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Urinary beryllium – a suitable tool for assessing occupational and environmental beryllium exposure?

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Abstract ***Objectives***: The reasons for the slow progress and lack of new knowledge in the biological monitoring of beryllium (Be) are to be found in the presumed small number of working activities involving exposure to the metal, and the lack of adequate analytical methods. The reference values for urinary Be reported earlier in the literature appear to be too high, due to the poor specificity and sensitivity of the adopted methods. The aim of this study was to correlate Be air concentrations and Be urinary levels to ascertain whether the biological indicator was suitable for assessing occupational exposure to the metal. ***Methods***: To investigate the relationship between the Be concentrations in air and those excreted in urine, we examined 65 metallurgical workers exposed to very low levels of the metal, and 30 control subjects. The exposed workers were employed in two electric steel plants and two copper alloy foundries. The alloys were produced in electric furnaces, starting with scrap containing Be as an impurity. The Be concentrations in the air were monitored by area samplers and the levels of Be in the urine of the workers were determined in samples taken at the end of the shift. Both determinations were carried out by ICP-MS. ***Results***: The median airborne Be concentrations in the copper alloy plants were 0.27 μg/m^3 in the furnace area and 0.31 μg/m^3 in the casting area. Median values of 0.03 to 0.12 μg/m^3 were determined in the steel plants, the relatively wide range probably due to differing amounts of Be in the scrap. Regression analysis was performed on the median values from four work areas and the corresponding urinary samples. A significant correlation was found for the relationship between external and internal exposure. The urinary Be levels were in the range between 0.12 and 0.15 μg/l with observation of the recommended TLV-TWA for inhalable dust of 0.2 μg/m^3 (0.2 μg/l at the upper 95th percentile). ***Conclusions***: Sufficient data are not currently available to be able to propose a BEI for urinary Be. Our results show that new investigations are necessary to improve the evaluation of dose indicators and the relationship between external and internal exposure to Be.

Key words Beryllium · Ambient and biological monitoring · Electric steel plant · Copper alloy foundries

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Introduction

Ten years ago the monograph on Beryllium (Be) for the CEC series on "Biological Indicators for the Assessment of Human Exposure to Industrial Chemicals" [6], stated that the urinary excretion of Be was higher in exposed subjects than in the general population, although occupational exposure to the metal was low and the urinary Be levels were higher at the end of the work shift. The relationships between internal and external exposure and between internal exposure and (early) effects were, however, not known, and the need for more research was emphasized.

Advancements in the biological monitoring of Be have been quite modest over the past decade, as demonstrated by the small number of papers published on the subject. When, for example, the articles quoted in the period 1989–1999 in the MED LINE data bank are examined, one finds few references regarding Be and human health [1, 8, 9, 14, 18–20, 25]. Some of these articles deal with ambient pollution or Be diseases, but without using any biological indicator of the metal.

Two papers mention the biological monitoring of Be: the first in the context of an investigation about

the urinary reference values for 13 metals in the general population of the USA [24], the second in the context of the theoretical significance of biomonitoring for carcinogenic metals [25]. In addition we found a recent article on gemstone cutters exposed to beryls in which urinary Be is specifically investigated as a biological indicator in occupationally exposed subjects [30].

In our opinion the range of industrial processes in which occupational exposure to Be occurs has, on the contrary, increased over the past two decades, and it is very likely that unknown or not easily identifiable sources of exposure to the metal exist. This is confirmed by the recent evaluation carried out by Kauppinen et al. [17] of the number of EU workers exposed to carcinogens: in this review the number of individuals occupationally exposed to Be is given as 67,000 and Be is classed as a carcinogen of the same potency as ceramic fibres and styrene-7,8-oxide.

The environmental sources of Be may also be of interest for the general population, in particular the emissions from plants directly or indirectly processing Be, from incinerators and from electric power plants using coal or mineral oil. There are, however, conflicting data about the presence and amount of Be in the environment. Another important non-occupational source of the element is tobacco smoke [1, 11, 26].

The effects of Be on human health has long been a concern of occupational medicine. Of the diseases related to Be, only the acute Be pulmonary syndrome is clearly dose-related, being caused by short-term exposure to high concentrations of Be [12]. Pulmonary chronic Be disease (CBD), on the other hand, is an immunologically mediated syndrome, defined as the occurrence of lymphocyte proliferation coupled with the presence of alveolar granulomas. This proliferation can be detected using the beryllium lymphocyte proliferation test (BLPT) and the granulomas are harvested by transbronchial biopsy [22, 23].

As suggested some years ago [13], it has not been possible to diagnose many cases of disease induced by exposure to Be. Particularly with cases of pulmonary granulomatous diseases, it is advisable to investigate the possible existence of occupational exposure to Be. At a symposium organized by the ACGIH entitled ''Beryllium: Effect on worker health'', held on September 23rd, 1999, in Washington, D.C., it was suggested that positive results in the BLPT is the most appropriate effect indicator (critical endpoint) upon which to base the occupational limit for Be in air [2].

The other well-known effect of occupational exposure to Be is lung cancer. For this reason Be is classified as an A1 human carcinogen by the ACGIH, and a carcinogen of group 1 by the IARC. When we consider CBD and cancer, exposure to low and very low concentrations may be of great interest, and the ACGIH is going to propose a ''notice of intended changes'' for Be, with a TLV-TWA of 0.2 $\mu g/m^3$ as inhalable particulate, instead of the current TLV-TWA of 2 $\mu g/m^3$ [2].

Crucial for the assessment of low exposures on the basis of ambient and biological monitoring, is the availability of adequate analytical methods. For the biological monitoring of subjects with low exposure to Be, the sensitivity and specificity of the analytical method determines the accuracy with which the amount of Be in biological matrices is measured.

The determination of Be has generally been performed using graphite furnace atomic absorption spectrometry (GFAAS) and more recently by inductively coupled plasma atomic emission or mass spectrometry (ICP-OES/MS).

Direct analysis by GFAAS is, however, the technique most frequently used for biological samples, and when correctly performed allows detection limits to be reached adequate to determine Be concentrations in urine, for example in the range 0.1–1 μg/l [4, 7, 15, 24].

Therefore, analytical performance and the identification of possible exposures are critical for Be biological monitoring, and would appear mandatory for assessing the new threshold limits for Be in air and (possibly) related biological limit values.

To assess the feasibility of the biological monitoring of occupational exposure to Be it would therefore be useful to take into consideration some of the investigations carried out in working environments with low and very low exposure to the metal as a starting point.

Materials and methods

Groups and workplaces

We investigated four groups of metallurgical workers, and a control group of mechanical workers employed in activities without exposure to metals (in particular Be). The exposed workers ($n = 65$) were employed in two electric steel plants and in two copper alloy foundries. Steel and non-copper alloys were produced in electric furnaces starting with scrap. In each plant we examined the more highly polluted working areas: furnace charging, melting and casting.

The furnace workers were exposed to metals during the following process phases: selection and preparation of raw materials, scrap charging, refining and melting.

The casters were employed in pouring of molten metal into the tundishes or the ingots. Both groups were therefore exposed to a mixture of metals, including Be. Possible sources of Be is the presence of the element in dust and smoke from raw materials or from steel and copper alloys during and after the melting process.

The exposure to dust and smoke containing the metals was not constant during the work shift and all workers used respiratory protective devices irregularly.

Our control group was composed of workers employed in mechanical activities (assembling, finishing trucks) known not to be exposed to metals.

The general characteristics of the groups investigated are reported in Table 1.

Ambient monitoring

The very low Be concentrations in the air meant that great volumes had to be sampled. Consequently, personal samplers could not be used. Stationary samplers with a flow rate of 10–15 l/min were used for periods of 5–6 h.

Table 1 Characteristics of the studied groups

Workplace	*n*	Age (years)		Job duration (years)		Smoking habits[a]		Alcohol consumption[b]	
		Mean	SD	Mean	SD	%	Mean	Mean	SD
Electric steel plants									
Furnace	25	39.5	10.3	13.4	6.3	56	22	0.7	0.5
Casting	18	38.6	9.8	12.5	6.5	45	19	0.6	0.4
Copper alloy foundries									
Furnace	12	43.1	6.7	15.3	7.4	62	21	0.7	0.6
Casting	10	44.5	7.9	16.8	7.6	58	18	0.6	0.5
Controls	30	38.3	11.5	12	6.6	52	17	0.5 0.6	0.3

[a] Percentage of smokers and mean no. of cigarettes smoked per day
[b] Consumption of wine (l/day)

The airborne particles (previous evaluations yielded particle sizes below 5 μm for 30 to 40%) were collected on cellulose membrane filters (size 25 mm, pore size 0.8 μm).

The filters were dissolved by overnight digestion with nitric acid, cc. Suprapure. The digestion solutions were diluted with water before analysis by ICP-MS. The method is characterized by a detection limit of 1 ng/m^3 (0.01 μg/l) and by a precision within series of 5% and between series of 8% at 100 ng/m^3 (10 μg/l).

The accuracy of the method was checked by certified material from NIST, in which Be was certified for a concentration of 12.5 μg/l. The precision between series was around 10%.

Biological monitoring

The levels of Be were determined in urine spot samples collected at the end of the work shift from workers employed in areas monitored by static samplers. The urinary specific gravity was measured by optical refractometry and only samples with a specific gravity between 1015 and 1035 were examined.

The urinary Be analysis was carried out by ICP-MS adapting the method of Schramel et al. [28]. The detection limit was 0.03 μg/l and the precision between series for a concentration of 0.5 μg/l 9.5%. Twenty percent of the samples were also measured using atomic absorption spectroscopy according to our previously published method [7], and the results were found to correlate well.

Results

The results of ambient and biological monitoring are reported as medians and ranges in Table 2. The urinary Be concentrations for the occupationally exposed subjects were different from the values in the general population, which, according to our experience, are below 0.03 μg/l urine.

The ambient Be concentrations exceeded the proposed TLV-TWA of 0.2 μg/m^3 only in the copper alloy foundries: four stationary measurements at the copper alloy furnace yielded values in the range from 0.4 to 0.8 μg/m^3, three at the casting area from 0.3 to 0.9 μg/m^3.

Analysis of the relationship between external and internal Be exposure revealed a significant correlation (Fig. 1). For the recommended TLV-TWA of 0.2 μg/m^3, urinary Be excretion corresponded to approximately 0.15 μg/l.

Discussion

As a result of the increasing industrial use of Be, occupational exposure to the metal may be an important issue. Owing to its physical-chemical characteristics, Be is ideal for use in alloys with other metals (in particular Cu and Ni, and to a lesser extent Co, Cr, Fe and Mg), for improving hardness and resistance to corrosion, wear, vibration and collision [2].

In addition to the traditional processes in which Be is intentionally used, other working activities also have to be considered, mainly in the metallurgical sector, in which the metal may be present in traces (impurities), sometimes not suspected. Also for these reasons, the presence of Be does not appear to be regularly investigated at various workplaces, and recent estimations, such as that of Kauppinen et al. [17], might not correctly evaluate the number of workers subject to Be exposure.

The Be levels usually encountered in past years at workplaces were in the order of micrograms per cubic

Table 2 Results of ambient and biological monitoring (*Be-Air* ambient beryllium concentrations, *Be-U* renal beryllium excretion, *DL* analytical detection limit)

Groups	*n*	Be-Air (μg/m^3)		*n*	Be-U (μg/l)	
		Median	Range		Median	Range
Electric steel plants						
Furnace	14	0.11	0.03–0.18	25	0.09	< 0.03–0.45
Casting	10	0.025	0.02–0.05	18	0.06	< 0.03–0.40
Copper alloy foundries						
Furnace	12	0.4	0.04–0.8	12	0.25	< 0.03–0.49
Casting	9	0.2	0.1–0.9	10	0.125	< 0.03–0.54
Controls	–	–	–	30	< 0.03 (DL)	–

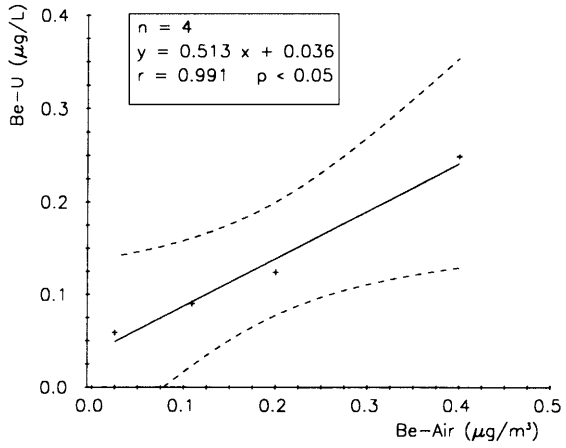

Fig. 1 Correlation diagram for the relationship of ambient beryllium concentrations (*Be-Air*) and renal beryllium excretion (*Be-U*). (Median values from 4 work areas)

metre, while at the present it ranges between some nanograms to some hundred nanograms per cubic metre [5, 6, 10, 16, 27]. Also, under these exposure conditions the use of biological monitoring for the assessment of internal exposure may be interesting, but the significance of Be determination in biological media, urine in particular, has not yet been clearly stated. It is generally accepted that the urinary Be levels of groups of exposed subjects differ significantly from those observed in the general population. Considering the reference values defined in the 1990s, we can observe that the urinary Be levels measured in the general population (Table 3) range from undetectable (0.03–0.06 µg/l) to ca. 0.5 µg/l.

In a survey from the beginning of the 1990s [7], urinary Be was measured in a population not occupationally exposed, and a mean value of 0.2 µg/l (SD 0.16; range < 0.03–0.8) was found. 15–20% of the individuals were found to have undetectable levels.

With the analytical methods used in the present study, all the controls were found to have urinary Be levels below the detection limit (< 0.03 µg/l).

This is in agreement with the experience of the laboratories of the Institute of Occupational, Social and Environmental Medicine of the University of Erlangen-Nuremberg, and with the study of Wegner et al. [30], which reports for the general population urinary Be concentrations below the analytical detection limit of 0.06 µg/l urine.

The survey by Wegner et al. [30] is worthy of detailed examination. The authors investigated in a cross-sectional study 57 gemstone cutters, employed for 24.8 ± 15.4 years in 12 German workshops. For 27 cutters working on average 21 ± 13 h/week with beryls, Be could be detected in 17 pre-shift and 12 post-shift urine specimens. The median for the pre-shift urine samples was 0.09 µg/l; the values were in the range from < 0.06 to 0.56 µg/l. The corresponding median for the post-shift urine samples was < 0.06 µg/l (detection limit); the range was < 0.06 to 0.029 µg/l urine. For a second group of 30 cutters employed in the treatment of beryls for 0.7 ± 1.2 h/week, Be was not detectable in any of the urine specimens. The Be concentrations in air were in the range from < 0.4 to 20 µg/m^3. At the workshop with the highest level of external exposure, urinary Be could be quantified for all employees ($n = 9$, mean ± SD 0.18 ± 0.19 µg/l in the pre-shift samples, and 0.12 ± 0.15 µg/l for the post-shift samples). Analysis of the correlation between external and internal exposure was not carried out.

Also in our study stationary air sampling was performed, and only workers employed in areas monitored by stationary air monitoring were considered for biological monitoring.

The Be concentrations in the air samples exceeded the proposed TLV-TWA of 0.2 µg/m^3 only in some samples from the copper alloy foundries, where the medians of 0.27 µg/m^3 (furnaces) and 0.31 µg/m^3 (casting) were above this limit (Table 2). Much lower values were determined in steel plants, probably due to the different amounts of Be present in the raw materials for two different metallurgical processes.

Regression analysis was performed with the median values from four work areas, and the corresponding median urinary Be concentrations. A significant correlation ($r = 0.991$) was found for the relationship between external and internal exposure (Fig. 1). It must be taken into consideration, however, that 19 values for the urinary Be concentration were below the analytical detection limit. The confidence limits for the regression line show the wide range of scatter of the values.

For the recommended TLV-TWA of 0.2 µg/m^3 for inhalable dust, the corresponding Be levels in urine were between 0.12 and 0.15 µg/l. Taking into account the upper 95th percentile, a corresponding urinary excretion

Table 3 Urinary beryllium concentrations of persons not occupationally exposed (data from literature published after 1990) (*DL* detection limit)

Authors	Year	Subject no.	Method	Values µg/l	
				Mean	SD
Minoia et al. [21]	1990	579	GF-AAS	0.4 (range < 0.02–0.82)	–
Apostoli et al. [7]	1992	163	GF-AAS	0.2 (range < 0.03–0.8)	0.16
Aitio et al. [3]	1997	–	GF-AAS	0.13 (reference limit)	–
Paschal et al. [25]	1998	496	ICP-MS	0.28	–
				25th percentile < 0.07	–
				95th percentile 0.79	–
Wegner et al. [30]	2000	34	GF-AAS	< 0.06 (DL)	–
This study	2000	30	ICP-MS	< 0.03 (DL)	–

of 0.2 μg/l was evaluated. These calculations are based on a limited database and can be interpreted only with reservations.

To conclude, the aspects to be discussed when evaluating a biological limit value for urinary Be may be summarized as follows:

- The "normal" urinary Be concentrations reported earlier in the literature are too high, mainly as a result of the poor specificity and sensitivity of the analytical methods previously adopted. Using adequate GF-AAS or ICP-MS techniques, the Be concentrations in urine samples of persons not occupationally exposed are below the detection limits of 0.06 μg/l–0.03 μg/l.
- The amount of Be taken in at the workplace in view of the current TLV, and the proposed TLV of 0.2 μg/m^3. Assuming exposure at the level of the latter TLV, ventilation of 10 m^3 per shift and 100% absorption, intake of the metal might be ca. 2 μg/day, and urinary excretion of the same order or lower.
- The significance in preventive and diagnostic terms of the availability of ways of measuring the toxicologically relevant concentration of the metal for the more interesting clinical and epidemiological features of Be, i.e. the immunologically mediated diseases and cancer.

The BLPT, for example, is strongly recommended in health surveillance programmes [29]. Wegner et al. [30] showed that for one subject the BLPT was positive, and stimulation indices were significantly higher in subjects with detectable Be in urine than in those with urinary Be below the detection limit.

The determination of Be in urine may therefore be useful, together with other laboratory tests, also on an individual basis, in improving health surveillance programmes or diagnostic pathways.

References

1. AAVV (1996) Conference on beryllium related diseases. Environ Health Perspect 104: 935–1001
2. ACGIH (1999) Symposium on Beryllium: "Effects on Worker Health", Sept. 23, Washington D.C., Cincinnati, Ohio and 2000 TLVs and BEIs booklet, ACGIH 2000, Cincinnati, Ohio
3. Aitio A, Kalio A, Kiilunen M, Valkonen S, Ahlstrom L (1997) Kemikaalilaltistumisen biomonitorointi. Tyoterveyslaitos, p 24
4. Angerer J, Schaller KH (eds) (1997) Beryllium. Analysis of hazardous substances in biological materials, vol 5. Wiley-VCH, Weinheim
5. Apostoli P, Porru S, Alessio L (1989) Behaviour of urinary beryllium in the general population and in subjects with low-level occupational exposure. Med Lav 80: 390–396
6. Apostoli P, Porru S, Minoia C, Alessio L (1989) Biological indicators for the assessment of human exposure to industrial chemicals: beryllium. Commission of the European Communities, Brussels-Luxembourg, pp 5–21
7. Apostoli P, Minoia C, Gilberti ME (1992) Determination of beryllium in urine by Zeeman GFAAS. In: Minoia C, Caroli S (eds) Application of Zeeman graphite furnace atomic absorption spectrometry in chemical laboratory and toxicology. Pergamon Press, London, pp 495–516
8. Barnard AE, Torma J, Viet SM (1996) Retrospective beryllium exposure assessment at the rocky flat environmental technologies site. Am Ind Hyg Assoc J 57: 804–808
9. Cotes JE, Gilson JC, McKerrow CB, Oldham PD (1983) A long-term follow up of workers exposed to beryllium. Br J Ind Med 40: 13–21
10. Cullen MR (1987) Chronic beryllium diseases in precious metal refinery. Am Rev Respir Dis 135: 201–208
11. Drury JF, Shriner CR, Lewis EG, Twill LE, Hammons AS (1978) Review on the environmental effects of pollutants: VI. Beryllium report N. EPA – 600/1-78-028, US Environmental Protection Agency, Cincinnati, Ohio, pp 1–191
12. Eisenbund M, Lisson J (1983) Epidemiological aspects of beryllium induces non-malignant lung disease: a 30 year update. J Occup Med 25: 196–202
13. Hardy HL (1980) Beryllium diseases: a clinical perspective. Environ Res 21: 1–9
14. Hirtle B, Teschke K, van Netten C, Brauer M (1998) Kiln emission and potters' exposure. Am Ind Hyg Assoc J 59: 706–714
15. Hurlbut JA (1978) Determination of beryllium in biological tissues and fluids by flameless atomic absorption. At Absorpt Newsl 16: 121–124
16. Johnson JS, Foote KL (1999) AWE Cardiff Beryllium Facility workplace control program and assessment of personal and static sampling data (1981–1997). Presented at Symposium on Beryllium: Effect on Worker Health, Washington DC, Sept. 23, ACGIH
17. Kauppinen T, Toikkanen J, Pedersen D, et al (2000) Occupational exposure to carcinogens in the European Union. Occup Environ Med 57: 10–18
18. Kreiss K, Wasserman S, Mroz MM, Newman LS (1993) Beryllium disease screening in the ceramic industry: blood lymphocyte test and exposure disease relations. J Occup Med 35: 267–274
19. Leonard A, Bernard A (1993) Biomonitoring of exposure to metal compounds with carcinogenic properties. Environ Health Perspect 101: 127–133
20. McGarvan PD, Rood AS, Till JE (1999) Chronic beryllium disease and cancer risk estimates with uncertainty for beryllium released to the air from the rocky flats plant. Environ Health Perspect 107: 731–744
21. Minoia C, Sabbioni E, Apostoli P, Alessio L, Capodaglio E (1990) Trace elements reference values in tissue from inhabitants of European Community. A study of 46 elements in urine blood and serum of Italian subjects. Sci Total Environ 95: 89–105
22. Newman LS, Lloyd J, Daniloff E (1996) The natural history of beryllium sensitization and chronic beryllium disease. Environ Health Perspect 104: 937–943
23. Nikula KJ, Swafford DS, Hoover MD (1997) Chronic granulomatous pneumonia and lymphocytic responses induced by inhaled beryllium metal. Toxicol Pathol 25: 2–12
24. Paschal DC, Bailey GC (1986) Determination of beryllium in urine with electrothermal atomic absorption using the I'Vov platform and matrix modification. At Spectrosc 7: 1–3
25. Paschal DC, Ting BG, Pirkle JL, Miller DT, Caldwell KL (1998) Trace metals in urine of United States residents: reference range concentrations. Environ Res 76: 53–59
26. Petzow G, Zorn P (1974) Toxicology of Be containing materials. Chem Ztg 98: 236–241
27. Ridenour PK, Preuss OP (1991) In: Rossmann MD, Preuss OP, Power MB (eds) Acute pulmonary disease. In: Beryllium, biomedical and environmental aspects, Williams and Wilkins, Baltimore, pp 103–112
28. Schramel P, Wendler I, Angerer J (1997) The determination of metals in urine samples by inductively coupled plasma mass spectrometry. Int Arch Occup Environ Health 69: 219–223
29. Stange AW, Furman FJ, Hilmas DE (1996) Rocky flats beryllium health surveillance. Environ Health Perspect 104: 981–986
30. Wegner R, Heinrich-Ramm R, Nowak D, et al (2000) Lung function, biological monitoring, and biological effect monitoring of gemstone cutters exposed to beryls. Occup Environ Med 57: 133–139
31. WHO IPCS (1990) Environmental health criteria 106 beryllium. WHO, Geneva