Epidemiological survey of workers exposed to cobalt oxides, cobalt salts, and cobalt metal

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Abstract

Several organs (lung, skin, thyroid, heart, bone marrow) are potential targets of cobalt (Co). Whereas there is no doubt that inhalation of Co alone may cause bronchial asthma, its role in the occurrence of hard metal disease is still controversial because most cases were reported in workers exposed not only to Co but also to other substances such as tungsten carbide, titanium carbide, iron, silica and diamond. To assess whether exposure to pure Co dust (metal, oxides, or salts) may lead to adverse health effects a cross sectional study was carried out among 82 workers in a Co refinery. The results were compared with those in a sex and age matched control group. The Co group had been exposed for 8.0 years on average (range 0.3-39.4). The geometric mean time weighted average exposure assessed with personal samplers ($n = 82$) was about $125 \mu\text{g}/\text{m}^3$ and 25% of the values were higher than $500 \mu\text{g}/\text{m}^3$. The concentrations of Co in blood and in urine after the shift were significantly correlated with those in air. Concentration of Co in urine increased during the workweek. A slight interference with thyroid metabolism (decreased T3, T4, and increased TSH), a slight reduction of some erythropoietic variables (red blood cells, haemoglobin, packed cell volume) and increased white cell count were found in the exposed workers. The exposed workers complained more often of dyspnoea and wheezing and had significantly more skin lesions

(eczema, erythema) than control workers. Within the exposed group a dose-effect relation was found between the reduction of the forced expiratory volume in one second/vital capacity and the intensity of current exposure to Co assessed by the measurement of Co in air or in urine. The prevalence of dyspnoea was related to the dustiness of the workplace as reflected by a statistically significant logistic regression between this symptom and the current levels of Co in air and in urine. No difference between lung volumes, ventilatory performances, carbon monoxide diffusing capacity, and serum myocardial creatine kinase and procollagen III peptide was found between the Co and control groups and no lung abnormalities were detected on the chest radiographs in both groups. The results suggest that exposure to high airborne concentrations of Co alone is not sufficient to cause pulmonary fibrosis. This finding is compatible with experimental studies indicating that interaction of other airborne pollutants with Co particles play a part in the pathogenesis of parenchymal lung lesions.

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Excessive exposure to Co compounds has been associated with adverse effects in several organs (skin, lung, thyroid gland, myocardium, bone marrow). In occupational settings, the respiratory tract is the main target organ.¹

There is ample evidence that exposure to Co dust, alone or in association with other substances, may cause bronchial asthma.²⁻⁵ The symptoms (wheezing, chest tightness, dyspnoea, cough) usually improve after removal from exposure. A type I allergic reaction has been postulated, because specific IgE antibodies against a complex of Co with albumin can sometimes be detected.⁶ This, however, does not exclude a non-specific irritative action of Co on the bronchial tree.³ The incidence of bronchial asthma induced by Co is low (5%).

Another pulmonary disease, also associated with

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exposure to dust containing Co, is the so called "hard metal disease", an interstitial lung disease ranging from alveolitis to pulmonary fibrosis. It has the typical clinical features of a progressive interstitial lung disease: dry cough, dyspnoea during exercise and subsequently at rest, weight loss, and cyanosis. In the later stages cor pulmonale may develop. Lung function tests reveal reduced lung volumes and diffusing capacity. Chest radiographs often show fine or coarse linear and/or round opacities.^{3 4 7-10}

Since the first report by Jobs and Ballhausen in 1940,¹¹ it has often been questioned whether Co alone is responsible for this particular disease.¹² Several animal experiments with Co metal and salts have failed to reproduce the typical pulmonary lesions found in humans.¹³⁻¹⁵

It is also important to note that most cases of interstitial disease were described in hard metal and diamond polishing industries, where workers are exposed not only to Co metal powder but also to other constituents such as tungsten carbide, titanium carbide, diamond particles etc.^{2 3 9 16-19}

The few studies so far carried out in Co refineries, where exposure is to pure Co dust, never identified typical cases of interstitial disease.^{20 21}

Therefore, to evaluate whether exposure to pure Co dust may lead to adverse health effects, a cross sectional health survey was carried out in a Co refinery in Belgium. At the same time, an environmental and biological monitoring programme was set up to characterise exposure to Co.

Subjects and methods

STUDY POPULATION

The Co plant, which is part of a large metallurgical concern, uses a wide variety of raw materials, mainly Co metal cathodes and scraps. These materials are dissolved in acid, sometimes after a preliminary treatment such as ball milling. The Co solution is then subjected to several hydrometallurgical purification steps. Various Co salts, oxides, and fine Co metal powders are obtained as final products. Several steps involve the manipulation of powdered material that generates dust. The exposed group included 82 male workers from the Co plant who had not suffered from lung diseases before employment or had never been occupationally exposed to other pneumotoxic chemicals.

A group of 82 age matched control workers not exposed to lung irritants was recruited in the mechanical workshops of a nearby plant belonging to the same company. Because both plants are located in the same area and apply similar hiring criteria and occupational health programmes an efficient matching between the Co and control groups was achieved for educational and socioeconomic state.

CLINICAL EXAMINATION AND TESTS OF LUNG FUNCTION

Each participant was asked to complete a slightly modified European Coal and Steel Community (ECSC) questionnaire on chronic bronchitis. Detailed information was collected on occupational history, respiratory complaints, and smoking habits. The worker was then submitted to a routine clinical examination.

Vital capacity (VC), forced expiratory volume in one second (FEV₁), peak expiratory flow (PEF), and maximal expiratory flow rate at 75 (MEF₇₅) and 50 (MEF₅₀) % of VC were measured with a rolling seal spirometer (Volugraph, Mijnhardt). Total lung capacity (TLC) and residual volume (RV) were estimated by the helium dilution method. Measurement of carbon monoxide diffusing capacity (TLCO) was performed by the single breath technique²² in a seated position with the Mijnhardt Diffusimat 2000. For each subject, the results were also expressed as percentages of the predicted values, which were calculated on the basis of age, weight, and height. The prediction equations were obtained from the following sources: Jouasset²³ for static and dynamic lung volumes; Bass²⁴ for maximal expiratory flow rates; Frans *et al*²⁵ for lung diffusing capacity.

A full size chest radiograph was interpreted blindly by two independent readers who were consultants in radiology.

BIOLOGICAL ANALYSES

Venous blood and a spot urine sample were collected before and after the shift on Monday and Friday for Co determination. The blood sample withdrawn on Monday morning was also used for the other biological analyses. Routine haematological analyses—namely, red blood cell count (RBC), white blood cell count (WBC), haemoglobin (Hb), haematocrit (Htc), mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), mean corpuscular haemoglobin concentration (MCHC), and platelet count were performed on a Coulter Counter (S5 model).

Total T3, T4, TSH, and T3 uptake were analysed by radioimmunoassay with the kits purchased from Monobind (Costa Mesa, CA, USA).

Myocardial creatine kinase (CPK) activity in serum was determined with the CK-MB (NAC-act) Monotest from Boehringer Diagnostica (Mannheim, Germany). The procollagen III peptide (PC-III-P) was determined with the radioimmunoassay-gnost P-III-P from Behringwerke AG (Marburg, Germany). The concentrations of Co in whole blood and in urine were determined by flameless atomic absorption spectrometry with a Perkin-Elmer 5000 Zeeman spectrometer. Urinary

Table 1 Characteristics of the study population

	Control group			Exposed workers		
	Non-smokers (n = 31)	Smokers (n = 51)	Total (n = 82)	Non-smokers (n = 23)	Smokers (n = 59)	Total (n = 82)
Age† (y)	31.0 (19–56)¶	40.0 (20–55)	38.0 (19–56)	32.0 (20–58)	33.0 (19–58)	33.0 (19–58)
Duration of exposure‡ (y)	—	—	—	6.6 (0.4–39.4)	8.2 (0.3–31.2)	8.0 (0.3–39.4)
Height§ (cm)	177.2 (164–190)	175.0 (164–189)	175.8 (164–190)	174.1 (163–183)	175.2 (160–199)	174.9 (160–199)
Weight‡ (kg)	76.3 (55–105)	78.0 (59–127)	77.3 (55–127)	78.8 (62–98)	73.6 (54–120)*	75.0 (54–120)
Pack-years†	—	12 (1–61)	—	—	9 (1–78)	—

*Significantly different from the control group (t test: $p < 0.05$)

†median; ‡geometric mean; §arithmetic mean; ¶range.

creatinine concentration was measured according to Jaffé's picrate method.

AIR SAMPLING AND ANALYSES

The exposure of each worker to airborne Co (total dust) was characterised by personal sampling. The Co concentration was determined in the breathing zone of the workers with a CIP10 dust sampler (MSA, Saint-Ouen-L'Aumône, France) equipped with two 45 grade and one 60 grade polyurethane foam filters. Air was sampled at a mean flow rate of 10 l/min for six hours. For each Co worker two measurements were made (on Monday and on Friday). After dissolution in a 10% sulphuric acid and 1% nitric acid solution, the Co content of the filters was determined by flameless atomic absorption spectrometry (Perkin Elmer, Zeeman 5000).

STATISTICAL ANALYSIS

Statistical analyses were by SAS procedures (SAS Institute). When variables were not normally distributed analysis was performed on log transformed data; non-parametric tests were used when log transformation did not normalise the distributions. A p value of ≤ 0.05 was considered as the criterion of statistical significance.

Results

POPULATION CHARACTERISTICS

Table 1 summarises some characteristics of the control workers and those exposed to Co. The ex-smokers were combined with the smokers. The Co group had been exposed to Co metal and Co salts for 8.0 years on average (range 0.3 to 39.4). Both populations were well matched for age, height, and smoking habits. The mean weight of the control smokers was slightly higher than that of smokers in the exposed group.

ENVIRONMENTAL AND BIOLOGICAL EXPOSURE VARIABLES

Figure 1 gives the results of the current airborne Co determinations performed by personal sampling (total dust) during two days. The geometric mean time weighted average exposure (TWA) was not

significantly different at the beginning and at the end of the week. These data are representative of the usual exposure of the workers. About 70% of the workers were exposed to a TWA higher than the current American Conference of Governmental Industrial Hygienists' (ACGIH) TLV ($50 \mu\text{g}/\text{m}^3$) and about 25% were exposed to a TWA higher than $500 \mu\text{g}/\text{m}^3$.

Figures 2 and 3 present the cumulative frequency distribution of Co in urine and in blood of the exposed workers before and after the shift on Monday and Friday. Concentrations of Co in urine increased during the shift (the difference between the post and preshift geometric mean concentrations was to about $30 \mu\text{g}/\text{g}$ creatinine) and also during the workweek. The cumulative frequency distribution of the preshift values were significantly different (χ^2 , $p < 0.05$) on Monday and Friday. Although the concentrations of Co in blood followed a similar pattern as Co in urine during the

Figure 1 Cumulative frequency distribution of time weighted average concentration of airborne Co dust collected with personal sampling.

Figure 2 Cumulative frequency distribution of Co concentration in urine.

Figure 3 Cumulative frequency distribution of Co concentration in blood.

workshift and the week, the relative changes in concentrations were less than for urine. Concentrations of Co in urine (postshift sample) and in blood were correlated with Co in air both on Monday and on Friday ($r = 0.72$ and 0.61 for urine and $r = 0.64$ and 0.60 for blood respectively $p < 0.001$).

In control workers all the results of Co in urine and Co in blood were below $2 \mu\text{g/g}$ creatinine and $0.2 \mu\text{g/dl}$ respectively. A few determinations of Co in air were performed in the control plant. All the results were below $0.05 \mu\text{g/m}^3$ confirming the absence of exposure to Co in the control group.

Table 2 Respiratory symptoms

Respiratory symptom	Control group			Exposed workers		
	Non-smokers (n = 31)	Smokers (n = 51)	Total (n = 82)	Non-smokers (n = 23)	Smokers (n = 59)	Total (n = 82)
Cough in cold season:						
Morning	0 (0.0)	4 (7.8)	4 (4.9)	2 (8.7)	6 (10.2)	8 (9.8)
Whole day	1 (3.2)	2 (3.9)	3 (3.7)	3 (13.0)	5 (8.5)	8 (9.8)
Whole day, 3 months a year	0 (0.0)	2 (3.9)	2 (2.4)	1 (4.4)	5 (8.5)	6 (7.3)
Sputum in cold season:						
Morning	0 (0.0)	4 (7.8)	4 (4.9)	4 (17.4)*	6 (10.2)	10 (12.2)
Whole day	0 (0.0)	2 (3.9)	2 (2.4)	3 (13.0)	4 (6.8)	7 (8.5)
Whole day, 3 months a year	0 (0.0)	3 (5.9)	3 (3.7)	2 (8.7)	4 (6.8)	6 (7.3)
Dyspnoea:						
During heavy exercise	0 (0.0)	1 (2.0)	1 (1.2)	2 (8.7)	11 (18.7)*	13 (15.9)*
During normal exercise	1 (3.2)	1 (2.0)	2 (2.4)	2 (8.7)	8 (13.6)*	10 (12.2)*
During light exercise	0 (0.0)	1 (2.0)	1 (1.2)	1 (4.4)	6 (10.2)	7 (8.5)*
At rest	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.5)*	5 (6.1)*
Wheezing:						
Ever	3 (9.7)	6 (11.8)	9 (11.0)	2 (8.7)	11 (18.6)	13 (15.9)
Daily	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	5 (8.5)*	5 (6.1)*
Rhinitis:						
Daily, 3 months a year	3 (9.7)	5 (9.8)	8 (9.8)	1 (4.4)	10 (17.0)	11 (13.4)
Hay fever	1 (3.2)	2 (3.9)	3 (3.7)	0 (0.0)	3 (5.1)	3 (3.7)
Acute bronchitis in past 3 years	1 (3.2)	5 (9.8)	6 (7.3)	2 (8.7)	7 (11.9)	9 (11.0)

*Significantly different from the corresponding control group (χ^2 , $p < 0.05$).
Values are numbers of workers (%).

Table 3 Lung function tests

Test	Control group			Exposed workers		
	Non-smokers (n = 31)	Smokers (n = 51)	Total (n = 82)	Non-smokers (n = 23)	Smokers (n = 58)	Total (n = 81)
FVC (l)*	5.23 (93-17) (3.76-6.62)	4.87 (90-77) (3.40-6.38)	5.01 (91-67) (3.40-6.62)	4.92 (92-60) (3.12-7.01)	4.91 (90-81) (3.35-7.12)	4.92 (91-32) (3.12-7.12)
RV (l)†	1.73 (107-30) (1.06-3.00)	1.97 (119-45) (1.08-3.36)	1.88 (114-70) (1.06-3.36)	1.57 (99-50) (0.92-3.41)	1.85 (115-26) (1.02-3.30)	1.76 (110-54) (0.92-3.41)
TLC (l)*	7.02 (97-01) (4.89-9.09)	6.91 (98-34) (5.29-8.37)	6.95 (97-83) (4.89-9.09)	6.57 (95-33) (5.08-8.13)	6.84 (97-44) (4.80-9.45)	6.76 (96-84) (4.80-9.45)
RV/TLC (%)‡	24.95 (112-05) (16.86-34.84)	28.78 (121-49) (17.91-45.40)	27.27 (117-84) (16.86-45.40)	24.09 (104-86) (13.78-52.22)	27.33 (119-23) (16.32-45.80)	26.36 (114-96) (13.78-52.22)
FEV ₁ (l)‡	4.05 (91-14) (3.07-5.36)	3.63 (94-53) (2.65-5.20)	3.95 (94-22) (2.65-5.36)	3.98 (99-17) (2.46-5.23)	4.07 (95-61) (1.96-5.38)	4.04 (96-30) (1.96-5.38)
FEV ₁ /VC (%)	82.48 (63.89-94.23)	84.69 (60.18-92.53)	83.51 (60.18-94.23)	83.91 (74.06-91.88)	84.88 (63.64-92.80)	84.38 (63.64-92.80)
PEF (l/s)*	9.18 (109-27) (5.50-12.80)	9.22 (112-10) (5.60-12.60)	9.20 (111-03) (5.50-12.80)	9.06 (109-49) (5.40-11.90)	8.89 (107-86) (4.80-13.10)	8.94 (108-33) (4.80-13.10)
MEF ₇₅ (l/s)‡	2.00 (102-15) (1.00-4.10)	1.80 (99-33) (0.70-5.00)	1.85 (99-70) (0.70-5.00)	2.00 (111-09) (1.20-3.50)	2.00 (107-03) (0.70-4.20)	2.00 (107-61) (0.70-4.20)
MEF ₅₀ (l/s)‡	4.60 (86-82) (2.50-6.90)	4.65 (90-05) (2.00-8.80)	4.63 (88-82) (2.00-8.80)	4.91 (92-39) (3.20-8.20)	4.90 (94-66) (1.20-8.10)	4.90 (94-01) (1.20-8.20)
TLCO (ml/min/mm Hg)*	39.70 (117-10) (25.85-51.00)	35.34 (109-17) (25.80-59.45)	36.99 (112-16) (25.80-59.45)	38.00 (116-83) (26.75-46.55)	34.64 (105-32) (18.40-47.80)	35.59 (108-59) (18.40-47.80)
TLCO/VA (ml/min/mm Hg/l)†	5.74 (110-92) (3.81-7.76)	5.23 (103-70) (3.63-8.37)	5.42 (106-37) (3.63-8.37)	5.83 (114-18) (4.87-7.42)	5.15 (100-68) (3.01-6.88)	5.33 (104-34) (3.01-7.42)

*arithmetic mean; †geometric mean; ‡median, % of predicted value and range in parentheses.

EFFECT VARIABLES QUESTIONNAIRE

The questionnaire on respiratory symptoms was analysed separately for smokers and non-smokers and for both groups combined (table 2). Dyspnoea during exercise and at rest and wheezing was more often reported by the exposed workers and especially by the smokers (χ^2 , $p < 0.05$). No statistically significant interaction was found, however, between smoking and exposure to Co. These symptoms were mainly prevalent among workers occupied in the dry process of Co production. For the other symptoms, the analysis did not show any statistical difference between the control and Co groups.

CLINICAL EXAMINATION AND TESTS OF LUNG FUNCTION

The clinical examinations detected more subjects with skin problems (eczema, erythema) (51% *v* 25%, $p \leq 0.001$) and wheezing (16% *v* 6%, $p < 0.05$) in the exposed than in the control group. No difference between control and Co groups was found for lung volumes, ventilatory performances, and single breath lung diffusing capacity (table 3). Likewise the prevalences of measurements of lung function (RV, TLC, RV/TLC (%)) below the 5 or above the 95 percentile values of the control group were not significantly different between control and Co groups (results not shown).

No lung abnormalities were detected on the chest radiographs in both groups.

BIOLOGICAL VARIABLES

The thyroid hormone T3 and the erythropoietic

variables (RBC, Hb, Htc) showed a statistically significant trend towards lower values in the Co group whereas WBCs were significantly higher (table 4).

The other measurements, particularly PC-III-P,

Table 4 Biological analyses

Variable	Control group (n = 82)	Exposed workers (n = 82)
T3 (ng/dl)†	150.00 (92.00-207.00)¶	140.18* (82.00-215.00)
T3 uptake (%)‡	41.86 (32.20-55.60)	43.23 (29.20-60.10)
T4 (µg/l)‡	79.00 (48.00-111.00)	76.00 (19.00-118.00)
TSH (µIU/ml)‡	4.72 (1.85-7.63)	4.78 (3.33-9.18)
CPK (IU/l)‡	9.00 (1.00-18.00)	8.00 (3.00-18.00)
PC-III-P (ng/ml)‡	7.34 (4.57-11.95)	7.39 (1.33-13.80)
Sedimentation rate (mm/h)‡	3.00 (1.00-29.00)	5.00 (1.00-17.00)
WBC (10 ⁹ /l)	6.74 (4.1-11.8)	8.03* (4.8-14.8)
RBC (10 ¹² /l)†	5.08 (4.49-5.77)	4.85* (3.96-5.49)
Hb (g/100ml)†	15.59 (12.70-17.50)	15.05* (13.70-17.50)
Htc (%)†	45.54 (40.70-51.10)	44.03* (39.50-50.40)
MCV (fl)‡	90.00 (79.00-97.00)	90.00 (84.00-101.00)
MCH (pg)‡	31.00 (25.00-34.00)	31.00 (28.00-35.00)
MCHC (g/100 ml)‡	34.00 (31.00-36.00)	34.00 (33.00-36.00)
Platelets (10 ⁹ /l)†	239.93 (132.00-421.00)	247.56 (112.00-390.00)

*Significantly different from the control group (t test, $p < 0.05$).

†Arithmetic mean; ‡median; §geometric mean; ¶range; for abbreviations, see text.

a potential biological marker of a fibrotic process, were not significantly different between the groups. The prevalences of abnormal values of T3, T4, TSH, CPK, WBC, and RBC were significantly higher in the Co workers than in the controls (table 5).

DOSE-EFFECT AND DOSE-RESPONSE RELATIONS

We have examined whether the intensity of the biological disturbance or the prevalence of abnormal biological results and respiratory complaints were associated with the intensity of exposure to Co (expressed in terms of Co in blood, Co in urine, Co in air, duration of exposure, and the product of duration of exposure with Co in air or in urine). The results for RV and TLC (% predicted values) were positively associated with duration of exposure (Pearson $r = 0.40$ and 0.37 respectively; $p < 0.001$) whereas the FEV₁/VC ratio was negatively associated with current exposure variables—namely, Co in urine and Co in air (Spearman r between -0.25 and -0.28 , $p \leq 0.01$). No significant dose-effect relations were found for the biological measurements. A logistic regression model was used to assess the probability of abnormal results as a function of the exposure variables. Only dyspnoea during exercise was found to be related to current concentrations of Co in air (figure 4) or in urine (results not shown).

Discussion

The present cross sectional epidemiological study compared male workers exposed to Co metal, Co oxides, and Co salts with a well matched control

Figure 4 Probability of dyspnoea during exercise as a function of current airborne concentration of Co dust.

group. The workers were exposed for 8.0 years on average (range 0.3–39.4) to a mean airborne Co concentration of $125 \mu\text{g}/\text{m}^3$ but for about 25% of the workers, the TWA exceeded $500 \mu\text{g}/\text{m}^3$. Exposure to Co was clearly reflected by an increase in the concentration of Co in urine at the end of the workshift. Although selection bias (healthy worker effect) cannot be formally excluded in the framework of a cross sectional study, it is unlikely that it may significantly affect our estimate because of the stability of the workforce in both plants. A slight interference with thyroid metabolism (decreased T3, T4, and increased TSH) was found in the exposed workers. Although no clinical case of hypothyroidism was found, this study suggests that Co may interfere with thyroid function. This result is in agreement with findings made in the past among patients treated with Co.²⁶ At variance with the present results, increased concentrations of total and free serum T4 have been found in female Danish plate painters exposed to Co-zinc silicate (mean urinary Co concentration of $1.17 \mu\text{g}/\text{mmole creatinine}$). No significant effect on gland volume or serum TSH could be detected.²⁷ In the present study, a few haematological variables were also significantly different between both groups. By contrast with previous animal experiments suggesting that administration of high doses of Co may cause polycythemia,²⁸ the workers exposed to Co had a tendency to show a reduction in erythropoietic variables. We have no evident explanation for the

Table 5 Biological analyses: prevalences of abnormal values

Variable†	Cut-off value	Control group (n = 82)	Exposed workers (n = 82)
T3	<102.20‡	1 (1.2)§	6 (7.3)
T3-UPTAKE	>48.88	4 (4.9)	13 (15.9)*
T4	<57.80	2 (2.4)	15 (18.3)*
TSH	>6.16	3 (3.7)	10 (12.2)*
CPK	>12.40	3 (3.7)	10 (12.2)*
PC-III-P	>11.10	2 (2.4)	2 (2.4)
WBC	>9.70	8 (9.8)	22 (26.8)*
RBC	<4.56	5 (6.1)	13 (15.9)*
	>5.69	2 (2.4)	0 (0.0)
Hb	<13.54	1 (1.2)	0 (0.0)
	>17.34	3 (3.7)	1 (1.2)
Htc	<40.70	2 (2.4)	4 (4.9)
	>49.34	6 (7.3)	2 (2.4)
MCV	<82.00	1 (1.2)	0 (0.0)
	>95.00	9 (11.0)	6 (7.3)
MCH	<27.40	1 (1.2)	0 (0.0)
	>33.00	7 (8.5)	7 (8.5)
MCHC	<32.20	2 (2.4)	0 (0.0)
	>36.00	7 (8.5)	5 (6.1)
Platelets	<164.20	4 (4.9)	2 (2.4)
	>351.20	2 (2.4)	3 (3.7)

*Significantly different from the control group (χ^2 ; $p < 0.05$).

†For units and abbreviations see table 4 and text; ‡5th or 95th percentile value of the control group; §percentage.

increased WBC in exposed workers, which persists after standardisation for smoking habits. Animal experiments have also indicated that inhalation of Co could affect WBC.¹⁴ The haematological changes, however, were not dose related.

Two different respiratory syndromes involving either the bronchial tree or the lung parenchyma have been described among workers exposed to dust containing Co. Bronchial asthma has been clearly associated with exposure to Co. A bronchial provocation test with Co alone may induce acute bronchoconstriction.⁶ In this study, the exposed workers complained more often of dyspnoea and wheezing compared with a control group. The prevalence of dyspnoea was clearly related to the dustiness of the workplace as reflected by the statistically significant logistic regression between this symptom and the current concentrations of Co in air and urine. The lung auscultation also revealed an increased prevalence of wheezing in the exposed workers. Furthermore, a dose-effect relation was found between the reduction of the FEV₁/VC ratio and the intensity of current exposure to Co as reflected by the concentration of Co in air and in urine. On the other hand, RV and TLC were positively correlated with the duration of exposure. Although the average lung function tests were not significantly different between the two groups, all these findings suggest an airway involvement in workers exposed to Co. The risk of respiratory complaints seems to be low when the exposure to Co alone does not exceed a TWA of 50 µg/m³ (fig 4). The results of other authors, however, suggest that when exposure is not to Co alone, an interaction between various components of the inhaled aerosol may lower the threshold effect level for the respiratory tract. Kusaka *et al*³ found a 5% prevalence of occupational asthma among hard metal workers exposed to Co dust ranging from 4 to 32 µg/m³. Recently reduced FEV₁ values were reported in diamond workers who used polishing discs containing Co and who were exposed not only to Co but also to other substances such as iron, silica, and diamond^{16,29}; mean concentration of Co in air ranged from 0.7 to 42.8 µg/m³ (personal sampling).

Acute alveolitis possibly leading to lung fibrosis has also been associated with inhalation of dust containing Co in the hard metal industry and among diamond polishers. Several authors^{2,7,8,16,30} have attributed the parenchymal lesion solely to Co. Roto did not find any lung impairment in workers exposed to Co metal powder in a Co refinery in Finland (80–190 µg soluble Co/m³).²⁰ Morgan and Verhamme reported their experience of the health surveillance of workers in plants producing Co oxide, Co salt, and Co metal powder; they never found evidence of an increased risk of

lung fibrosis.^{21,31} In our exposed population, there was no indication of pulmonary fibrosis as lung volumes, lung diffusing capacity, serum PC-III-P concentration, and chest radiographs were within normal limits.

These results, together with recent experimental work (see later), lead us to conclude that exposure to Co alone (metal, oxides, or salts) does not cause parenchymal change, contrary to the observations in the hard metal and diamond polishing industries. This discrepancy cannot be simply explained by a lower exposure in Co producing plants; as confirmed during this study, high airborne concentrations of Co and increased concentrations of Co in the urine of workers are found in Co refineries. It is also interesting to note that in the cemented tungsten carbide industry, hard metal disease has often been found in grinders who have only ground on sintered (hard) tungsten carbide, an operation generating low air concentrations of Co.² These findings suggest that the role of other constituents and their possible interaction with Co particles must be considered in the pathogenesis of interstitial lung lesions.

This view is supported by recent *in vitro* and *in vivo* experimental studies^{32–35} performed in our laboratory which show that the biological reactivity of Co-tungsten carbide mixture is much greater than that of Co metal particles alone. The bioavailability of Co is also enhanced in the presence of tungsten carbide. For example, a tungsten carbide-Co mixture as prepared by the hard metal industry was almost as toxic towards rat alveolar macrophages as crystalline silica whereas pure tungsten carbide had no effect and pure Co metal powder only slightly impaired cell viability. The uptake of Co by macrophages was also increased in the presence of tungsten carbide.³² In rats, the intratracheal instillation of a tungsten carbide-Co mixture (16.67 mg/100 g body weight corresponding to 1.0 mg Co/100 g) caused a severe alveolitis and fatal pulmonary edema whereas the corresponding dose of Co powder alone only caused a moderate inflammatory response.³⁵

Preliminary results also indicate that the delayed fibrotic reaction is only seen after administration of the tungsten carbide Co mixture. The amount of Co excreted in urine was also significantly higher when the animals were exposed to this mixture than to an equivalent amount of pure Co particles, confirming the increased bioavailability of Co metal when combined with tungsten carbide.

These experimental data may explain why parenchymal lesions are rarely, if ever, seen in workers exposed to pure Co dust. The simultaneous inhalation of other compounds such as tungsten carbide seems a necessary condition to induce a severe alveolitis leading to lung fibrosis. This sug-

gests that acceptable exposure to the metal might have to vary depending on whether exposure is to Co alone or to a combination of Co and other substances.

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