffusion capacity, or lung fibrosis, is not yet known with certainty. The purpose of this study was to determine which respiratory effects and symptoms are associated with long-term (at least 10 years) exposure in cobalt production.

SUBJECTS AND METHODS

The cobalt plant of this study is located in Kokkola on the western coast of Finland. This plant is the one and only Finnish cobalt plant studied also by Dr. Roto [Roto, 1980].

STUDY POPULATION

All the workers who had ever worked in cobalt-powder or cobalt-compound production for at least 10 years were invited to participate in the study. They were all men; 88 of the 142 workers were still working in the plant. Persons who had worked in other metallurgic plants were excluded. Because welding can affect lung function, those who had regularly welded 6 months or more were also excluded (two persons). One current and 29 former workers did not wish to participate.

The reference group consisted of 76 plant employees (stockroom/store men and 68 white-collar workers) who had worked at least 10 years without exposure in cobalt production or to other irritative agents (e.g., welding fumes) and 64 male blue-collar maintenance workers of the city of Kokkola, who had worked at least 10 years, but not in the cobalt factory, and who had not been exposed to harmful dusts or fumes (e.g., from welding).

EXPOSURE

Between 1966 and 1987, cobalt powder was produced from pyrite ore concentrate. Thereafter cobalt powder, inorganic cobalt and nickel compounds have been produced using byproducts of the metallurgic industry as a raw material. The flow sheet of the processes is given in Figure 1. After changes in the process in 1987, workers were not exposed to sulfur dioxide anymore and exposure levels to cobalt decreased slightly.

In the sulfatizing roasting, dust in the ambient air has been shown to contain 15–20% iron, 1% zinc, 0.4% cobalt, and 0.2% nickel, whereas in the leaching building dust consisted of metal sulfides and sulfates. Cobalt and nickel
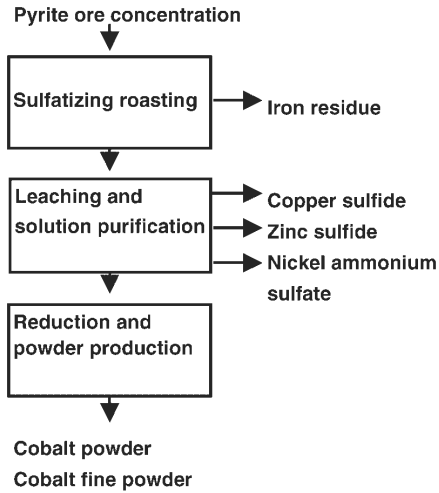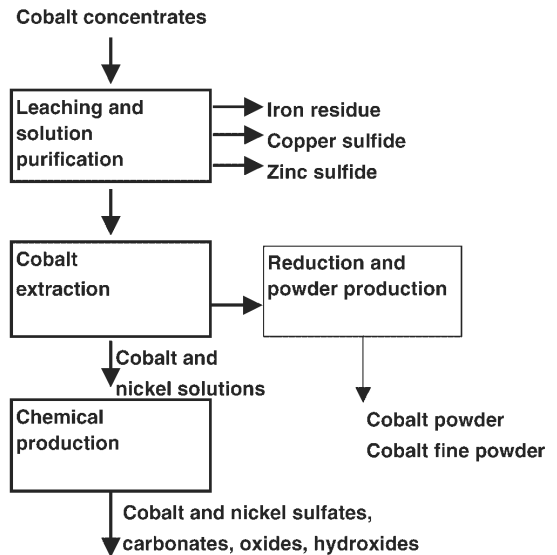

FIGURE 1. Raw materials, processes, and products in the Kokkola cobalt plant in 1966–1987 and 1987–1997.

were present as water-soluble sulfates. In the reduction plant and powder production facility, cobalt is mainly in the form of cobalt powder and fine powder [Roto, 1980]. In the chemical department, the cobalt and nickel compounds have been mainly sulfates, carbonates, oxides, and hydroxides.

According to biological monitoring, exposure to cobalt has been highest in the reduction department. The highest urinary content of cobalt has been about 16,000 nmol/L (level of unexposed persons being <40 nmol/L). In the solution purification and chemical departments, the urinary cobalt levels have been between 300 and 2,000 nmol/L and the urinary nickel concentration has been as low as 0.06 μmol/L (level of unexposed persons being <0.06 μmol/L).

Exposure to most dusts and gases in the process has been regularly monitored in every job task several times yearly since 1966. Air samples have been collected by an authorized hygienist both from stationary points and with personal samplers from the workers' breathing zones. (The mean exposure levels are presented in Fig. 3.) In this study, cumulative exposure was calculated for each worker using a job-exposure matrix based on ambient air measurements. The exposure to dusts is presented as mg-years, and that to gases as ppm-years. (The principle of forming these numbers by using exposure levels (mg/m^3, ppm) and exposure time (years) is shown in Fig. 2.) The mg-years were calculated for total dust, cobalt, and nickel, and the ppm-years were used for sulfur dioxide (SO_2), hydrogen sulfide (H_2S), and ammonia (NH_3). In workplace documents, accurate descriptions can be found of the number of hours the workers were exposed during their 8-hr workshifts; therefore, this factor could be taken into account in the calculations. The number of men who had been exposed to other agents was small, and therefore this exposure has not been discussed separately.

Questionnaire

A questionnaire was sent to the participants 2 weeks before the health examination. Data on work history, earlier lung diseases, allergies, medication, smoking habits, and current respiratory and eye symptoms were requested. Questions on work history included current and previous tasks in the cobalt plant and also previous occupations, especially those with exposure to hazardous dusts (metal industry, farming, construction work, etc.). Asbestos exposure in all jobs was queried. The reasons for changing work tasks or jobs and workplaces were also requested.

All the questions concerning lung diseases and health symptoms were based on the Tuohilampi questionnaire that has been constructed [Susitaival and Husman, 1996] and validated for epidemiological use by a Finnish expert group [Kilpeläinen et al., 2001]. The outcome parameters were defined in three groups as follows [Susitaival and Husman, 1996]:

- Definition of reported diseases: Allergic rhinitis, asthma, and pneumonia if diagnosed by a physician.
- Definition of diseases based on criteria of the questionnaire: Suspected asthma; if a person of adult age had had cough or dyspnea with wheezing or had had attacks of shortness of breath with wheezing and breathing had been normal between the attacks. Suspected work-related asthma; if the person had suspected asthma or reported
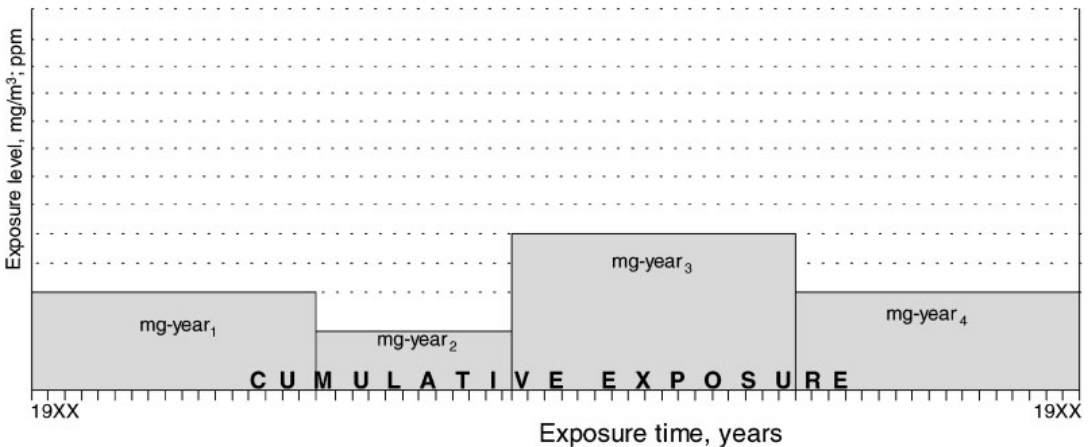

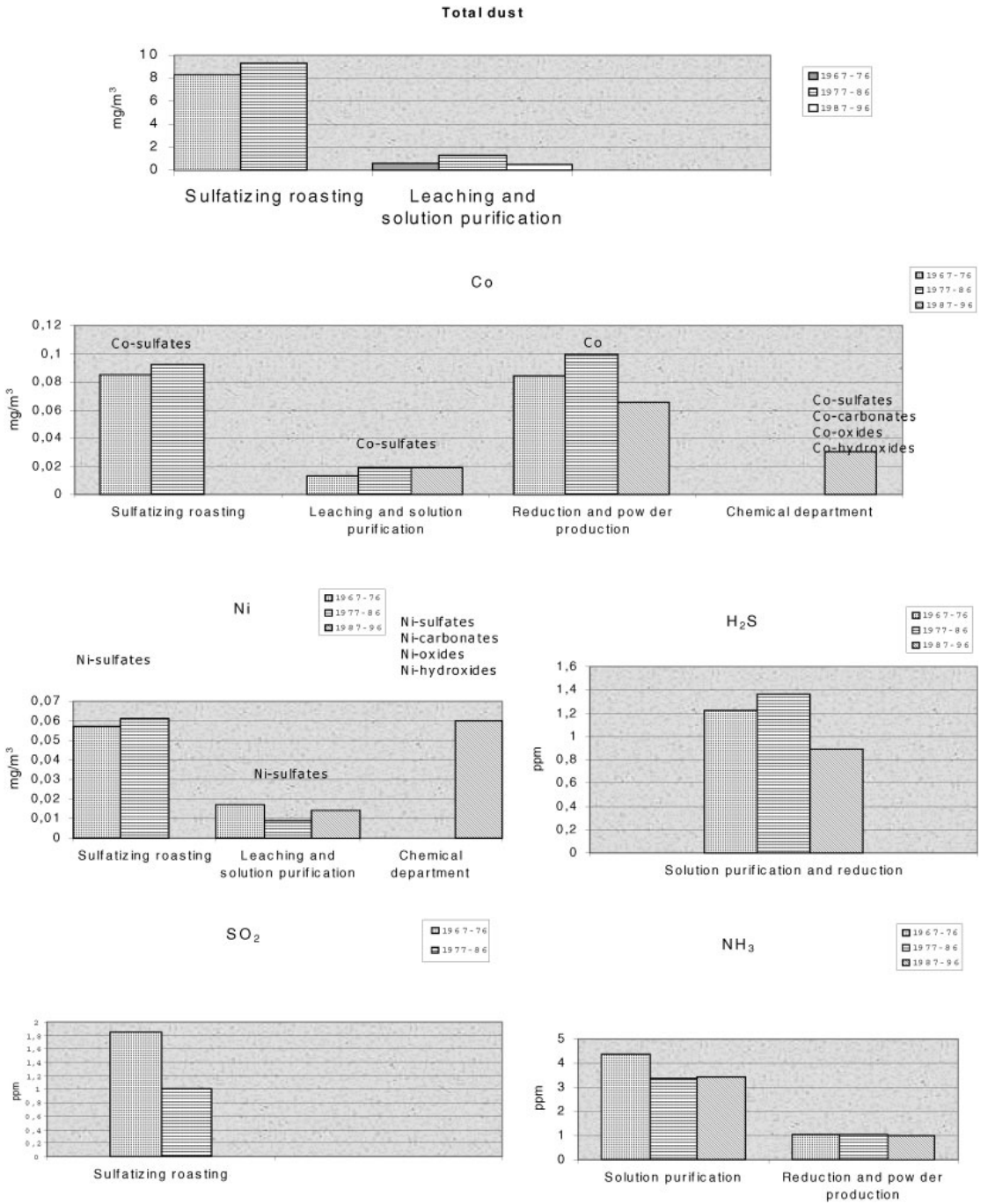**FIGURE 2.** Principle of forming cumulative values for worker exposure.

FIGURE 3. Mean exposure levels in the Kokkola cobalt plant during 1967—1996.

asthma and reported that the symptoms worsened at work or the symptoms worsened at the beginning or end of the work period or any time during the work period or the person associated the worsening with some particular exposure at work.

Chronic bronchitis; if the person had suffered from chronic phlegm and cough or phlegm almost daily for at least 3 months during two consecutive years before filling out the questionnaire and had not reported having asthma. The questions concerning chronic bronchitis were modified from the 1986 version of the MRC questionnaire [MRC, 1986].

Chronic rhinitis; if the person reported long-lasting symptoms of rhinitis also at times other than in connection with common cold or influenza.

Definition of symptoms

Cough and phlegm, which lasted more than 3 months per year, as well as cough with wheezing, dyspnea with wheezing and breathlessness on exertion, were reported as a direct distribution in the analysis.

Pulmonary function tests and chest X-ray

Spirometry, measurement of diffusing capacity, a chest X-ray, and laboratory tests were carried out by experienced laboratory technicians in the mobile research unit of the Finnish Institute of Occupational Health. The laboratory technicians were not aware as to whether or not the workers studied were exposed to cobalt compounds.

A computerized flow-volume spirometer M905 (Medikro OY, Kuopio, Finland) was used for the lung function tests. The spirometer was calibrated daily. At least three acceptable forced maximal expirations were performed according to the standards of the [American Thoracic Society, 1987]. From the maximum expiratory flow volume curves, the highest forced vital capacity (FVC), forced expiratory volume in 1 second (FEV_1), and flow rates at 50 and 25% of the vital capacity (MEF_{50}, MEF_{25}) and the mean flow (MMEF) were read. Each subject was seated wearing a nose clip. All the values were also expressed as percentages of predicted values in Finland [Viljanen et al., 1982]. One trained laboratory technician performed measurements.

Diffusing capacity of the lungs for carbon monoxide (DLCO) was measured with the Vmax (Sensormedics Co., Yorba Linda, CA) transfer test and a single breath method. Alveolar volume (VA) is the total lung capacity at the time the DLCO was measured. The specific diffusion capacity was DLCO/VA. At least two satisfactory acceptable measurements for each person were performed. The mean of the two nearest measurements was chosen [Make et al., 1982]. The values were adjusted to the real-time hemoglobin measure-

ment [Cotes, 1975]. The results were expressed as percentages of predicted values for Finland [Viljanen et al., 1982].

Two trained laboratory technicians examined an equal number of people in the exposed and unexposed groups. The technicians' performance of the diffusing capacity measurements was tested before the study. The mean difference in the results was 3.4%.

In the radiographic examination a full-size, posteroanterior chest X-ray was taken if such an X-ray had not been taken within the past year. Only the current and former workers from the production departments were examined. High and low cobalt-exposure groups were compared. The X-rays of each exposed subject were classified according to the modified ILO classification [ILO, 1980]. The X-rays were classified separately by two radiologists, one of whom is a NIOSH B-reader. The inter-observer error was small; only for two X-rays (2%) was there a difference between the readers, one small profusion category (0/0 and 0/1); differences greater than one small ILO category were not noted.

Statistical Methods

Frequency tables were constructed to explore the differences in the occurrence of symptoms (outcome variables) between the exposed and control groups. Tables were analyzed with chi-square and Fisher's exact tests. The multivariate analysis was based on a stepwise (forward) logistic regression model. The possible explanatory variables were study group and smoking status as dichotomous variables and age as a continuous variable. Further analysis of respiratory symptoms in the exposed group was carried by the same method, but, instead of study group, the possible explanatory variables included the exposure to the total dust, cobalt, nickel, hydrogen sulfide, sulfur dioxide, and ammonia. The effect of exposure on pulmonary function was studied using Student's t-tests and analyses of variance and covariance. Student's t-test was used for non-smokers and smokers (including ex-smokers) separately. In the analysis of variance, the variation in each lung function measurement was explained by the smoking status and the study group to explore the possible interaction in addition to the main effects of these factors. When the effect of different exposure substances on the lung function measurements was studied, the workers were divided into the following three groups: high, moderate, or no exposure to the substance. The exceptions were made for total dust and cobalt, for which the moderate and no exposure groups were merged. The limit between the high and moderate exposure was the median of the exposed persons, and in the additional analysis the upper quartile was used. Smoking was included as pack-years in the model as a covariate. The limit for statistical significance was set equal to 0.05. The computation was carried out using Statistica/Win (Version 98) and SPSS/Win (Version 8.0) software.

RESULTS

Thirty-seven of the 54 former workers (64%) answered the questionnaire, and 25 participated in the clinical study. Thus, we examined 85 current workers and 25 ex-workers. Most of them were or had been process workers; some were or had been maintenance men and foremen. The ex-workers had left their jobs at the plant 0–15 years ago.

Characteristics of the Groups and Exposure

The characteristics of the examined groups are given in Table I. Smoking, reported as the number of pack-years, was greater in the exposed group than in the control group. The range of mg-years and ppm-years is shown in Table II. All the workers in the exposed group had been exposed to cobalt or to cobalt compounds, about 80% to nickel and nickel compounds, about 50% to sulfur dioxide, hydrogen sulfide, and ammonia.

Thirty-six percent of the workers in the exposed group had been slightly exposed to asbestos. In the 1960s and 70s, some asbestos string was used as insulation material in the roasting ovens, and the insulation was replaced several times a month.

TABLE I. Characteristics of the Study Groups

Characteristics	Exposed group n = 110		Control group n = 140
Age (years)			
Mean (SD)	50.3 (6.0)		48.8 (5.1)
Range	37–67		37–61
Height (cm)			
Mean (SD)	174.7 (5.7)		176 (5.2)
Range	158–193		163–191
Weight (kg)			
Mean (SD)	82.8 (12.8)		83.7 (11.2)
Range	59–145		59–130
Work history (years)			
Mean (SD)	22.1 (7.8)		24.7
Agricultural work (%)	22		9
Asbestos exposure (%)	36		21
Smoking status (%)			
Non-smoker	24.5		32.9
Ex-smoker	41.8		37.9
Current smoker	31.8		29.3
Pack-years (smokers and ex-smokers)			
Mean (SD)	21.2 (13.8)	P < 0.05	15.8 (11.4)

TABLE II. Cumulative Exposure of the Workers as mg-Years or ppm-Years

	Exposure		
	Mean	Median	Range
Total dust (mg-years)	19.4	19.0	0.1–38.0
Co (mg-years)	1.0	0.6	0.1–4.6
Ni (mg-years)	0.4	0.3	0.0–2.2
H_2S (ppm-years)	7.5	0.0	0.0–59.0
SO_2 (ppm-years)	3.7	0.0	0.0–39.7
NH_3 (ppm-years)	27.0	16.0	0.0–187.4

Respiratory Diseases and Symptoms

The prevalences of the reported respiratory diseases and symptoms are presented in Table III. There was no difference in the prevalence of reported asthma between the groups, but asthma based on questionnaire criteria appeared three times more frequently in the exposed group than in the control group. There was no overlapping of persons with reported asthma with persons with suspected asthma on the basis of the questionnaire criteria. The production of phlegm, cough with wheezing, shortness of breath with wheezing, and breathlessness on exertion were significantly more frequent in the exposed group than in the control group. The results remained the same also after the multivariate analysis in which the effect of age and smoking was taken into account. In the exposed group, exposure to any of the chemicals did not have a significant effect on increasing the risk of any of the studied respiratory diseases or symptoms. The number of suspected cases of work-related asthma was 15 (14%) among the exposed workers. Seven of the 15 men with suspected work-related asthma reported long-lasting rhinitis. Ten of the 19 exposed workers with suspected asthma reported chronic rhinitis. An occupational physician (AL) referred the suspected cases of asthma for further examination. The suspected cases of occupational asthma were studied in Finnish institute of occupational health (FIOH). One new case of occupational asthma (cobalt) was diagnosed in a specific provocation test. The other asthma was non-occupational, allergic asthma. Seven persons of the nine with chronic bronchitis in the exposed group were smokers; in the control group four out of five were smokers. There were no cases of allergic alveolitis in the exposed group. Three out of the 25 retired persons who participated in the study had retired because of occupational asthma (cobalt). All these cases were also diagnosed at FIOH. In the exposed group, 22 pneumonias were reported, six during adult worklife and 16 during childhood or adolescence. Five of the pneumonia diagnoses made during worklife could be verified in the patients' records, but one could not. Similarly, in the un-exposed group, there were two cases of pneumonia during

TABLE III. Respiratory Diseases and Symptoms

Disease or symptom	Exposed group (n = 110) (%)		Control group (n = 140) (%)
Prevalence of reported respiratory diseases diagnosed by a physician			
Bronchial asthma	7.3		5.0
Chronic bronchitis	8.1		2.1
Pneumonia	20		5
Pneumonias during worklife	5		1
Allergic rhinitis	2.8		2.9
Allergic alveolitis	0		1.4
Prevalence of respiratory diseases based on questionnaire criteria			
Suspected asthma	17.3	$P < 0.01$	5.8
Suspected work-related asthma	14	$P < 0.008$	3
Chronic bronchitis	8.2		3.6
Allergic rhinitis	8.2		15.8
Prevalence of symptoms			
Cough > 3/12 months	9		6
Phlegm > 3/12 months	21	$P = 0.01$	9
Cough with wheezing	27	$P = 0.04$	16
Dyspnea with wheezing	23	$P < 0.01$	8
Breathlessness on exertion[a]	24	$P < 0.01$	9

Fisher's exact two-tailed test.
[a]Shortness of breath when hurrying on level ground.

working age and five cases had occurred during childhood or adolescence. All of the pneumonia diagnoses made during worklife were verified radiographically.

Lung Function Studies

The smokers had lower lung functions in both the exposed and the control groups. The FEV_1, MEF_{50}, and MEF_{25} values of the smokers in the exposed group were lower than those of the smokers in the control group (Table IV). In the analysis of variance, the difference in the MEF_{50} and MEF_{25} values remained when smoking (pack-

years) was included as a covariate in the model. Among the non-smokers, none of the values of the measured lung function parameters differed between the groups. In the analyses of variance, smoking was the only significant factor explaining lower lung functions; no occupational chemical exposure alone, or in a combination, had any significant effect on lung function.

Chest X-Rays

Table V shows the radiological findings. Profusion of small opacities higher than 1/1 did not exist. Six out of 10

TABLE IV. Lung Function Measurements as the Percentage of the Predicted Values (Mean and SD)

Lung function variable	Exposed group		Control group	
	Non-smokers	Smokers	Non-smokers	Smokers
FVC	97.1 (12.9)	94.7 (10.2)	96.8 (12.9)	95.7 (12.0)
FEV_1	97.1 (14.6)	88.7 (13.6)[a]	96.4 (14.6)	93.4 (13.0)[a]
MEF_{50}	93.3 (27.4)	71.7 (25.1)[a]	96.6 (24.2)	81.5 (21.9)[a]
MEF_{25}	98.7 (36.3)	71.0 (28.5)[a]	102.4 (45.9)	82.8 (31.3)[a]
DLCO	97.2 (13.1)	87.2 (16.9)	95.0 (13.6)	89.1 (14.8)
DLCO/VA	99.6 (15.4)	90.7 (15.4)	96.8 (12.5)	92.0 (14.2)

Student's two-tailed t-test.
[a]< 0.05 when comparing smoker groups.

TABLE V. Radiological Findings

Profusion of small opacities n (%)				Pleural plaques n (%)	
0/0	0/1	1/0	1/1	Unilateral	Bilateral
100 (90.8)	7 (6.4)	1 (0.9)	2 (1.8)	3 (2.7)	10 (9.0)

persons with small opacities (ILO 0/1) had been exposed to asbestos, one of them had bilateral pleural plaques. In the logistic regression analysis, smoking and asbestos exposure significantly explained the profusion of small opacities. The three persons with classification 1/0 (one person) and 1/1 (two persons) were further studied with high-resolution computed tomography (HRCT). They were all exposed to asbestos. The one with a rating of ILO 1/0 had a normal HRCT finding without plaques and without fibrosis. Both workers with a rating of ILO 1/1 were heavy smokers. One suffered from lung sarcoidosis, and the other had been diagnosed with severe chronic obstruction pulmonary disease. The worker with sarcoidosis had bilateral plaques and diffuse fibrosis in his HRCT; the other worker had no plaques and no fibrosis. All the persons with bilateral pleural plaques had been exposed to asbestos during their worklife.

DISCUSSION

Our aim was to study various non-specific long-term effects on the respiratory system by choosing workers exposed for at least 10 years. A priori, asthma, acute cases of alveolitis, or hard metal disease were not selected outcomes of this study. It is known that asthma may develop during shorter periods of exposure. Chronic forms of hard-metal disease or bronchitis do not usually appear before 10 years of exposure [Waldron, 1994]. Even if the participation rate of the former workers was rather poor, 86% of all the current and former workers participated in the study. The turnover of the staff has been low. All the persons, including retired workers, have been examined annually in periodic health examinations. If a disease or a symptom has been a reason for leaving the company, the health care personnel are aware of this. On the other hand, symptomless outcome such as mild lung fibrosis does not cause selection. Thus, the selection bias of our study was small, and it can be concluded that the study population formed a good representation of all workers in the Kokkola cobalt plant. In a subsequent study in this plant, concluded in 2001, we obtained additional information on retired persons. A questionnaire was sent to all the workers who had ever worked in the cobalt factory for 1 year or longer. Respiratory symptoms were reported as a reason for leaving the cobalt plant as often as leaving the reference zinc production plant (6 and 5%).

The differences in the background factors between the groups indicated that the control group had less leisure-time exposure, for example, exposure in farming, than the exposed group. On the other hand, if these factors had had an adverse effect on the study population, it would have increased the differences in the outcomes between the groups. Confounders such as differences in pack-years were taken into account in the statistical analyses.

The exposure information of this study has been carefully recorded with standardized procedures. As an only exception, the total dust value has not always been shown in the documents, only values of single metals and gases. This regular monitoring of exposure provides a unique opportunity to evaluate the respiratory effects of long-term exposure to cobalt and other exposures in cobalt production. Thus, even though the plant has been functioning for 34 years and many employees have been working in different departments and exposed to various mixtures of chemicals, it was possible to assess their cumulative exposure with use of a job-exposure matrix based on hygienic measurements.

The mean exposure levels to cobalt and its compounds have been slightly under the current Finnish occupational exposure limit (0.05 mg/m^3) since the new process was introduced (in 1987). The biomonitoring data indicated considerable exposure to cobalt, especially in the reduction and powder production department and in the chemical department. Compared with biomonitoring samples from hard metal blade sharpening processes, where the urinary cobalt values averaged 241 nmol/l (range 8–2,705 for 131 samples) [Linnainmaa and Kiilunen, 1997], cobalt workers have had manyfold-higher values (average 300–2,000 nmol/L, highest 16,000 nmol/L). It is noteworthy that hard metal disease has occurred among persons with lower urinary cobalt concentrations than the levels measured for cobalt production workers. This observation supports the hypothesis that cobalt alone, or water-soluble cobalt compounds, do not cause hard metal disease. Of course, our study does not exclude the possibility that pulmonary changes could appear in heavier exposure conditions.

There was a higher incidence of pneumonias in the exposed group, when cases of adult life pneumonias (5% vs. 1%) were compared; this finding was unexpected. Diseases in the exposed group were documented with radiography, according to their patient records, and there were no signs of pneumonitis. Asthma on the basis of questionnaire criteria and asthmatic, obstructive symptoms like wheezing cough and dyspnea after control for smoking were significantly more frequent in the exposed group. In the questionnaire, even one episode was counted, and this criterion may partly explain the high prevalence. Nineteen workers with asthmatic symptoms were studied further. One of them had new cobalt asthma and another new allergic asthma. The others were not given an asthma diagnosis in the clinical examination.

Symptoms of allergic rhinitis were more common in the control group than in the exposed group. One explanation

may be that people with an earlier history of allergic disease, like asthma or allergic rhinitis, had been excluded in the pre-employment examinations. In addition, most exposed workers with asthmatic symptoms also had symptoms of rhinitis. For over 50% of persons with asthma symptoms, allergic rhinitis prevails [Mackay and Cole, 1987]. Early prevention of cobalt asthma could be focused on workers with an allergic type of rhinitis and wheezing, because these symptoms may precede the appearance of asthma.

Although, in the analysis of variance, smoking explained most of the respiratory effects observed, exposure and smoking had an interactive effect on the MEF_{50} and MEF_{25} values. No exposure to any chemical compound alone or in combination with others (including total dust) could explain the effect. In the former study in this Kokkola cobalt plant, no association of exposure with pulmonary function was observed after controlling for smoking [Roto, 1980].

No one in the study group had findings of hard metal disease. Only three persons had small opacity profusion (1/0 or 1/1), and only one of these persons had diffuse fibrosis in HRCT. He suffered from sarcoidosis and had been exposed to asbestos; thus the etiology of the fibrosis remains unclear. Our results seem to indicate that lung fibrosis is not associated with exposure in Kokkola cobalt production. This finding is supported by the experience of the occupational health personnel of the company in that no cases of hard metal disease or fibrosing alveolitis have been found during the existence of the Kokkola cobalt plant.

We conclude that cobalt production in plants like the one in Kokkola does not cause serious chronic effects (asthma excluded) on the respiratory tract of non-smoking cobalt workers. This conclusion is congruent with the findings of previous studies [Swennen et al., 1993; Barceloux, 1999]. It seems evident that the occupational health personnel of the plant should, therefore, direct their efforts towards preventing occupational asthma.

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PUBLICATION
II

Cobalt asthma—a case series from a cobalt plant

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Cobalt asthma—a case series from a cobalt plant

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Background	Cobalt has been shown to induce mainly asthma, allergic contact dermatitis and hard metal disease. The data on cobalt asthma are mainly based on case reports.
Aims	To characterize all the cases of occupational cobalt asthma encountered in a cobalt plant at the time of diagnosis and 6 months later. We also evaluated the incidence of cobalt asthma in different departments on the basis of data on occupational exposures.
Methods	We identified cases of cobalt asthma confirmed with specific bronchial challenge tests in the Kokkola cobalt plant in Finland where exposure levels have been regularly monitored.
Results	Between 1967 and 2003, a total of 22 cases of cobalt asthma were diagnosed in the cobalt plant. On challenge tests, mostly late or dual asthmatic reactions were observed. The incidence of cobalt asthma was the highest in the departments with the highest cobalt exposure levels. All cases of cobalt asthma were encountered in departments where irritant gases were present in the ambient air in addition to cobalt. At the time of the follow-up examination 6 months later, non-specific hyperreactivity had mostly remained at the same level or increased.
Conclusions	The incidence of cobalt asthma correlated with the exposure levels of cobalt in corresponding departments. An irritating effect of gaseous compounds may enhance the risk of cobalt asthma and even the smallest amounts of cobalt may be harmful to susceptible workers. Symptoms of asthma may continue despite the fact that occupational exposure to cobalt has ceased.
Key words	Cobalt exposure; occupational asthma.

Introduction

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

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

of asthma, cobalt production workers could be anticipated to be exposed to a high risk of occupational asthma.

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

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

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

Methods

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

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

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

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

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

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

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

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

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

According to biological monitoring surveillance, exposure to cobalt was highest in the reduction and powder production department. The highest urinary content of cobalt was ~16 000 nmol/l (level of unexposed persons being <40 nmol/l). In the solution purification and chemical departments, the urinary cobalt levels were between 200 and 2000 nmol/l. Respirators were available since the plant started operating, and mandatory in the last 10 years in the powder production and chemical departments. Results of the biological monitoring show that a marked exposure still exists regardless of the intensified use of respirators [20].
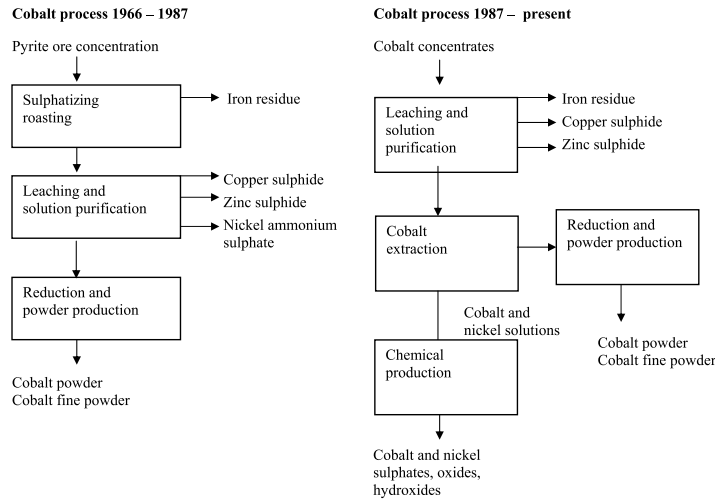
Cobalt process 1966 – 1987

Pyrite ore concentration

Sulphatizing roasting → Iron residue

Leaching and solution purification → Copper sulphide → Zinc sulphide → Nickel ammonium sulphate

Reduction and powder production

Cobalt powder Cobalt fine powder

Cobalt process 1987 – present

Cobalt concentrates

Leaching and solution purification → Iron residue → Copper sulphide → Zinc sulphide

Cobalt extraction → Reduction and powder production

Cobalt and nickel solutions → Cobalt powder Cobalt fine powder

Chemical production

Cobalt and nickel sulphates, oxides, hydroxides

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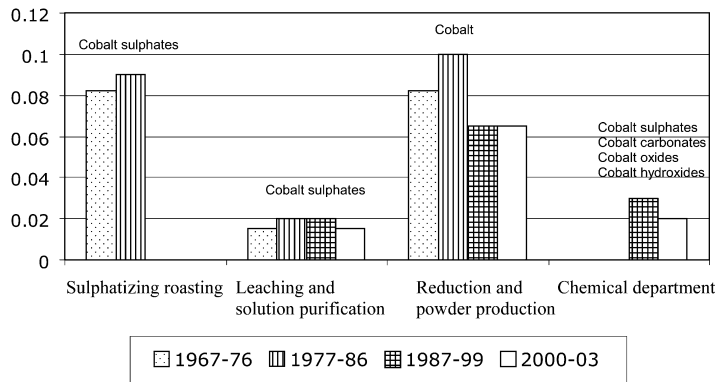

Figure 2. Mean exposure levels in the Kokkola cobalt plant in 1967–2003.

Results

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

Table 1. General characteristics and allergy testing of study patients

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

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

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

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

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

Discussion

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

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

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

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

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

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

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

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

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

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

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

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

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

Key points

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

Conflict of interest

None declared.

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PUBLICATION
III

Exposure to cobalt in the production of cobalt and cobalt compounds and its effect on the heart

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ORIGINAL ARTICLE

Exposure to cobalt in the production of cobalt and cobalt compounds and its effect on the heart

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Aims: To investigate whether exposure to cobalt in cobalt plants has any measurable effect on the cardiovascular system.

Methods: Occupational, cross sectional study, using a self administered questionnaire, blood pressure measurement, electrocardiography, and laboratory tests in which 203 male workers with at least one year of exposure to cobalt and 94 unexposed controls participated. Echocardiography was performed on a subset of 122 most highly exposed cobalt workers, of which 109 were analysed, and on 60 controls, of which 57 were analysed. Analysis of covariance and a multiple regression analysis were used to evaluate the data.

Results: Two of the echocardiography parameters measured were associated with cobalt exposure. In the higher exposure group the left ventricular isovolumic relaxation time (mean 53.3, 49.1, and 49.7 ms in the high exposure, low exposure, and control groups respectively) and the deceleration time of the velocity of the early rapid filling wave (mean 194.3, 180.5, and 171.7 ms for those in the high exposure, low exposure, and early filling wave (mean 194.3, 180.5, and 171.7 ms for those in the high exposure, low exposure, and early filling.

Conclusion: Cumulative exposure to cobalt was found to be associated with the results of Doppler echocardiography measurements, indicating altered diastole. This finding supports the hypothesis that cobalt accumulation in the myocardium could affect myocardial function. Whether this finding has clinical implications remains to be evaluated.

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A n epidemic of cardiomyopathy occurred in the 1960s in Canada, the United States, and Belgium among persons who drank large amounts (that is, several litres per day) of beer containing cobalt.[1–3] The disease was severe, and almost half of the diseased persons died. According to postmortem analyses, the patients' hearts were dilated and the walls of the left chamber had thickened. It was assumed that heavy drinking and dietary deficiencies, in addition to exposure to cobalt, played a role in causing the disease.[4]

Single cardiomyopathy cases have been reported among persons exposed to cobalt at work.[5 6] Exposure levels have been high in these cases (that is, 0.1–5 mg Co/m^3). These workers have been diagnosed as having a cardiac condition similar to dilative cardiomyopathy.

In a study among hard metal workers, a weak but still significant inverse correlation was found between exposure time and the left ventricular ejection fraction, as measured by radionuclide ventriculography.[7] The study group consisted of 30 men, and the exposure levels were not mentioned. In a second echocardiogram and radionuclide study (31 men, exposure levels 0.09–13.6 mg Co/m^3), men who had been diagnosed with hard metal disease (n = 12) were found to have a significantly lower left ventricular ejection fraction during both rest and exercise than persons who had not been diagnosed with hard metal disease.[8] In the study group, the left ventricular peak filling rate at rest was lower than the average of the general population. The researchers assumed that this finding might have been due to increased diastolic pressure caused by increased wall stiffness and fibrosis due to cobalt deposits in the myocardium.

Alexandersson and Attehög discovered that persons who had been exposed to an average cobalt concentration of 0.01 mg Co/m^3 in hard metal work had more hypertension and reversible electrocardiographic (ECG) changes (depressed ST and T waves, arrhythmias) than persons in

their control group.[9 10] In another study it was found that female porcelain workers who had been exposed to cobalt blue colour (average exposure level of 0.8 mg Co/m^3) had a higher heart rate than control subjects, but there were no differences in the ECG findings between the groups.[11]

The inhibition of cellular respiration due to the inhibition of mitochondrial dehydrogenase is considered to be one of the possible mechanisms of cobalt toxicity.[3] In the case of beer drinkers' cardiomyopathy, two or three factors may be responsible for the early fulminant cardiotoxic manifestation of cobalt. It is possible that hard metal workers develop heart failure more readily than other people when challenged with coronary heart disease, hypertension, valvular heart disease, viral infections, and alcohol.[7]

Since the 1960s cobalt exposure and cardiomyopathy has been a subject of discussion. Even though case reports have been published, a need still exists for epidemiological studies, especially in cobalt and cobalt chemical production, regarding possible changes in the heart and vascular system as a result of cobalt exposure. The purpose of our study was to determine whether any differences in echocardiographic, ECG, blood pressure, heart rate, and laboratory parameters of those exposed and those not exposed to cobalt and cobalt compound production could be ascribed to cobalt exposure.

SUBJECTS AND METHODS

Cobalt process and exposure

The cobalt plant of this study is located in Kokkola on the western coast of Finland. Between 1966 and 1987 cobalt

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Abbreviations: DT, deceleration time; ECG, electrocardiography; EF, ejection fraction; FS, fractional shortening; IVRT, isovolumic relaxation time; IVSD, diastolic interventricular septum; LVEDD, left ventricular end diastolic diameter; LVPWD, left ventricular posterior wall; S-ANP-N, N-terminal atrial natriuretic peptide; S-CDT, carbohydrate deficient transferrin; S-GT, gamma-glutamyl transferase

Main messages

- Cumulative cobalt exposure was associated with echocardiographic changes indicating altered left ventricular relaxation and early filling.
- No clinically significant cardiac dysfunction due to cobalt exposure was found. In case studies involving cardiomyopathy exposure levels have been higher, and in epidemiological studies in which cobalt exposure has been associated with hypertension or ECG changes, exposure levels have been similar or higher than in our study (mean level approximately 0.05 mg Co/m^3).

Policy implications

- The current Finnish occupational exposure limit (OEL) of 0.05 mg Co/m^3 is not low enough to prevent echocardiographic changes. A lower OEL should be considered.
- The clinical significance of the findings needs further evaluation. A cause specific longitudinal study, including the retired workers, would give more information on effect of cobalt exposure on incidence of heart disease.

powder was produced from pyrite ore concentrate. Thereafter cobalt powder, inorganic cobalt, and nickel compounds have been produced using by-products of the metallurgic industry as raw material (fig 1).

Exposure to most dusts and gases in the process has been regularly monitored several times every year since 1966. Air samples have been collected by an authorised hygienist both at stationary points and with personal samplers in the workers' breathing zones. Exposure to cobalt has varied in large ranges according to job title even within same department. The range has been 0.02–1.0 mgCo/m^3 in the sulphatising roasting department, 0.01–0.05 mgCo/m^3 in the leaching and solution purification department, 0.05–0.25 mgCo/m^3 in the reduction and powder production department, and 0.01–0.20 mgCo/m^3 in the chemical department. The mean exposure levels to cobalt and its compounds were slightly over the current Finnish occupational exposure limit (0.05 mg/m^3) before 1987, and they have been slightly under the limit since the new process was initiated (fig 2). Substantial uptake of cobalt occurs through the lungs, although limited data are available on humans.[12]

Experiences from the biomonitoring of exposed workers have shown no notable differences in the bioavailability of the produced compounds. According to biological monitoring surveillance, exposure to cobalt has been highest in the reduction department. The highest urinary content of cobalt

has been about 16 000 nmol/l (level of unexposed persons being <40 nmol/l). In the solution purification and the chemical departments the urinary cobalt levels have primarily been between 300 and 2000 nmol/l. In our present study, cumulative exposure to cobalt, presented as milligram-years (mg-y), was calculated for each worker using a job exposure matrix based on ambient air measurements. Workers in the cobalt plant are not exposed to zinc. In the control group (zinc plant workers) all the workers were exposed to zinc. For four fifths of the zinc workers the exposure level was 0.1–0.2 mg/m^3, and for one fifth it was around 1 mg/m^3.

Study population
The employees who were working at the end of 1999 in the cobalt plant and had been exposed to cobalt for at least one year were invited to participate in the study. The control group consisted of a stratified random sample of male workers in a zinc plant located in the same industrial area. Age group was taken as the stratum. The motivation for the stratified sampling was to control the confounding effect of age. The control group had not been exposed to cobalt, arsenic, or lead.

Questionnaire
Data on working history in the plant and earlier possible exposure to cobalt, lead, carbon disulphide, and arsenic were requested in the self administered questionnaire. The reasons for changing work tasks or jobs and workplaces were also
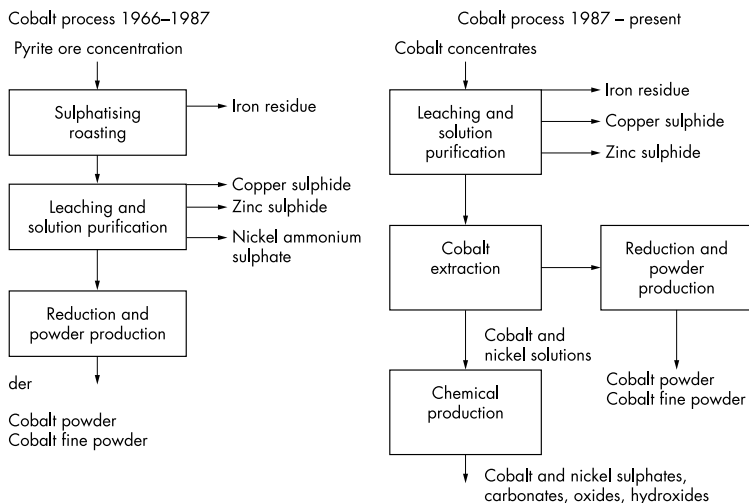

Figure 1 Cobalt production process in the Kokkola cobalt plant in 1966–87 and 1987–present.
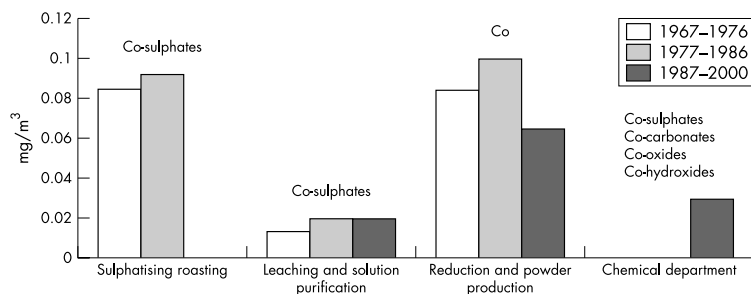
Figure 2 Mean exposure levels of the cobalt workers in the Kokkola cobalt plant in 1967–2000.

requested. There were also questions regarding physical exercise, smoking, alcohol consumption, cardiovascular and pulmonary diseases, and diabetes. There were 352 male workers who had been employed and exposed to cobalt for at least one year before leaving the factory. The 321 cobalt factory workers who were still living and the 318 ex-workers with a similar age distribution from the zinc plant were sent the same questionnaire with an additional question regarding reasons for leaving the plant.

Echocardiography

According to the assessment of the statistical power, 122 cumulatively most exposed cobalt workers and 60 controls with the same age distribution underwent echocardiography. Persons with congenital or acquired cardiac valvular disease and those with a history of myocardial infarction were excluded from the echocardiographic analysis. Transthoracic echocardiography was performed in the standard fashion,[13] using a Vingmed System Five Premium (Horten, Norway) with a 2.5 MHz or 3.5 MHz probe from the parasternal, apical, subcostal, and supracostal windows with the subject in the left lateral recumbent position. M-mode dimensions were normalised for body surface area. The mean of at least three consecutive beats was used. The left ventricular ejection fraction (EF) was calculated from the fractional shortening (FS) using the method of Pombo. Spectral Doppler measurements of blood flow were performed by aligning the interrogating beam with the direction of flow according to anatomical and colour Doppler information. Mitral and tricuspid flows were obtained with the pulsed Doppler sampler at the valve tips. Intraventricular relaxation time was measured using the technically better pulsed or continuous wave recording of mitral inflow and left ventricular outflow tract flow. No angle correction was used. Valvular regurgitation was quantified using colour Doppler information from multiple views. Images were stored on videotape in a Sony videocassette recorder (SVO-9500MDP), on optic disks in an Echopac Workstation, and on paper using a thermal printer UP-890CE.

The echocardiograms were analysed by two experienced clinicians without knowledge of the status of the examined persons (exposed/control). Abnormalities were agreed on by consensus. MH performed the measurements of cardiac size and function.

Blood pressure measurement and electrocardiography

Blood pressure was measured after 10 minutes of rest in the sitting position using an automatic Omron 705CP (Omron Matsusaka CO Ltd, Japan), which was tested and validated by the importer before and after the study. After two measurements the lower systolic and diastolic pressure and pulse were noted. A standard 12 lead electrocardiogram was obtained with 12 channels ECG equipment (Marquette Electronics Inc., Milwaukee WI, USA) at a paper speed of 50 mm/s. The recordings were analysed independently by two experienced clinicians, who both coded the recordings without knowing their origin (exposed/control). Coding was performed according to the Minnesota 1982 method.[14]

Laboratory tests

Gamma-glutamyl transferase (S-GT) and carbohydrate deficient transferrin (S-CDT) were analysed to study alcohol consumption. Thyroid gland function (serum free thyroxine, S-T₄-V, and thyroid-stimulating hormone, S-TSH), vitamin B1 deficiency (thiamin, B-B1-vit), and the serum lipid and glucose values were studied as possible confounding factors of cardiomyopathy and ischaemic cardiac disease.

N-terminal atrial natriuretic peptide (S-ANP-N) was determined to complement possible findings of cardiac failure.[15] It was analysed by radioimmunoassay with kits purchased from BIOTOP Oy, Oulu, Finland.

Statistical methods

The normality of the variables was checked, and logarithmic transformation was applied if the distribution of the variable was skewed. Crude means and standard deviations have been reported in the tables.

A regression analysis and an analysis of covariance (ANCOVA) were used to study the echocardiographic data. A forward stepwise regression analysis was performed on all echocardiographic parameters. The potential explanatory factors included exposure as mg-years, age, blood pressure, smoking status, overuse of alcohol, and physical activity. Body mass index was included if the outcome variable had not been divided by body surface area, and heart rate if the outcome variable was time related. ANCOVA was additionally used to study the differences in echocardiographic parameters between various designated exposure groups. The first categorisation of exposure to cobalt used a time related definition. The exposure was called recent if the person was working (or had worked during the last year) in conditions in which he could be regularly exposed to a cobalt concentration of 0.01 mg/m³ or more; otherwise the exposure was called past. In another classification of exposure the grouping was determined according to the length of exposure time to cobalt. Exposure time was defined by the number of years worked with cobalt, with two groups being defined above and below the median length of time of 24 years. In the final analyses high and low exposure was determined on the basis of being above or below the median mg-years of cobalt exposure (0.47 years for the subset in the echocardiography analysis). The effect of age on several important echocardiographic parameters is known. It was included as a continuous variable in the regression analyses and categorised above and

below 50 years,[17] which allowed its interaction with exposure to be studied in the ANCOVA.

Blood pressure (as raised or as hypertension), overuse of alcohol (weekly consumption more than 20 drinks or S-GT >80 or S-CDT >20), smoking (never smokers versus ex or current smokers), physical activity, and, in some calculations (see above), body mass index and heart rate were included in the model as covariates because they were considered to be confounders.

Statistical power calculations (requiring the power of at least 0.8 at the significance level of 0.05) were performed to assess the number of echocardiographic analyses needed in the study. Calculations were carried out in relation to the deceleration time (DT) and the isovolumic relaxation time (IVRT), which were considered to be the most important outcome variables because of their ability to reflect the earliest changes in the cardiac function.[16] The power calculations were based on ANCOVA, the difference to be detected in outcome variables being 10%, with a standard deviation of 30.0 ms for DT and 10.0 ms for IVRT in each group. Calculations showed a need for 186 analyses altogether (62 in each group) when the differences between three groups in DT were studied, and a need for 180 analyses in IVRT respectively.

Simple statistics were used to describe the data. The 95% confidence intervals (95% CI) were calculated for the differences between two percentages. The level of significance in ANCOVA was set at equal to 0.05, but exact p values are reported. Computations were carried out using Statistica/Win (1998 edition) and SPSS/Win (version 12.0) software.

RESULTS

Table 1 presents the characteristics of the examined groups and calculated mg-year values. The cobalt exposure of 132 workers was considered recent, and that of 71 workers was recorded as past. All analyses were carried out on all measures of exposure. The results are presented in relation to the cumulative amount of exposure only, because it was the most reliable and accurate method of assessing the exposure, and the other measures did not show indication of association.

All the invited current workers were men, and all 203 participated. We used age groups of 4 years as a stratum when selecting the control group. Because the zinc plant employed fewer workers who had been born in the 1960s and 1970s than the cobalt plant, the number of controls remained small. From the control group (n = 96), two persons did not want to participate.

In the exposed group two persons had been exposed to arsenic, and two had had lead exposure when working outside the plant. Two workers in the control group had been exposed to carbon disulphide for a short time (six months and three months) during their working history. In the control group more workers were or had been competing athletes than in the exposed group. When leisure time sports activities were taken into account, there were no significant differences in the amount of physical exercise between the workers of the exposed and control groups.

Echocardiography

Persons with congenital or acquired cardiac valvular disease (n = 14) and those with a history of myocardial infarction (n = 2) were excluded from the echocardiographic analysis. Thirteen of these persons belonged to the exposed group, and three were controls. Only the results from the ANCOVA are presented. The results from the multiple regression analysis broadly concurred on the inclusion of the cobalt exposure variable in the explanation of the echocardiographic parameters.

Table 1 Characteristics of the study groups

Characteristic	Exposed group n = 203	Control group n = 94
Age (y)		
Mean (SD)	42.0 (10.5)	42.2 (10.6)
Median (range)	45 (23–62)	44 (24–60)
Height (cm)		
Mean (SD)	177.9 (5.8)	177.5 (6.6)
Median (range)	178 (165–193)	178 (164–196)
Weight (kg)		
Mean (SD)	83.6 (11.3)	83.7 (12.6)
Median (range)	82 (58–142)	82 (62–133)
Work history (y)		
Mean (SD)	17.0 (11.9)	19.1 (10.8)
Median (range)	20 (2–34)	25 (3–36)
Exposure time to cobalt, (y)*		
Mean (SD)	15.0 (11.6)	
Median (range)	9 (1–34)	
Exposure to cobalt, (mg-y)		
Mean (SD)	0.40 (0.47)	
Median (range)	0.18 (0.02–2.52)	
Smoking status (%)		
Non-smokers	33.5	32.6
Ex-smokers or smokers	66.5	67.4
Pack-y		
Mean (SD)	10.8 (13.6)	9.2 (11.1)
Median (range)	7 (0–76)	6 (0–51)
Consumption of alcohol		
Drinks/week		
Mean (SD)	4.8 (4.5)	5.6 (4.8)
Median (range)	3 (0–20)	4 (0–20)
Competing athlete status (%)		
No	84.7	75.0
Now or earlier	15.3	25.0
Leisure time sport activities (%)		
No, never	8.9	8.7
Yes, two times a week or less	52.0	46.7
Yes, at least three times a week	39.1	44.6

*Regularly >0.01 mg Co/m^3.

Table 2 gives the characteristics and calculated mg-year values of the groups who underwent echocardiography. Table 3 presents the echocardiographic results. Two exposed persons and one control had a left ventricular end diastolic diameter index (LVEDIDI) that was over 32 mm/m^2. The ratio between the wall thickness and the left ventricular diameter measured at end diastole [(IVSD+LVPWD)/LVEDD] was greater among the highly exposed workers than among the controls. The interaction of age and exposure was not significant (p = 0.06), but the effect seemed stronger for younger persons. Among the younger persons the highly exposed workers differed from the less exposed and the controls, but for older people there were no differences between the groups (fig 3).

In the highly exposed group the left ventricular isovolumic relaxation time (IVRT) was longer than in the less exposed and control groups. Both exposure level and age contributed to the explanation of the variation in the IVRT, the values being shorter for younger people. The ratio of the peak early rapid filling wave to peak filling wave due to atrial contraction (E/A ratio) did not differ between the exposure groups. The E/A ratio was lower for older people. The deceleration time of the velocity of the early rapid filling wave (DT) was longer among the highly exposed subjects than among the less exposed persons or the controls. The systolic parameters of the left ventricular function did not differ between the groups.

In order to be able to assess the reproducibility of the echocardiography measurements, two experienced clinicians (MH, KG) measured the same parameters in 20 echocardiograms.

The mean coefficients of variation were 1.42% for the left ventricular end diastolic diameter (LVEDD), 5.21% for the
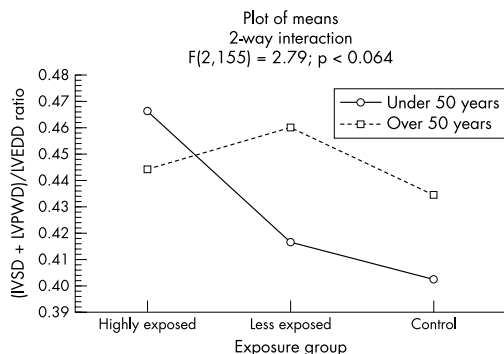
Plot of means
2-way interaction
$F_{(2,155)} = 2.79; p < 0.064$

Figure 3 The ratio between wall thickness and left ventricular diameter measured at end diastole in different exposure and age groups

diastolic interventricular septum (IVSD), 4.16% for the diastolic left ventricular posterior wall (LVPWD), 3.7% for the ejection fraction (EF), 4.7% for the isovolumic relaxation time (IVRT), and 2.3% for the deceleration time (DT).

Electrocardiographic findings

There were no significant differences in the ECG findings or conduction parameters between the exposure group and the control group (table 4).

The readers coded 20 recordings from the same persons in order to test the reproducibility. In 17 cases the coding was identical. In three there were differences: in two recordings one reader had not noticed the ORS axis deviation of −30 to −90 in leads I, II, III, and in one recording an ST segment increase of 1 mm in the anterior leads had not been marked.

Blood pressure and laboratory tests

Table 5 shows the results of the blood pressure measurements and the laboratory tests. In an ANCOVA analysis the S-ANP-N values were the highest in the group with high exposure, 0.43 nmol/l (SD 0.3). The corresponding values of the low exposure and control groups were 0.36 (SD 0.11) and 0.37 (SD 0.08) respectively. The p value was 0.008 for

Table 2 Characteristics of cumulatively most exposed workers and age stratified controls participating in the echocardiographic examination

Characteristic	Exposed group (n = 122)	Control group (n = 60)
Age (y)		
Mean (SD)	46.8 (8.1)	47.2 (8.1)
Median (range)	49 (27–62)	49 (28–60)
Height (cm)		
Mean (SD)	177.6 (5.7)	176.2 (6.5)
Median (range)	178 (165–193)	175 (164–192)
Weight (kg)		
Mean (SD)	84.4 (12.2)	84.9 (11.5)
Median (range)	84 (59–142)	82 (67–118)
Work history (y)		
Mean (SD)	22.9 (9.7)	24.6 (7.7)
Median (range)	25 (2–34)	26 (3–36)
Exposure time to cobalt (y)*		
Mean (SD)	21.2 (9.9)	
Median (range)	24 (1–34)	
Exposure to cobalt (mg-y)		
Mean (SD)	0.58 (0.51)	
Median (range)	0.47 (0.03–2.52)	

*Regularly >0.01 mg Co/m³.

exposure group effect and 0.017 for age. The p value for the interaction of age and group was not significant (p=0.485).

Diseases

There were no significant differences between the exposure group and the control group in the prevalence of reported cardiovascular diseases, diabetes mellitus, or pulmonary diseases, except asthma, diagnosed by a physician (table 6).

Former workers

Of the former cobalt and zinc plant workers, altogether 404 persons responded to the questionnaire (that is, 76% of the former cobalt plant workers and 51% of the former zinc plant workers). Twelve workers (5%) had left their work in the cobalt plant due to some form of cardiovascular disease: 10 cases of coronary artery disease or myocardial infarction, one diagnosed case of heart failure, and one diagnosed case of cardiac arrhythmias. In four cases (2.5%) the reason for leaving the zinc plant had been some form of cardiovascular disease: three cases of coronary artery disease and one case of hypertension.

DISCUSSION

This study is the first to have a large occupationally exposed study population and to use modern methods to assess the possible effects of cobalt on the cardiovascular system. Cobalt exposure had been monitored with exceptional accuracy from the early days of the studied plant. The cobalt plant and the zinc plant, from which the controls were taken, have both been business units of the same corporation. Therefore the employees had been recruited using similar criteria, for example, by using the expertise of the company's occupational health professionals. Most of the workers who were invited to take part in the study, 98% of the controls, and all the workers in the exposed group participated. The characteristics of the groups, including the measured confounding factors of cardiomyopathy and ischaemic cardiac disease, were very similar. The health reasons for leaving the job were equally distributed in both groups of retired persons.

Because the minimum exposure requirement for cobalt was one year (ever), there were many workers in the exposed group who had changed job tasks and were not exposed to cobalt at the time of the study. Some of them had not been exposed to cobalt for many years, even decades. Therefore, we studied those with recent or past exposure and those with cumulatively high or low exposure separately. Since cumulative exposure becomes higher with age and several echocardiographic parameters are age related, we used age limits (that is, workers under and over 50 years) similar to those used by the European Study Group on Diastolic Heart Failure.[17]

The production processes in the cobalt and zinc plants have several phases, and, therefore, the plant workers had been exposed, for example, to several metals and gases. Workers exposed to lead or arsenic were excluded from the study, and, as far as we know, the two environments offered no exposure to agents that would have harmful effects on the cardiovascular system.

Cardiomyopathy has been reported (in case reports) in relation to industrial cobalt exposures, sometimes with alcohol consumption, after the inhalation of cobalt concentrations of 0.1 mg/m³ or higher for varying periods of time.[18] The mean levels of cobalt in the ambient air in this plant have been generally at the level of the current occupational exposure limit in Finland (that is, 0.05 mg/m³). During the first years of cobalt production the cobalt levels may have been considerably higher (that is, over 1 mg/m³), especially in the roasting department. The Finnish occupational limits have often been exceeded also in the reduction and powder

Table 3 Echocardiographic results

| Variable | Group | | | | | | Age (p value) | Group (p value) | Age* group (p value) | Covariates (p value) |
| | Exposure to cobalt >0.47 mg·y n=55 | | Exposure to cobalt <0.47 mg·y n=54 | | Control n=57 | | | | | |
	Mean (SD)	Adjusted mean	Mean (SD)	Adjusted mean	Mean (SD)	Adjusted mean				
LA (mm/m²)*	19.7 (2.6)	–	18.7 (2.0)	–	19.7 (2.6)	–	0.054	0.218	0.692	–
RVD (mm/m²)	11.3 (2.3)	–	11.2 (2.3)	–	11.5 (2.1)	–	0.012	0.821	0.498	–
RVS (mm/m²)	10.5 (1.6)	–	10.6 (1.9)	–	10.9 (1.8)	–	0.036	0.394	0.425	–
LVEDD=LVEDIDI (mm/m²)	26.7 (2.5)	–	26.5 (2.5)	–	27.0 (2.3)	–	0.679	0.453	0.618	–
LVESD (mm/m²)	16.7 (2.4)	–	16.7 (2.1)	–	17.0 (1.9)	–	0.626	0.368	0.224	–
IVSD (mm/m²)	6.2 (1.0)	6.3	6.0 (0.8)	6.0	6.1 (0.7)	6.0	0.075	0.198	0.294	bp (0.012)
IVSS (mm/m²)*	8.3 (1.1)	8.3	7.9 (1.0)	8.1	8.0 (0.9)	8.0	0.026	0.292	0.370	bp (0.009)
LVPWD (mm/m²)*	5.7 (0.8)	–	5.3 (0.6)	–	5.25 (0.6)	–	0.024	0.005	0.058	–
LVPWS (mm/m²)*	8.2 (1.0)	–	7.9 (1.0)	–	7.9 (1.1)	–	0.208	0.196	0.158	bp (0.009)
LVMASS (gr/m²)	149.9 (28.1)	150.9	145.1 (24.0)	145.2	145.5 (29.3)	145.2	0.865	0.481	0.998	bp (0.016)
(IVSD+LVPWD)/LVEDD ratio	0.45 (0.09)	0.46	0.44 (0.06)	0.44	0.42 (0.05)	0.42	0.263	0.017	0.064	bmi (0.009)
IVRT (ms)*	53.3 (7.9)	53.6	49.1 (7.2)	49.2	49.7 (10.0)	49.8	0.022	0.010	0.243	hr (0.034)
E/A ratio*	1.33 (0.33)	1.32	1.41 (0.36)	1.37	1.37 (0.34)	1.39	0.041	0.398	0.197	bp (0.002)
DT (ms)*	194.3 (32.1)	192.4	180.5 (28.2)	179.1	171.7 (28.5)	172.0	0.179	0.001	0.151	hr (<0.001)
EF (%)	75.2 (6.2)	–	74.9 (5.2)	–	74.5 (5.2)	–	0.060	0.527	0.138	hr (<0.001)
FS (%)	37.6 (5.1)	–	37.3 (4.2)	–	36.9 (4.5)	–	0.124	0.522	0.161	–

*Logarithmic transformation was made for the outcome variable before the analysis.
LA, left atrium; RVD, right ventricle (diastolic); RVS, right ventricle (systolic); LVEDD, left ventricular end diastolic diameter; LVEDIDI, left ventricular end diastolic diameter index; LVESD, left ventricular end systolic diameter; IVSD, interventricular septum (diastolic); IVSS, interventricular septum (systolic); LVPWD, left ventricular posterior wall (diastolic); LVPWS, left ventricular posterior wall (systolic); LVMASS, left ventricular mass; IVRT, isovolumic relaxation time; E, early rapid filling wave; A, filling wave due to atrial contraction; DT, deceleration time; EF, ejection fraction; FS fractional shortening.
The diameters and LVMASS normalised for body surface area.

Table 4 Electrocardiographic findings and conduction parameters

Findings, classified according to the Minnesota method	Exposed group (n = 203) %	Control group (n = 94) %	Difference*	95% CI†
Q and QS patterns	0.5	3.3	−2.8	−6.6 to 1.0
QRS axis deviation	2.5	1.1	1.4	−1.6 to 4.4
High amplitude R waves	21.2	23.9	−2.7	−13.1 to 7.7
T wave items	0.5	2.2	−1.7	−4.9 to 1.5
A-V conduction defect	3.9	1.1	2.8	−0.6 to 6.2
Ventricular conduction defect	1.5	6.5	−5.0	−10.3 to 0.3
Arrhythmias	8.4	9.8	−1.4	−8.6 to 5.8
S-T segment increase	3.9	2.2	1.7	−2.3 to 5.7
Conduction parameter				
PR time (ms)				
Mean (SD)	164 (24)	165 (23)		
QRS time (ms)				
Mean (SD)	98 (11)	99 (9)		
QTc time (ms)				
Mean (SD)	407 (19)	411 (17)		
QT time (ms)				
Mean (SD)	418 (39)	418 (34)		
Heart rate/minute				
Mean (SD)	59 (10)	60 (11)		

*Difference between the percentages.
†95% confidence interval for the differences between the percentages.

production departments. Results from the biological monitoring show that marked exposure still exists regardless of an intensified use of respirators. Since the workers have been exposed to many different cobalt compounds, it was not possible to study the differences in the toxicity of the compounds.

In most cardiac diseases the initial sign of dysfunction is impaired relaxation.[16] We found that higher cobalt exposure

Table 5 Blood pressure, heart rate, and laboratory test results

	Exposed group (n = 203)	Control group (n = 94)
Blood pressure, systolic (mm Hg)		
Mean (SD)	134 (15)	137 (15)
Median (range)	134 (102–188)	137 (102–179)
Blood pressure, diastolic (mm Hg)		
Mean (SD)	87 (10)	88 (11)
Median (range)	86 (64–121)	87 (68–124)
Heart rate/minute		
Mean (SD)	69 (11)	68 (12)
Median (range)	68 (44–113)	66 (45–102)
Serum gamma-glutamyl transferase, S-GT (U/l)		
Mean (SD)	50.0 (66.3)	41.2 (24.1)
Median (range)	32 (11–743)	35 (14–149)
Serum carbohydrate deficient transferrin, S-CDT (U/l)		
Mean (SD)	15.6 (4.8)	15.1 (4.3)
Median (range)	15 (8–38)	14 (8–30)
Blood vitamin B1, B-B$_1$-vit (nmol/l)		
Mean (SD)	148 (29)	153 (31)
Median (range)	145 (88–233)	149 (94–246)
Serum total cholesterol (mmol/l)		
Mean (SD)	5.5 (1.1)	5.4 (1.1)
Median (range)	5.4 (3.1–8.6)	5.3 (3.0–8.1)
Serum LDL cholesterol (mmol/l)		
Mean (SD)	3.6 (1.0)	3.5 (0.9)
Median (range)	3.5 (1.2–6.3)	3.5 (1.6–6.1)
Serum HDL cholesterol (mmol/l)		
Mean (SD)	1.3 (0.3)	1.3 (0.3)
Median (range)	1.2 (0.6–3.0)	1.2 (0.6–2.4)
Serum triglycerides (mmol/l)		
Mean (SD)	1.6 (0.9)	1.5 (0.9)
Median (range)	1.3 (0.3–6.3)	1.3 (0.5–5.5)
Serum glucose (mmol/l)		
Mean (SD)	5.4 (0.6)	5.4 (1.0)
Median (range)	5.3 (4.2–8.6)	5.3 (4.2–10.5)
Serum free thyroxine, S-T$_4$-V (pmol/l)		
Mean (SD)	12.8 (1.6)	13.6 (2.9)
Median (range)	12.7 (9.5–17.5)	13.3 (10.0–35.0)
Serum thyroid-stimulating hormone, S-TSH (mU/l)		
Mean (SD)	1.9 (1.2)	2.0 (0.9)
Median (range)	1.7 (0.3–13.7)	1.9 (0.6–4.8)

Table 6 Prevalence of reported diseases diagnosed by a physician

Disease	Exposed group (n = 203) %	Control group (n = 94) %	Difference†	95% CI‡
Ischaemic heart disease*	3.4	2.2	1.2	−2.7 to 5.1
Heart failure	0.5	0.0	0.5	−0.5 to 1.5
Heart arrhythmias	8.0	14.3	−6.3	−14.4 to 1.8
Cardiomyopathy	0.0	0.0		
Any other cardiac disease	2.5	2.2	0.3	−3.4 to 4.0
Hypertension	14.3	16.3	−2.0	−11.0 to 7.0
Stroke	0.5	0.0	0.5	−0.5 to 1.5
Claudicatio intermittens	0.5	1.0	−0.5	−2.8 to 1.8
Bronchial asthma	2.5	0.0	2.5	0.3 to 4.7
Chronic bronchitis	2.0	3.3	−1.3	−5.4 to 2.8
Emphysema	0.0	0.0		
Any other chronic lung disease	3.0	2.2	0.8	−3.0 to 4.6
Diabetes mellitus	1.0	3.2	−2.2	−6.0 to 1.6

*Coronary heart disease or myocardial infarction or both.
†Difference between the percentages.
‡95% confidence interval for the differences between the percentages.

was associated with altered left ventricular diastolic function, as measured by Doppler echocardiography. The isovolumic relaxation time (IVRT) was prolonged with higher exposure. This occurrence, as well as a prolonged deceleration time (DT) among the exposed persons, may support the theory of D'Adda and colleagues,[8] who reported that an accumulation of cobalt in the myocardium might result in increased myocardial stiffness. The fact that the level of cumulative exposure, rather than the time of the exposure, affected the results also supports this conclusion. The ratio between the wall thickness and left ventricular diameter measured at end diastole tended to increase as the exposure increased. Despite their limitations, these results concur with the findings on diastolic parameters. We contrasted the disease histories, including hypertension, between exposed and control workers, and concluded that they were sufficiently similar to have minimal effect on the outcome measures, but we did not obtain further information on risk factors such as stress and personality. In our earlier study of this cobalt plant, we found that cobalt exposure did not cause pulmonary fibrosis or hard metal disease.[19] Therefore, the echocardiographic changes described in our report, we believe, were not due to changes in pulmonary function, as some researchers have suggested.[7][8]

No signs of systolic cardiac dysfunction were found. The ejection fraction (EF), fractional shortening (FS), and left ventricular end diastolic diameter (LVEDD), were similar in the exposed and control groups.

In our study the same observer performed all the echocardiographic measurements. Because intra-observer errors are lower than those between two observers,[20][21] and because the inter-observer coefficients of variation in our reproducibility study were moderate, the results of the echocardiographic measurements can be considered reliable. Especially for LVEDD and DT, even the inter-observer coefficients of variation were low.

There were no differences in the ECG parameters, including heart rate, between the exposed and control workers. This finding contrasts with those reported by Alexandersson and colleagues[9][10] and Raffn and colleagues.[11] The cobalt exposure levels in these studies were similar or markedly higher than the levels of our study. This finding implies that cobalt exposure of this level in cobalt production does not cause ECG changes or the ECG may be too insensitive to register minor changes in the myocardium or the conduction system.

The S-ANP-N concentrations of the highly exposed group were greater than those of the other groups, but their dependency on parameters describing left ventricular size (the ratio IVSD+LVPWD/LVEDD) and left ventricular diastole (IVRT and DT) was poor.

In summary, we found no major cardiac dysfunction that could be directly attributed to cobalt exposure. Cumulative cobalt exposure was associated with echocardiographic changes that suggest altered left ventricular relaxation and early filling. Minor increases in left ventricular wall thickness concurred with these observations. A possible mechanism behind the findings in our study could be the accumulation of cobalt in the myocardium, the result being an increase in myocardial stiffness. The clinical significance of these changes, however, needs further evaluation.

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ECHO ....

Exposure to fume emitting heaters in the first year of life found to be associated with asthma in later childhood

Please visit the *Occupational and Environmental Medicine* website [www.occenvmed.com] for a link to the full text of this article.

Primary school children exposed to fume emitting heaters during their first year of life have been found to have more airway hyperresponsiveness (AHR) and wheeze than those not so exposed, according to a case-control study from New South Wales, Australia.

A total of 627 children aged between 8 and 11 years (51% of the target population) were tested for AHR by a histamine challenge test, and also for atopy by skin prick tests to common allergens. Parents completed questionnaires which included questions about exposure at home to pets and tobacco smoke and the type of heating and cooking appliances used–both during the first year of life and currently.

The predominant types of fume emitting appliances were non-flued gas type heaters and wood stoves. There was a strong association between the use of these appliances during the child's first year of life and the presence between the ages of 8 and 11 of AHR (adjusted relative risk 1.47, 1.06 to 2.03), recent wheeze (1.44, 1.11 to 1.86), and current asthma (2.08, 1.31 to 3.31). There was no association with atopy or with current use of fume emitting heaters.

This study reflects the importance of different exposures in early life in the aetiology of asthma. Although limited by a low response rate, if the findings were to be confirmed in other settings, there would be implications for the type of heating suitable for houses in which young children live.

▲ Phoa LL, et al. Thorax 2004;**59**:741–745.

PUBLICATION
IV

Effects of occupational cobalt exposure on the heart in the production of cobalt and cobalt compounds: a 6-year follow-up

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ORIGINAL ARTICLE

Effects of occupational cobalt exposure on the heart in the production of cobalt and cobalt compounds: a 6-year follow-up

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Abstract

Objective It has been suspected that cobalt is toxic to the heart. It can cause cardiotoxicity in heavily exposed humans and in experimental systems. The issue of interest for this study is whether cobalt also affects the myocardium at occupational exposure levels.

Methods To study the effect of occupational cobalt exposure on the heart, we conducted a follow-up of workers at a cobalt production plant. The workers' hearts had been examined by echocardiography in 1999–2000. Altogether 93 exposed and 49 non-exposed workers examined in 1999–2000 were re-examined in 2006. Occupational history and health data were collected with a questionnaire. Blood pressure was measured, and electrocardiography (ECG), laboratory tests, Holter registration, and echocardiography were conducted for all participants. Analysis of covariance (ANCOVA) was used to analyse the data.

Results No differences were found between the exposed and unexposed groups for any of the echocardiographic parameters in 2006. There were no differences in the laboratory values, the ECG parameters, or the results of the Holter registration of the exposed and unexposed workers.

Conclusions Although the previous results in 2000 suggested an association between cumulative exposure to cobalt and echocardiographic findings, the results of this new cross-sectional study with a tissue Doppler 6 years later did not confirm the association in the present cohort. If cobalt exposure affects heart muscle functions at this exposure level, the effects are smaller than those caused by physiological changes due to ageing, medication, and traditional cardiovascular risk factors, such as elevated blood pressure.

Keywords Cardiomyopathy · Cobalt exposure · Work-related heart symptoms and disease · Echocardiography

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Introduction

The toxic potential of cobalt and related health risks have been investigated thoroughly in animal and human toxicity studies. Systemic toxic reactions may arise when Co ions enter the blood and lymphatic circulation and subsequently disseminate to different organs. In vitro experiments have demonstrated that ionized cobalt (Co2 +) is the primary toxic form for systemic toxicity (Leyssens et al. 2017). Various pathogenetic mechanisms related to possible cardiac effects have been suspected in hard-metal workers. According to some authors, the most likely effect is the inhibition of cellular respiration due to the inhibition of mitochondrial dehydrogenase (Seghizzi et al. 1994). Systemic Co toxicity manifests as a clinical syndrome with a variable presentation of neurological, cardiovascular, sensitizing, and endocrine symptoms, depending on the systemic Co levels (blood/urine).

Single cardiomyopathy cases have been reported among persons exposed occupationally to cobalt (Kennedy et al. 1981; Jarvis et al. 1992). In two small groups of hard-metal workers studied earlier, a weak but still significant inverse correlation was found between exposure time and the left ventricular ejection fraction as measured by radionuclide ventriculography (Horowitz et al. 1988).

A significantly lower left ventricular ejection fraction during both rest and exercise was found among men exposed to cobalt and diagnosed with hard-metal disease compared to those who had not been diagnosed with this disease (d'Adda et al. 1994) when measured by radionuclide ventriculography and echocardiography. The researchers assumed that this finding may have been due to increased diastolic pressure caused by increased wall stiffness and fibrosis due to cobalt deposits in the myocardium. In addition, hypertension and reversible electrocardiographic changes (depressed ST segment and T waves) and arrhythmias have been found more frequently among persons who have been exposed to an average cobalt concentration of 0.01 mg Co/m^3 in hard-metal work than among persons in a reference group (Alexandersson and Atterhög 1980, 1983).

In our previous cross-sectional study in a cobalt production plant in 1999–2000, there seemed to be an association between cumulative cobalt exposure and two echocardiographic parameters, the deceleration time of the velocity (DT) of the early rapid filling wave and the left ventricular isovolumic relaxation time (IVRT). The results suggested that there were changes in the function of the myocardium during diastole (Linna et al. 2004). This finding supported the hypothesis that cobalt accumulation in the myocardium could affect myocardial function.

The aim of this 6-year follow-up was to assess the effects of cobalt exposure on functional or structural changes in the heart muscles of cobalt-exposed cobalt production workers who had been examined by echocardiography in 1999–2000.

Methods

Cobalt process and exposure

The cobalt plant featured in this study is located in Kokkola on the west coast of Finland. Between 1966 and 1987, cobalt powder was produced from pyrite ore concentrate. Thereafter, cobalt powder, inorganic cobalt, and nickel compounds have been produced using by-products of the metallurgic industry as raw material (Linna et al. 2004).

Exposure to most dusts and gases in the process has been regularly monitored several times annually since 1966. Air samples have been collected by an authorized hygienist both at stationary points and with personal samplers in the workers' breathing zones. Exposure to cobalt has varied greatly in range according to the job role even within the same department. The range has been 0.02–1.0 mgCo/m^3 in the sulphatising roasting department, 0.01–0.05 mgCo/m^3 in the leaching and solution purification department, 0.05–0.25 mgCo/m^3 in the reduction and powder production department, and 0.01–0.20 mgCo/m^3 in the chemical department (Fig. 1) (Linna et al. 2004).

The mean exposure levels to cobalt and its compounds were slightly above the current Finnish occupational exposure limit (0.05 mg/m^3) before 1987, and they have been slightly under the limit since the new process was initiated (Linna et al. 2004). According to the biological monitoring surveillance, exposure to cobalt has been the highest in the reduction department. The company's occupational health care unit has measured cobalt urinary concentrations (U-Co); in 1999–2000, levels of

Fig. 1 Exposure levels (mean) by departments (mg/m^3)
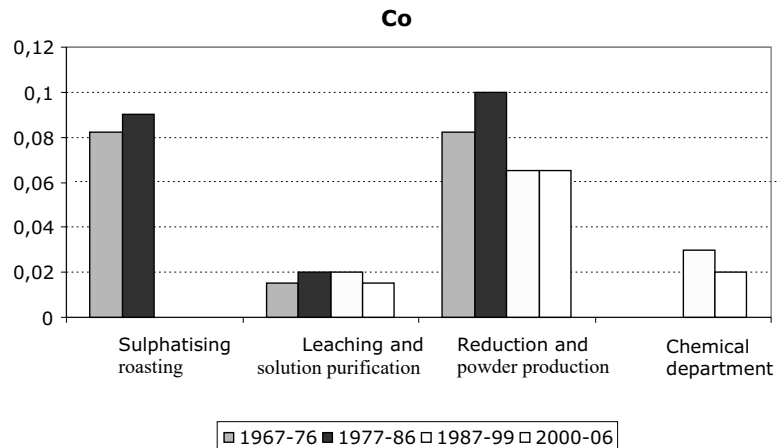
U-Co were 11–4107 nmol/l (median 240 nmol/l, $N = 29$), while in 2005–2006, they were 6–6278 nmol/l (median 230 nmol/L, $N = 113$).

Cumulative exposure to cobalt, presented as milligram-years (mg-years), was calculated for each worker using a job-exposure matrix based on ambient air measurements (Linna et al. 2004). In this study, we completed the information on cumulative exposure using the exposure data collected during the follow-up period. Between 2000 and 2006, there were no major changes in the technology or processes at the factory, and the exposure levels remained stable. In the control group (zinc plant workers), all the workers were exposed to zinc, but not to cobalt. For four-fifth of the zinc workers, the zinc exposure levels were 0.1–0.2 mg/m^3, and for the remaining fifth, the levels were around 1 mg/m^3.

Design and participants

The employees who participated in this study had already been working in the cobalt plant at the end of 1999, and they had been exposed to cobalt for at least 1 year (the exposed group). The reference group had not been exposed to cobalt. In both groups, workers exposed to confounding exposure agents, such as lead and arsenic, were excluded. Persons with congenital or acquired cardiac valvular disease and those with a history of myocardial infarction were excluded from the echocardiographic analysis. In this follow-up study, we invited all the workers who had been examined by echocardiography in 1999–2000 and whose results were included in the analyses. Four employees from the earlier exposed group and one from the unexposed group had died; the cause of death of one of the exposed workers was heart infarction. The deaths of the other deceased workers were not related to cardiovascular diseases. Altogether, 19 persons were unwilling to participate or could not be contacted. Of the previously examined workers exposed to cobalt ($n = 109$), 93 (85%) were re-examined, as were 49 (86%) of the 57 who had been in the unexposed reference group. The project was separate from routine health examinations by the occupational health services. The workers were examined in 2006 within a period of 6 months. Participation was voluntary, and all participants gave their written informed consent. The study plan was approved by the Coordinating Ethics Committee of the Helsinki University Hospital District.

Questionnaire

Data on working history at the plant after 2000 were requested with a self-administered questionnaire. The reasons for changing working tasks, jobs, or workplaces were also requested. We inquired about the level of stress, shift work, physical exercise, smoking, alcohol consumption, symptoms of chest pain or shortness of breath, diseases diagnosed by a physician (cardiovascular and pulmonary diseases, diabetes), and medication.

Blood pressure measurement and electrocardiography

Blood pressure was measured after 10 min of rest in a sitting position using an automatic Omron 705CP (Omron Matsusaka Co Ltd, Japan), which was tested and validated by the importer before and after the study. After two measurements, the lower systolic and diastolic pressure and pulse were noted. A standard 12-lead electrocardiogram was obtained using 12-channel ECG equipment (Marquette Electronics Inc., Milwaukee WI, USA) at a paper speed of 50 mm/s. The recordings were analysed independently by two experienced clinicians, who both coded the recordings without knowing their origin (exposed/referent). Coding was performed according to the Minnesota 1982 method (Rose et al. 1982).

Laboratory tests

As a random sample, we selected 76 persons from the exposed and unexposed groups. Serum gamma-glutamyl transferase (S-GT) and carbohydrate-deficient transferrin (S-CDT) levels were analysed. In addition, the serum lipid and glucose values of all participants, which had been recorded in health examinations during the previous 2 years, were also extracted from the files of the factories' occupational health centre.

Holter registration

Long-term ECG registration was recorded with Holter technics (24-h signal sampling with a three-channel device, Braemar Inc., USA). The results were interpreted by a physician (HL) who is specialized in clinical physiology. Registrations were started at the beginning of the work shift and continued overnight until the next day. The participants marked their activities and symptoms during the registration period in a diary.

Echocardiography

Echocardiography was performed in the standard fashion using a GE Medical Systems Vivid 7/2006 ultrasound device with a 2.5-Mhz transducer and an EchoPac workstation. Conventional echocardiographic images were obtained according to the guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging (Lang et al. 2005). Echo exams were performed by a single operator (MH). Left ventricular

mass (LVMASS) was calculated according to the formula of Devereux et al. (1986). We performed spectral Doppler measurements of blood flow by aligning the interrogating beam with the direction of flow according to anatomical and colour Doppler information. Mitral flow was obtained with the pulsed Doppler sampler (sample volume 4–5 mm in length) at the valve tips. Early diastolic filling velocity (E), peak atrial filling velocity (A), E/A ratio, E-wave deceleration time (DT), and slope were measured from the left ventricular filling recordings. We measured the isovolumic relaxation time (IVRT) using the technically better pulsed or continuous wave recording of the mitral inflow and the left ventricular outflow. No angle correction was used. Valvular regurgitation was quantified according to the colour Doppler information from multiple views. We recorded ventricular long-axis motion from the lateral and septal myocardium using pulsed-wave tissue Doppler imaging (TDI) in an apical four-chamber view with a small sample volume (2–3 mm in length) positioned in the myocardium of the basal ventricular wall, about 1 cm from the mitral annulus. Early diastolic myocardial tissue velocity (E_m), diastolic myocardial tissue velocity after atrial contraction (A_m), and their ratio (E_m/A_m) were recorded. E_m deceleration time and slope were also measured. The E/E_m ratio was calculated (Otto 2004). The mean of at least three consecutive beats was used. Images were stored on videotape on a Sony videocassette recorder (SVO-9500MDP), on optic disks in an Echopac Workstation, and on paper from a thermal printer (UP-890CE). The echocardiograms were analysed by a single experienced clinician without knowledge of the status of the examined persons (exposed/referent). MH performed the measurements, and another cardiologist (VV) checked the results of the measurements. The interobserver error was investigated from a sample of 30 echocardiograms, and no significant differences were observed, the coefficient of the variation of echo parameters being 2.3–18.5.

Statistical methods

The normality of the variables was checked, and logarithmic transformation was applied if the distribution of the variable was skewed. The crude means and standard deviations are reported in the tables. The paired t test, the independent samples t test, and the McNemar test were used in the analysis of the differences between the study groups.

An analysis of covariance (ANCOVA) was used to study the echocardiograph data. A backward stepwise regression analysis was performed on all the echocardiographic parameters so that age, exposure, and their interaction were always included in the model. Body mass index was included if the outcome variable had not been divided by body surface area, and heart rate was used if the outcome variable was time related. ANCOVA was also used to study the differences

in the echocardiographic parameters between the various designated exposure groups.

In the analyses, high and low exposure was determined based on being above or below the median mg-years of cobalt exposure (0.47 mg-years in 2000 and 0.55 mg-years in 2006). Age was included as a continuous variable in the ANCOVA analyses and categorized above and below 50 years and 56 years in the study in 2000 and in 2006, respectively. Independent factors, such as smoking (non-smoking vs current and ex-smoking), hypertension (as normal vs elevated (> 140/90) or as diagnosed hypertension), and competing athlete status (yes or no), were included in the model as dichotomous variables. In some calculations (see above), the use of alcohol (weekly consumption over 20 doses of 12 g of alcohol or SGT > 80), body mass index, and heart rate were included in the model as covariates because they were considered confounders. The echo values of the cross-sectional study in 2006 with the new tissue Doppler device were analysed and adjusted for the 2006 confounders. Those covariates with significant associations with outcome variables remained in the model because they were considered confounders.

The 95% confidence interval (95% CI) was calculated for the differences between two percentages. The level of significance in the ANCOVA was set equal to 0.05, but exact p values are reported. Computations were carried out using SPSS/Win (version 15.0) software.

Results

The characteristics of the examined groups and calculated mg-year values are given in Table 1.

There were no significant differences in characteristics between the exposed and unexposed groups in 2006. The BMI had increased significantly in the exposed group during the follow-up. Both groups seemed to have decreased their current smoking level. Alcohol consumption had increased in both groups—significantly in the exposed group. The participants in the exposed group tended to have increased their leisure-time sport activities, but not statistically significantly ($p = 0.065$). On the contrary, the participants in the unexposed group had decreased their leisure-time sport activities, especially the duration and level of strain (data not shown). There was no significant difference in reported stress between the exposed and unexposed groups (data not shown). In the study group, 71% worked shifts, whereas 50% of the controls worked shifts.

Table 1 Characteristics of the exposed and unexposed groups in 2000 and 2006

		Exposed group ($n=93$)		Unexposed group ($n=49$)	
		2000	2006	2000	2006
Age (year)	Mean (SD)	47 (8.3)	53 (8.3)	48 (7.8)	54 (7.8)
	Median (range)	50 (28–63)	56 (34–69)	50 (29–61)	56 (35–67)
Body mass index	Mean (SD)	26.9 (3.4)	27.7 (3.7)	26.9 (3.2)	27.5 (3.5)
	Median (range)	26.5 (21.6–35.0)	27.2 (20.5–37.9)	26.5 (21.6–35.0)	27.1 (21.2–36.9)
Work history (years)	Mean (SD)	22.5 (9.9)	28.1 (9.6)	23.8 (8.0)	29.5 (8.0)
	Median (range)	25 (2–34)	31 (8–40)	26 (3–25)	32 (7–41)
Exposure time to cobalt (years)[a]	Mean (SD)	20.7 (10.0)	25.7 (9.8)	–	–
	Median (range)	23.0 (0–34)	28.0 (0–39)	–	–
Exposure to cobalt (mg-years)	Mean (SD)	0.56 (0.51)	0.82 (0.79)	–	–
	Median (range)	0.45 (0.06–2.5)	0.55 (0.10–4.1)	–	–
Smoking status (%)	Non-smokers	29%	33%	33%	37%
	Ex-smokers or smokers	71%	67%	67%	63%
Consumption of alcohol (drinks/ week)	Mean (SD)	5.0 (4.8)	5.9 (5.6)	6.5 (5.4)	7.1 (6.3)
	Median (range)	3.0 (0–20)	4.3 (0–26)	6.0 (0–20)	5.0 (0–25)
Competing athlete status (%)	No	91%	85%	79%	88%
	Now or earlier	9%	15%	21%	12%
Leisure-time sport activities (%)	No, never	5%	3%	4%	8%
	Yes, two times a week or less	51%	52%	46%	47%
	Yes, at least three times a week	44%	45%	50%	45%

[a]Regularly > 0.01 mg Co/m^3

Symptoms, diagnosed diseases, and medication

There were no differences between the two study groups in relation to symptoms, diagnosed diseases, and medication in 2006, except for the participants in the exposed group more often reporting asthma and other pulmonary diseases (Table 2).

For both the exposed group and the unexposed group, hypertension was reported more often than 6 years earlier. In both groups, the increase in physician-diagnosed hypertension was significant during the follow-up period. In the unexposed group, the prevalence of high blood pressure had almost doubled. The proportion of persons using antihypertensive or other heart medication had increased in both groups. The use of beta-blockers was more common in the unexposed group.

Subjective complaints of irregular heartbeats (arrhythmia) had increased in the exposed group, but the prevalence was at the same level in both groups in 2006 (Table 2).

Blood pressure, electrocardiographic findings, and laboratory tests

There were no differences in measured blood pressure, electrocardiographic findings, or laboratory tests between

Table 2 Prevalence of reported diseases diagnosed by a physician in the exposed and unexposed groups in 2000 and 2006

	Exposed group ($n=93$)		Unexposed group ($n=49$)	
	2000 %	2006 %	2000 %	2006 %
Myocardial infarction	0	1	0	2
Coronary heart disease	2	3	4	4
Heart failure	0	0	0	0
Dilated heart	0	3	2	4
Heart arrhythmias	6	14**	21	16
Cardiomyopathy	0	0	0	0
Any other cardiac disease	1	3	0	0
Hypertension	23	32*	21	37**
Stroke	0	2	0	0
Claudicatio intermittens	1	3	2	2
Bronchial asthma	1	7	0	0
Chronic bronchitis	2	2	2	0
Emphysema	0	0	0	0
Other chronic lung disease	4	7	2	2

McNemar test: *$p < 0.05$; **$p < 0.01$

these two study groups in 2006, except that the exposed group had higher CDT values (Table 3). The S-CDT mean was increased in the exposed group, and the difference in the changes between the groups was significant. The S-LDL mean had decreased significantly in the unexposed group, but, again, the differences between the changes in the two groups between 2000 and 2006 were not significant (Table 3).

Both systolic and diastolic blood pressure had risen in the exposed group in 2006 when the levels were compared to the results from 2000 ($p < 0.05$ and $p < 0.001$, respectively), but the differences in the changes in 2000–2006 between the two groups were not significant (Table 3).

There were no significant differences in the changes in the ECG findings in 2000–2006 between the two groups (Table 4).

Table 3 Blood pressure, heart rate, and laboratory test results in the exposed and unexposed groups in 2000 and 2006

		Exposed group ($n=93$)			Unexposed group ($n=49$)			t test between the group differences
		2000	2006	Difference	2000	2006	Difference	p value
Systolic blood pressure, mmHg	Mean	135.2	142***	6.8	138.3	140.8	2.5	0.159
	SD	15.5	15.0	16.4	14.9	17.1	17.5	
Diastolic blood pressure, mmHg	Mean	87.7	90.1*	2.3	89.2	89.3	0.02	0.217
	SD	9.7	8.4	9.9	10.4	9.5	11.2	
Serum gamma-glutamyl transferase, S-GT (U/l)	Mean	50.4	52.8	2.40	35.5	41.7	6.2	0.482
	SD	56.4	47.6	29.9	15.5	31.7	27.7	
Serum carbohydrate-deficient transferrin, S-CDT (U/l)	Mean	1.5	1.6	0.09	1.6	1.3	−0.30	0.048
	SD	0.3	0.5	0.4	0.49	0.79	0.9	
Serum glucose (mmol/l)	Mean	5.4	5.5	0.09	5.7	5.5	−0.17	0.251
	SD	0.7	0.5	0.93	1.1	0.7	1.4	
Serum total cholesterol (mmol/l)	Mean	5.5	5.4	−0.08	5.7	5.4	−0.33	0.383
	SD	1.2	1.1	1.7	1.0	0.8	1.3	
Serum HDL cholesterol (mmol/l)	Mean	1.3	1.4	0.10	1.3	1.3	0.00	0.353
	SD	0.3	0.4	0.6	0.4	0.4	0.5	
Serum triglycerides (mmol/l)	Mean	1.6	1.6	−0.01	1.6	1.8	0.11	0.661
	SD	0.9	0.8	1.2	1.1	1.7	2.1	
Serum LDL cholesterol (mmol/l)	Mean	3.6	3.4	−0.24	3.6	3.3*	-0.38	0.578
	SD	1.0	0.9	1.4	0.9	0.7	1.1	

Paired t test: *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Table 4 Electrocardiographic (ECG) conduction parameters for the exposed and unexposed groups in 2000 and 2006

		Exposed ($n=93$)			Unexposed ($n=49$)			t test
		2000	2006	Difference	2000	2006	Difference	p value
PR time, ms #	Mean	164.4	166.4		167.9	169.8		
	SD	24.5	23.6		25.8	24.3		
QRS time, ms	Mean	97.1	96.3	−0.8	99.4	96.7	−2.8	0.296
	SD	10.3	11.9	10.6	8.8	13.3	10.6	
QTc time, ms	Mean	408.3	408.7	0.4	410.8	410.0	-0.8	0.762
	SD	20.3	18.5	22.1	16.8	15.7	20.1	
QT time, ms	Mean	417.7	399.3***	−18.4	416.1	414.7	−1.5	0.062
	SD	37.8	33.4	43.6	64.0	35.2	62.0	
Pulse/min	Mean	59.1	63.9***	4.8	58.0	60.3	2.3	0.173
	SD	8.2	10.5	10.3	9.6	10.7	9.9	

2006 values PQ time

Paired t test:*$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

Holter registration

Holter results were obtained only from the examinations in 2006. Abnormal results in the 24-h ECG registration appeared in 10.4% of the exposed and 9.7% of the unexposed groups. The exposed group had more ventricular extrasystolic (VES) beats than the unexposed group (mean 209 (SD 1098) vs 114 (SD 362), respectively), and the unexposed group had more atrial extrasystolic beats (AES) than the exposed group (mean 216 (SD 1296) vs 87 (SD 392), respectively). Only one case of severe arrhythmia was found, and it had already been recognized in one of the referents.

Echocardiography

One person with a history and echocardiographic signs of myocardial infarction was excluded from echocardiographic analysis in both groups. No signs of cardiomyopathy or cardiac failure/insufficiency were found clinically at the individual level.

The echocardiographic results for 2006 are presented in Table 5. Using the ANCOVA models, we considered the difference in the echo variables between the exposed and unexposed groups in 2006. In this analysis, the values of the echo parameters were adjusted to the other variables in 2006. There were no differences in any parameter measuring heart volumes, wall thickness, or muscle mass between the exposed and unexposed groups in 2006. Only A_m tissue was smaller in the unexposed group. There were no differences either in the DT and IVRT values between the study groups. There were no differences in any of the echocardiographic parameters in 2000 between those who participated in 2006 and those who did not (data not shown).

Discussion

This study is the first follow-up cohort study to assess the effects of occupational cobalt exposure on the cardiovascular system. We carried out a 6-year follow-up with echocardiography in a cobalt production plant. Cobalt exposure was not associated with detrimental effects on the function or structure of the heart muscle, and it did not seem to have caused damage to the cardiovascular system.

We performed a cross-sectional study in 2000 (Linna et al. 2004) and repeated it in 2006 for those who had been examined with echocardiography in 2000. There are several strengths to our study. All the participants were re-examined by the same investigator (a cardiologist). Our study was based on a large, occupationally exposed study population, and we could take the advantage of a reliable modern method, namely echocardiography with a tissue Doppler. Participation rate is high (85% and 86% in the exposed and unexposed groups, respectively). Another strength of the study was the exposure assessment, which was based on regular industrial hygienic measurement over decades. The weaknesses of the study include the limited number of participants in the unexposed group, which diminished the power of the study, and the subjective nature of the health data from the questionnaire. On the other hand, we decided to use the results of the laboratory tests as background variables to assess the possible changes in the lifestyle profiles of the groups in the follow-up. These test results were in concordance with the questionnaire results.

We have no accurate personal health information on those who did not participate in the follow-up. According to the information from the occupational health centre, no clinical cases of cardiomyopathy were found in this factory during the follow-up period. Occupational asthma has been associated with cobalt exposure, and we have published a case series on cobalt-induced asthma previously (Sauni et al. 2010). However, there is no evidence that occupational asthma is associated with a risk of heart failure. We could not see differences in any of the echocardiographic parameters in 2000 between those who participated in 2006 and those who did not. Thus, there does not seem to be a remarkable selection bias.

Echocardiography with a tissue Doppler was used in 2006, because we wanted to confirm previous findings with reliable, modern, and high-quality technology. Therefore, the results of the echo method with the tissue Doppler were not comparable with the previous Doppler echocardiography. The results in 2006 have, therefore, been analysed as a new cross-sectional study design using similar statistical models as employed in 2000.

Exposure levels of cobalt and other impurities in the air have been monitored regularly in the cobalt factory featured in our study, and this enabled individual assessment of the cumulative exposure to cobalt (Linna et al. 2004). The working environment in this study design offered no exposure to agents other than cobalt that would have had harmful effects on the cardiovascular system. Exposure to zinc does not cause effects on the heart muscle, and the group exposed to zinc was an epidemiologically ideal reference group, because it came from a factory in the same industrial area with the same recruitment criteria and similar pre-employment examination by the same occupational health unit.

These results should be applied and generalized to the exposure levels monitored in this factory. The mean exposure levels of cobalt and its compounds in the plant were slightly over the current Finnish occupational exposure limit (0.05 mg/m^3) before 1987, but they have been slightly under the limit since the new process was initiated. During the early years of cobalt production, the cobalt levels may have been considerably higher (i.e. over 1 mg/m^3), especially in the roasting department. Finnish occupational limits have

Table 5 Echocardiographic results in 2006 adjusted for age, exposure group and variables in 2006

Variable	Exposed to cobalt ≥ 0.55 mg-year (n=47) Mean (SD)	Adjusted mean	Exposed to cobalt < 0.55 mg-year (n=42) Mean (SD)	Adjusted mean	Unexposed (n=49) Mean (SD)	Adjusted mean	p value Age*	Exposure group	Age*Group	Covariates
LA	20.4 (2.2)	–	20.1 (2.1)	–	20.5 (2.5)	–	0.003	0.754	0.596	–
RVD	10.8 (2.2)	–	10.5 (2.5)	–	11.2 (2.1)	–	0.074	0.320	0.847	–
RVS	10.7 (1.7)	10.7	10.7 (2.1)	10.7	11.3 (1.7)	11.3	0.070	0.305	0.913	0.046 (bp)
LVEDD (mm/m^2)	27.4 (2.5)	27.4	27.1 (2.6)	27.1	27.5 (2.5)	27.4	0.620	0.862	0.534	0.042 (alc)
LVESD (mm/m^2)	17.1 (2.0)	17.2	16.9 (1.9)	16.9	17.1 (2.0)	17.1	0.144	0.811	0.727	0.006 (alc)
IVSD (mm/m^2)	5.5 (0.67)	–	5.7 (0.85)	–	5.6 (0.72)	–	0.008	0.247	0.326	–
IVSS (mm/m^2)	7.8 (0.80)	–	7.9 (1.0)	–	7.8 (0.91)	–	0.001	0.765	0.594	–
LVPWD (mm/m^2)	4.9 (0.49)	–	5.0 (0.54)	–	4.9 (0.53)	–	0.001	0.319	0.976	–
LVPWS (mm/m^2)	7.7 (0.77)	–	7.6 (0.85)	–	7.7 (0.81)	–	0.401	0.734	0.753	–
LVMASS	119.1 (18.4)	118.1	121.5 (26.4)	122.3	119.1 (22.6)	118.4	0.252	0.608	0.367	0.004 (bp), 0.014 (alc)
FS[a]	37.7 (4.1)	66.8	37.5 (5.2)	66.7	37.8 (5.9)	66.9	0.035	0.982	0.980	0.035 (bmi), 0.042 (alc)
EF[a]	66.9 (5.3)	66.8	66.7 (6.8)	66.7	66.8 (7.1)	66.9	0.034	0.991	0.989	–
IVSD+LVPWD/LVEDD[a]	0.40 (0.15)	–	0.39 (0.07)	–	0.38 (0.04)	–	0.018	0.737	0.484	0.002 (h)
IVRT (ms)[b]	66.9 (10.2)	66.8	68.5 (12.2)	69.4	69.6 (11.7)	68.9	0.115	0.545	0.602	0.003 (h)
DT (ms)[b]	187.4 (26.2)	186.6	183.4 (24.4)	184.2	193.9 (26.9)	192.4	0.019	0.278	0.117	< 0.001 (h)
E/A ratio[b]	1.3 (0.21)	1.3	1.5 (0.44)	1.5	1.5 (0.45)	1.5	0.104	0.115	0.860	–
E	0.67 (0.13)	–	0.68 (0.15)	–	0.70 (0.16)	–	0.314	0.622	0.297	< 0.001 (h), 0.055 (bp), 0.056 (bmi)
A	0.55 (0.15)	0.54	0.52 (0.13)	0.52	0.51 (0.11)	0.53	0.033	0.72	0.329	< 0.001 (h), 0.055 (bp), 0.056 (bmi)
E/A ratio	1.26 (0.24)	1.3	1.36 (0.33)	1.37	1.42 (0.33)	1.39	0.001	0.237	0.856	< 0.001 (h), 0.035 (bp)
DT	182.4 (26.2)	–	184.8 (26.3)	–	182.1 (25.8)	–	0.019	0.729	0.505	–
E_m tissue	0.083 (0.016)	0.084	0.081 (0.020)	0.081	0.086 (0.018)	0.085	0.003	0.498	0.244	0.028 (h)
A_m tissue	0.084 (0.014)	0.082	0.077 (0.014)	0.076	0.082 (0.014)	0.083	0.007	0.028	0.466	0.023 (bp), 0.021 (bmi), < 0.001 (h)
tissue E_m/A_m ratio	1.03 (0.27)	1.06	1.12 (0.34)	1.12	1.07 (0.30)	1.04	<0.001	0.325	0.818	0.017 (bp), < 0.001 (h)
E_mDT	93.1 (14.9)	–	90.7 (14.9)	–	94.2 (19.3)	–	0.104	0.635	0.749	–
E/E_m	8.5 (2.5)	8.4	8.6 (2.2)	8.6	8.6 (2.1)	8.6	0.021	0.83	0.314	0.002 (bmi)

Covariates in the model: exposure, age and their interaction are permanently in the model, in addition, following adjusting covariates have been put on the model, in addition, following adjusting covariates are shown, only the significant associations are shown: smoking, blood pressure > 140/90 in 2006 or earlier hypertension diagnosed by physician (bp), athlete sports (as)

E early filling wave velocity, DT deceleration time, A atrial filling wave velocity, E/A ratio ratio between velocity of early and atrial filling, E/E_m early filling wave velocity/tissue Doppler E velocity, E_m DT deceleration time, E_m tissue early filling wave velocity, A_m tissue atrial filling wave velocity, E_m/A_m ratio, LA left atrium, RVD right ventricle (diastolic), RVS right ventricle (systolic), $LVEDD$ left ventricular end diastolic diameter, $LVESD$ left ventricular end systolic diameter, $IVSD$ interventricular septum (diastolic), $IVSS$ interventricular septum (systolic), $LVPWD$ left ventricular posterior wall (diastolic), $LVPWS$ left ventricular posterior wall (systolic), $LVMASS$ left ventricular mass, FS fractional shortening, AO aorta, $LVOT$ left ventricular outflow tract, $IVRT$ isovolumic relaxation time

[a] Body mass index (bmi) (adjusted in the model in addition, only the significant associations are shown), [b] bmi, heart rate in echo (h) (adjusted in the model in addition, only the significant associations are shown) age groups <56v ja>=56v in 2006

often been exceeded also in the reduction and powder production departments. In the 2000s, the concentrations of cobalt in ambient air tended to decrease. The follow-up in biomonitoring U-Co showed that exposure remained at the same level.

A search of the literature found one Belgian epidemiologic cross-sectional study that did not find an association between cobalt exposure and incipient signs of cardiomyopathy (Lantin et al. 2013). The researchers studied 256 male refinery workers with electro- and echocardiography. Their results were adjusted to an exposure index reflecting long-term exposure to cobalt. No dose–response relationship was found between exposure to cobalt and parameters reflecting possible dilated cardiomyopathy in their exposed study population.

In our cross-sectional study in 2000, we found that higher cobalt exposure was associated with altered left ventricular diastolic function as measured by echocardiography (Linna et al. 2004) The isovolumic relaxation time (IVRT) was prolonged in the highly exposed group when compared with that of the less exposed and reference groups, and a prolonged deceleration time (DT) was observed among the exposed persons. These findings were in concordance with those of D'Adda et al. (1994), who reported that an accumulation of cobalt in the myocardium might result in increased myocardial stiffness. Contrary to the previous echo findings, in 2006, we found that DT and IVRT were similar in the exposed and unexposed groups. In the 2006 results, the use of the tissue Doppler, when adjusted for confounding variables, did not show any differences between the exposed and unexposed groups. Only the A_m tissue was smaller in the unexposed group; however, the higher age and heart rate (time-related variables) best explained these values. Furthermore, no significant differences were found between the exposed and unexposed workers in the laboratory values, ECG parameters—including heart rate—or Holter registration. These findings support the no-effect results of cobalt exposure found by the echocardiography.

The differences in the echo parameters between the study groups in 2000 were minimal when compared with the pathological findings in the context of clinical practice. Small changes in echo parameters are apt to become significant in group-level comparisons in epidemiological studies.

When there was no progression of the earlier changes in the exposed group compared to unexposed group, we consider the earlier findings from 2000 in the exposed group to have developed randomly; while these findings were statistically significant, they were not clinically significant. The changes in the echocardiographic parameters may have been associated with the process of ageing and its physiological changes on the cardiovascular system, which may explain many of our findings in these two cross-sectional studies with a 6-year interval.

In the questionnaire data, background factors—such as lifestyle habits—had changed in both groups during the follow-up. The BMI had increased in both groups, and the use of alcohol was more common among the unexposed participants. The exposed participants had increased their leisure-time sport activities, while unexposed participants had decreased such activities. It seemed that the lifestyle habits of the unexposed group tended to have changed more in an unhealthy direction compared to the exposed group. In this middle-aged male population, possibly the largest effect on heart function was due to hypertension and its medication. This explanation is supported by the more frequent reports of physician-diagnosed hypertension in both groups, which was present even more frequently in the unexposed group. The unexposed group used more beta-blockers as antihypertensive medication compared to the exposed group (18% vs 11%). Many of the echo variables are dependent on hypertension and heart rate and, therefore, we adjusted the variables to both factors in the analysis.

It is possible that our previous findings of a possible increased stiffness of the myocardium were not associated with cobalt exposure. It seems likely that even if cobalt exposure has a small effect on heart function, it is unlikely that this effect can be demonstrated in a middle-aged male population with many changing risk factors for cardiovascular diseases and medication affecting heart function. The exposed and unexposed groups did not differ from each other clinically or statistically significantly with respect to any echo variable, meaning we could not conclude there were detrimental effects on the heart due to exposure to cobalt. Based on the findings of this study, there is no need to add heart-specific tests to the health surveillance scheme of the cobalt-exposed workers when exposure levels do not exceed those reported in this study.

Conclusions

We found no cardiac dysfunction that could be attributed to cobalt exposure. If there are effects of cobalt exposure on the functions of the heart muscle, they are probably smaller than the effects of ageing, medication, and traditional cardiovascular risk factors, such as elevated blood pressure.

Compliance with ethical standards

Conflict of interest The authors declare that there is no conflict of interest.

Ethical approval The study plan was approved by the Coordinating Ethics Committee of the Helsinki University Hospital District. Participation was voluntary, and all participants gave their written informed consent. All procedures performed in the study were in accordance with the ethical standards of the Helsinki Declaration or comparable ethical standards.

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Errata

In Publication IV, Table 5,

the numbers	Exposed to cobalt ≥0.55 mg-year (n=47)	Exposed to cobalt <0.55 mg-year	Unexposed (n=**49**) (n=**42**)
should be	Exposed to cobalt ≥0.55 mg-year (n=47)	Exposed to cobalt <0.55 mg-year	Unexposed (n=**48**) (n=**45**)