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Biological monitoring of cobalt exposure, based on cobalt concentrations in blood and urine

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Summary. Cobalt exposure level and its concentrations in blood and urine were determined for 175 hard metal workers. For control data, the cobalt concentrations in blood and urine were measured for 20 office workers. The exposed workers had significantly higher cobalt concentrations in both blood and urine. The relationships between exposure level and cobalt concentrations in blood and urine were linear and positive. The results clearly showed that the cobalt concentration in the blood or urine can be used as an exposure indicator. With cobalt exposure of 100 μg/m^3, the cobalt concentration was 0.57 to 0.79 μg/dl in blood and 59 to 78 μg/l in urine with 95% confidence limits. In workers using respirators, the cobalt concentrations in the blood and urine decreased to 2/5 and 1/8, respectively, of those not using respirators.

Key words: Biological monitoring – Cobalt exposure – Cobalt in blood – Cobalt in urine – Exposure indicator

Introduction

Industrial use of cobalt has increased remarkably since the development of cemented tungsten carbide. Accompanying its widespread application has been an increase of lung diseases, including diffuse interstitial fibrosis and bronchial asthma, among hard metal workers in many countries [6, 7, 15, 22, 29]. Cardiomyopathy [4, 17], polycythemia [3] and allergic dermatitis [8, 20, 28] have also been found in these workers. The results of cobalt patch tests [8, 20, 21, 28], induction tests for bronchial asthma [8, 11] and animal experiments [12, 18, 26, 31] have shown that these adverse effects are mainly caused by cobalt.

Many reports [1, 2, 5, 13, 14, 23, 25] have dealt with cobalt concentration in the blood or urine of hard metal workers but none have clarified the relation-

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ship between cobalt concentration in the air and that in the biological fluids of the workers. To clarify this relation, we examined 175 cobalt workers in a hard metal tool factory with blood and urine tests and determined the cobalt concentrations in their breathing zones.

Materials and methods

Subjects

The subjects were 175 workers (170 men and 5 women) in a hard metal tool producing plant who were exposed to cobalt. The controls were 20 (all men) office workers. Of the 175 cobalt workers, 25 men working with dust respirators were placed in a separate group and the other 150 workers not using respirators were classified into ten groups according to the kind of work or workplace based on previous studies [19; Kusaka and Ichikawa, unpublished work]. The age and duration of exposure of the workers are summarized in Table 1.

Level of cobalt exposure

An air sample was taken from the breathing zone of each worker continuously for 6 to 7 h by a personal sampling procedure. The air-borne cobalt was collected on a cellulose ester membrane filter of 37-mm diameter (Millipore HA). The flow rate of the pump (Dupont, P-2500) was adjusted to 2.0 liters/min.

The total dust collected on the filter was weighed and combined with a mixture of 2.5*N* HNO_3 and 3*N* HCl at 20ml per 1mg of total dust in order to dissolve the cobalt. The mixture was left for 12h or more at room temperature, then diluted with a four-fold amount of deionized-distilled water.

Cobalt in the solution was analyzed with a Hitachi 518 atomic absorption spectrophotometer (AAS). A cobalt hollow cathode lamp (Hamamatsu TV) provided a characteristic line at 240.7nm. The detection limit for cobalt in air was 1 $\mu g/m^3$.

Table 1. Subjects' profiles

Subjects	No.	Age[a] Mean ± SD years		Duration of exposure[a] Mean ± SD years	
Powder handlers	2	28.5 ± 0.7	(28 + 29)	14.0 ± 0.7	(13.5 + 14.5)
Rubber press operators	6	38.0 ± 12.1	(24–55)	11.8 ± 5.3	(2.5–17.5)
Automatic press operators	11	43.0 ± 9.9	(24–54)	12.3 ± 3.1	(3.5–17.5)
Shapers (lathing)	7	40.0 ± 13.2	(26–54)	12.5 ± 5.4	(2.5–19)
Shapers (sawing)	21	40.5 ± 8.5	(27–51)	10.0 ± 3.6	(2 –15.5)
Sintering workers	21	40.2 ± 9.8	(20–51)	9.1 ± 4.7	(1.5–15.5)
Wet grinders A	27	38.4 ± 9.7	(20–54)	9.8 ± 4.7	(0.5–23)
B	18	34.7 ± 9.6	(20–49)	8.7 ± 4.0	(2.5–15)
C	12	31.2 ± 9.3	(20–46)	7.9 ± 5.8	(0.5–16)
D	25	38.0 ± 8.3	(19–50)	11.5 ± 5.0	(1.5–18.5)
Workers with respirators	25	39.2 ± 7.9	(25–50)	8.0 ± 5.4	(0.5–24)
Office workers	20	27.7 ± 5.7	(18–41)	–	

[a] The range of each value is given in parentheses
SD: standard deviation

Cobalt concentration in blood

A blood sample was taken during a work shift and 1 ml was frozen at −70°C and freeze-dried (Rabconco, FD-5) for 12 h. The dried sample was ashed for 48 h with a low temperature asher (Yanagimoto, LTA-152) under a pressure of 1 Torr and at an oxygen flow rate of 40 ml/min. The ashed sample was resolved in 0.5 ml of 1 *N* HNO_3 and analyzed for cobalt with a Hitachi 170-70 non-flame AAS, equipped with a Zeeman Effect background corrector. The operating conditions were as follows: wavelength 240.7 nm, lamp current 4 mA, slit 0.4 nm, cuvette pyro carbon tube, sample volume 10 µl. The heating program was dry 0–120°C 90 s (increasing at 1.5°C/s), ash 1000°C 40 s, atom 2700°C 12.5 s, clean 3000°C 3 s. A standard addition procedure using two different concentrations was used to determine the blood cobalt concentration, with the detection limit being 0.08 µg/dl. The variation coefficient of this method was 6.6% at a blood level of 0.50 µg/dl for ten measurements with the same sample.

Cobalt concentration in urine

A urine sample was taken toward the end of a work shift on Wednesday or Thursday of the week of the blood sampling. A 100-ml sample of the urine was wet-ashed with H_2SO_4, HNO_3 and H_2ClO_4. The ashed solution was adjusted to pH 3.5 and the cobalt in it was chelated with ammonium pyrrolidine dithiocarbamate (APDC), then the complex was extracted into methylisobutylketone (MIBK) by vigorous shaking. Cobalt in MIBK was analyzed with a Hitachi 518 AAS. The acetylene and air flow rates were 2.0 and 17 liters/min, respectively. The recovery rates of this procedure were 94.0 and 94.2%, respectively, when 20 and 100 µg/l of the cobalt solution were analyzed five times each, with the variation coefficients being 6.4 and 3.2%. The detection limit for cobalt in urine was 1 µg/l.

All reagents used in the cobalt analysis were of super special grade (Wako Pure Chem.). Sample containers and glass equipment were used after treatment to remove metal.

Linear relationships and differences of cobalt concentrations were tested with Student's *t*-test. In all calculations two-tailed tests were used. Differences were considered statistically significant when P was less than 0.05.

Results

Table 2 shows that the cobalt concentrations in both the blood and urine of all exposed groups, even those of the sintering workers who displayed the lowest exposure levels, were significantly higher than those in the control group ($P<0.05$ in the blood and $P<0.01$ in the urine).

The relation between cobalt concentrations in the breathing zones and those in the blood was linear with a significant correlation ($r=0.96$, $P<0.001$) as shown in Fig. 1. Linear relations were also found between cobalt concentrations in the breathing zones and those in the urine ($r=0.99$, $P<0.001$) and between cobalt concentrations in the blood and those in the urine ($r=0.96$, $P<0.001$) in Figs. 2 and 3. These results clearly showed that cobalt concentrations in both the blood and urine can be used as indicators of cobalt exposure.

From Figs. 1 and 2, we estimated with 95% confidence limits that cobalt concentrations in the blood and urine in response to exposure of 100 µg/m^3 were 0.57 to 0.79 µg/dl and 59 to 78 µg/l, respectively.

As for the 25 workers using respirators, the mean cobalt concentration in the breathing zones was 317 ± 307 µg/m^3, but the concentrations in the blood and urine were 0.65 ± 0.86 µg/dl and 26 ± 30 µg/l, respectively. As shown in Table 2,

Table 2. Cobalt exposure concentrations and amounts in the blood and urine of subjects examined

Subjects	No.	Co in air[a] Mean ± SD μgIm^3		Co in blood[a] Mean ± SD μg/dl		Co in urine[a] Mean ± SD μg/l	
Powder handlers	2	186 ± 108	(110+ 262)	1.08 ± 0.28	(0.88+1.28)	148 ± 14	(138+158)
Rubber press operators	6	367 ± 324	(92– 859)	1.87 ± 1.96	(0.40–5.30)	235 ± 182	(41–392)
Automatic press operators	11	56 ± 60	(9– 210)	0.57 ± 0.53	(0.10–0.95)	34 ± 43	(4– 73)
Shapers (lathing)	7	33 ± 15	(15– 62)	0.67 ± 0.44	(0.14–1.34)	33 ± 30	(11– 95)
Shapers (sawing)	21	50 ± 35	(8– 144)	0.52 ± 0.31	(0.15–1.15)	41 ± 60	(6–266)
Sintering workers	21	28 ± 30	(4– 145)	0.26 ± 0.10	(0.09–0.45)	10 ± 10	(2– 46)
Wet grinders A	27	44 ± 48	(4– 227)	0.42 ± 0.31	(0.10–1.30)	35 ± 34	(2–180)
B	18	45 ± 50	(3– 161)	0.33 ± 0.10	(0.16–0.52)	19 ± 15	(2– 67)
C	12	92 ± 92	(15– 291)	0.43 ± 0.39	(0.12–1.90)	68 ± 87	(3–265)
D	25	44 ± 54	(3– 205)	0.35 ± 0.20	(0.10–1.00)	17 ± 16	(1– 69)
Workers using respirators	25	317 ± 307	(7–1203)	0.65 ± 0.86	(0.20–3.90)	26 ± 30	(1–119)
Office workers	20	–		0.19 ± 0.11	(0.08–0.40)	2 ± 1	(1– 4)

[a] The range of each value is given in parentheses
SD: standard deviation

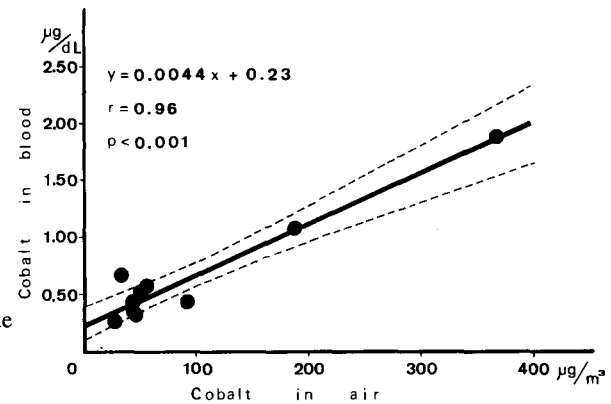

Fig. 1. Relation between mean cobalt exposure and mean blood concentration of cobalt from ten groups of exposed workers. The workers did not use respirators. Solid line, regression line obtained; broken lines, upper and lower 95% confidence limits of the estimated blood concentration

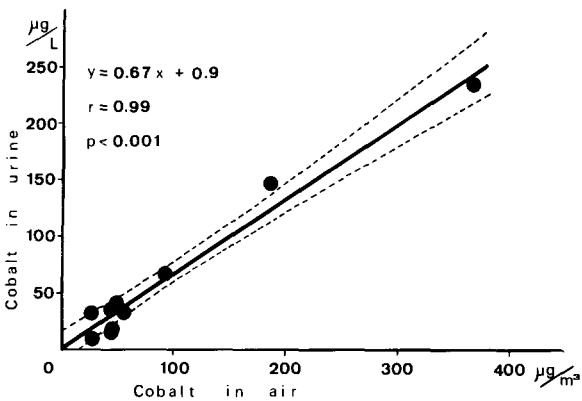

Fig. 2. Relation between mean cobalt exposure and mean urine concentration of cobalt from ten groups of exposed workers. The workers did not use respirators. Solid line, regression line; broken lines, upper and lower 95% confidence limits of the estimated urine concentration

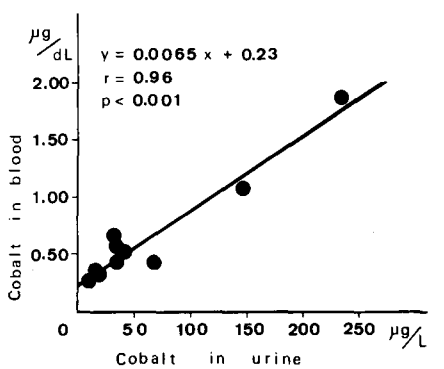

Fig. 3. Relation between mean urine concentration and blood concentration of cobalt from ten groups of exposed workers. The workers did not use respirators

wearing a respirator decreased the blood and urine cobalt levels. Workers without respirators who were exposed to the same concentration of cobalt had estimated blood and urine cobalt levels of 1.36 to 1.89 µg/dl and 189 to 235 µg/l, respectively. Thus, using a respirator reduced the cobalt concentration in the blood to 2/5 and that in the urine to 1/8.

Discussion

Table 2 shows clear differences in the cobalt concentrations in both the blood and urine between exposed workers and controls.

Cobalt concentration in the blood of our controls was higher than those of unexposed people reported earlier [1, 9, 16, 32], but the urinary cobalt concentration of our control group was almost equal to or only slightly higher than the control values of earlier reports [1, 9, 10, 13], with the exception of one report of a very high concentration [27]. Although one reason for the higher concentrations in our controls may have been the poor sensitivity of our analytical procedure, the major reason was probably the fact that our control group may have been exposed to cobalt to some extent for many years (average employment 7.8 years) because they worked in the office of the same factory.

We tried estimating blood-cobalt concentrations based on our findings. Alexandersson and Lidums [1] reported that in five hard metal workers exposed to 0.09 mg/m^3 of cobalt and in another five exposed to 0.01 mg/m^3, the cobalt concentrations in the blood were 1.05 ± 1.09 μg/dl and 0.07 ± 0.02 μg/dl, respectively. According to our data, exposure to these would give cobalt levels in the blood of 0.63 ± 0.11 μg/dl and 0.28 ± 0.14 μg/dl, respectively, with 95% confidence limits, which differed from the reported values. In our study, cobalt concentration in the breathing zone covered a very wide range of 28 to 367 μg/m^3. In the range of 0 to 100 μg/m^3, the blood concentrations did not lie on the straight line which was obtained when the entire range was considered. Also, the blood concentration of hard metal workers has been reported to decrease slowly after cessation of exposure [1], and others have reported long retention of ^{60}Co in the body [24, 30]. Therefore, we think that the non-linear relationship over the lower exposure range and the difference between our estimated values and the data of Alexandersson and Lidums [1] may have resulted from a complicated relation among the history of exposure to cobalt, the retention of cobalt in the body, a rather long biological half-time of blood cobalt and other factors. In spite of these problems, the linear relationship obtained over a wide range of exposure shows that blood concentration can be used as an indicator of cobalt exposure.

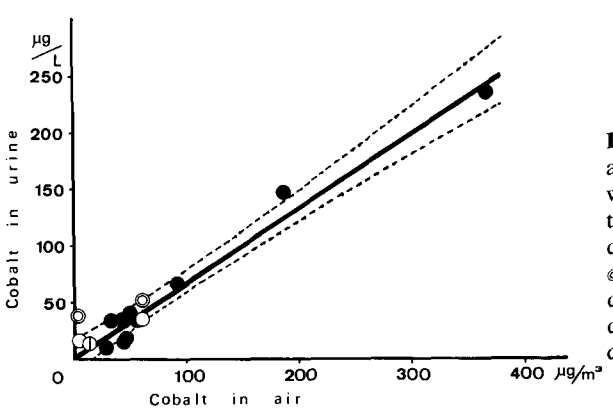

Fig. 4. Data from Alexandersson and from Hartung et al. are shown with our data on the relation between cobalt exposure and urine concentration. ●: our data; ◎: smokers in Alexandersson's data; ○: non-smokers in Alexandersson's data and ⊙: Hartung's data

Urinary cobalt concentrations of hard metal workers have been reported by Alexandersson [2], Hartung et al. [13, 14], Moline et al. [23] and Barborik [5], although no description of cobalt exposure was included in the last two reports. Alexandersson reported that urinary cobalt concentration in workers exposed to 0.005 to 0.01 mg/m^3 was 37.9 ± 67.3 µg/l in 16 smokers and 16.7 ± 82.7 µg/l in 18 non-smokers, while in workers exposed to 0.06 mg/m^3, it was 51.6 ± 64.3 µg/l in 33 smokers and 35.0 ± 63.9 µg/l in 32 non-smokers. Hartung et al. found the mean urinary cobalt concentration of 65 wet grinding workers to be 12.6 µg/l (range 3.1 to 58.4 µg/l), when the cobalt concentration in the air was 4.3 µg/m^3 from a stationary sampling and 13.5 µg/m^3 from a personal sampling. The results from these studies and our findings are described in Fig. 4. Their results agreed with our regression line, showing that cobalt concentration in the urine can be used as an indicator of cobalt exposure.

Lower cobalt concentrations in the blood and urine were found in workers using respirators. Since these concentrations are considered to express the real uptake of cobalt into the body, they can be used to evaluate the effectiveness of a respirator. However, after cessation of exposure, blood-cobalt decreases slowly while urinary cobalt decreases rapidly [1, 25]. This difference may result from differences in the duration or history of exposure because, although these workers had worn respirators for the last 1 to 5 years, most had been exposed to high cobalt concentrations with no respirators.

Further studies are needed to clarify whether blood-cobalt increases with repeated exposure and to find the biological half-time of blood and urinary cobalt.

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