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RESEARCH ARTICLE

Lack of correlation between blood lead and serum prolactin levels among lead exposed workers

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Abstract
A cross sectional case (241 males occupationally exposed to lead)–control (102 males unexposed to lead) study was performed with the aim of evaluating the relationship between serum prolactin (S-PRL) and lead blood (PbB) levels. A meta-analysis of S-PRL levels in similar studies was also carried out. No difference of S-PRL between groups or any relationship between PbB and S-PRL levels was found. The meta-analysis showed a slight increase of S-PRL levels among exposed people, the weighted means falling within the reference values of the biomarker. The results do not support a routine use of S-PRL as a biomarker of effect in lead exposed workers.

Keywords: Prolactin, lead, neurotoxicity, occupational exposure, effect biomarker

Introduction

The central nervous system is one of the main targets of the toxic activities of lead (Pb). The neurological and neurobehavioral disorders caused by the metal are well known (Lanphear et al. 2000; Pohl et al. 2011). Despite a progressive reduction in recent decades of clinical intoxications giving rise among others to encephalopathy and peripheral neuropathy, lead continues to represent a public health concern, the attention being focused on the current low occupational–environmental levels.

Serum prolactin (S-PRL) has been reported as a biomarker of early neurotoxic effect related to lead exposure (Roses et al. 1989; Lucchini et al. 2000). Higher S-PRL levels would result from lead-induced decrease of the tonic inhibitory control exerted by the dopaminergic tuberoinfundibular system (TIDA) on the lactotroph cells of anterior pituitary. Rats experimentally dosed with lead show a reduction of dopamine turnover and dopamine receptor density both in the hypothalamus and pituitary, and an increase of S-PRL concentrations (Govoni et al. 1984, 1986; Doumouchtsis et al. 2009).

The relationship between occupational exposure to lead and S-PRL levels has been investigated by the studies resumed in Table 1. Govoni et al. (1987) classified lead exposed workers into four subgroups according to their blood lead (PbB) and zinc protoporphyrin (ZPP) levels, the latter as a biomarker of early hematotoxic effect with a kinetics slower than PbB. For both the biomarkers, a cut-off level of 400 μg/L was chosen. Only subjects exceeding the cut-off value for ZPP, independently from PbB levels, displayed S-PRL values significantly higher than controls, in any case falling within the reference range. Two other Italian studies (Bergamaschi et al. 1993; Lucchini et al. 2000) reported significantly higher S-PRL levels in occupationally exposed workers, in both cases with a higher prevalence of workers exceeding the upper reference limit (URL) of S-PRL values. Other studies looking at workers with comparable lead exposure levels, failed to find any significant association between PbB

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Table 1. Main descriptive parameters of studies investigating the association between S-PRL (ng/mL) and PbB (μg/L) in males occupationally exposed (and unexposed in case–control studies) to lead. Mean ± standard deviation or median (with range) of distributions are given. The upper reference limits (URL) of S-PRL values and the prevalence of subjects exceeding the URL for S-PRL (N > URL) are also shown.

		Exposed				Unexposed				
Studies	URL	N	PbB	S-PRL	N > URL	N	PbB	S-PRL	N > URL	p
Assennato et al. 1986	20	21	550 ± 140	5.9 ± 2.1	NA	21	220 ± 70	7.1 ± 4.6	NA	NS
Govoni et al. 1987	10	33	603 ± 193	5.06 ± 2.26	0	22	282 ± 71	3.44 ± 1.69	0	<0.02
Roses et al. 1989	17	56	(90–860)	16.3 ± 10.0	NA	58	(80–280)	9.9 ± 7.3	NA	NS
Ng et al. 1991	NA	122	351 ± 120	8.98 ± 5.12	NA	49	83 ± 28	9.21 ± 5.87	NA	NS
Bergamaschi et al. 1993	11.5	44	553 ± 91	9.5 ± 1.73	8	36	n.a.	8.19 ± 3.0	3	<0.05
Telisman et al. 2000	NA	98	387 ± 125	6.6 ± 4.2	NA	51	109 ± 30	6.3 ± 4.5	NA	NS
Lucchini et al. 2000	12.8	66	275 ± 110	10.65 ± 6.33	21	86	81.1 ± 44.7	7.42 ± 2.82	2	0.0001
Telisman et al. 2007	NA	240	49.2 (11.3–149.1)	5.8 (1.9–19.60)	NA	NA	NA	NA	NA	<0007*
Meeker et al. 2009	NA	219	15.0	9.8 (7.4–12.4)	NA	NA	NA	NA	NA	0.0002*

NS, not significant; NA, not applicable.
*Significance level of multivariate regression analyses showing inverse association between PbB and S-PRL.

and S-PRL levels (Assennato et al. 1986; Ng et al. 1991; and Telisman et al. 2000). More recently, an inverse relationship between S-PRL and PbB levels has been demonstrated in males occupationally unexposed to metallic elements by two independent studies. Telisman et al. (2007) showed a significant inverse association between PbB and S-PRL values ($p < 0.007$), after adjusting for covariates such as age, smoking, alcohol and other circulating metallic elements (cadmium, copper, zinc and selenium); the same behavior was observed not only for lead but also for other metallic elements (arsenic, cadmium, copper, manganese, molybdenum, and zinc) by Meeker et al. (2009) in 219 men through a multiple linear regression models adjusted for age, body mass index and smoking, whereas for chromium the relationship was positive.

The present cross-sectional case–control study was performed with the main aim of investigating the differences of PbB and S-PRL levels in two groups of males either occupationally exposed or unexposed to lead. Obtained results were pooled with those of previous similar studies and subjected to a meta-analysis.

Methods

Study population and design

We updated the sample of a multicentric study supported by the Ministry of Public Instruction, University and Research and entitled "Environmental and Occupational Exposure to Inorganic Lead: assessment of human health effects due to current doses and preventive measures" (Apostoli et al. 2005). The study enrolled 241 male workers employed in foundry and in battery manufacture with a lead exposure ranging from 60–800 μg/L and a control group of 102 males not occupationally exposed to chemicals or metals. Informed consent to participate to the study was obtained from each subject, who received an explanation of the purpose and procedure of the study.

A questionnaire was used to collect information about smoking habit, hobbies and alcohol consumption, whereas the health status was assessed by a physician (Alinovi et al. 2005; Apostoli et al. 2005). Subjects were excluded if having a diagnosis of neuropsychiatric illness or assuming drugs known to interfere with PRL secretion. In order to avoid any influence of circadian rhythm or other confounding factors, such as stress, both workers and controls were examined between 8.00 and 9.00 a.m. and were left supine for 10 min prior to blood sampling.

Biological monitoring

Exposure to lead was characterized by evaluating the blood (PbB) concentration of the metal in 10 mL venous blood samples drawn into test tubes containing lithium–heparin. PbB was determined by a published direct method (Romeo et al. 2009). Briefly, samples were diluted with a 0.1% Triton X100 solution, in an ETA–AAS graphite furnace, and background corrected with Zeeman effect using a Perkin Elmer SIMAA 6100 spectrophotometer (Waltham, MA, USA). The detection limit was 15 μg/L and intra-assay coefficient of variations (CVs) ranged from 3.5 to 6.4%.

The accuracy was assessed using specific certified materials urine 2A/B from the German Society of Occupational and Environmental Medicine (Erlangen, Germany).

Prolactin assay

Five millilitre of aliquot of venous blood samples were drawn in vials without coagulant and centrifuged to obtain serum. The sera were frozen immediately and stored at –20°C until analysis, which was performed blindly and in duplicate. PRL was measured by immune-enzymatic assay (Adaltis Italia, Bologna, Italy), which includes two high-affinity monoclonal antibodies and uses magnetisable solid phase separation. Standards were calibrated against the WHO International Standard for human prolactin (83/573). This method can be used for samples over 250 ng/mL without dilution. The

detection limit was 0.5 ng/mL, and the intra- and inter-assay CVs 4.9 and 8.7% percent, respectively.

No subject showed S-PRL values higher than 35 ng/mL, thus excluding the release of circulating macroprolactin, the larger (150.00–170.00) of the three species in which prolactin has been classified and can be separated from human serum on the basis of molecular mass.

The indicative reference range reported on the technical instructions of our kit are 6.9 (3.4–16.2) ng/mL for males younger than 45 years and 5.2 (2.5–14.2) ng/mL for others.

Statistical methods

Statistical analysis was carried out using both the PASW Statistics 19.0 for Windows™ (IBM SPSS Inc., Chicago, IL, USA) and the GraphPad Prism 5 (GraphPad Software Inc., La Jolla, CA, USA) statistical packages. The normal distribution of variables was assayed by Kolmogorov–Smirnov test. Variables with a skewed distribution were log-transformed to approximate the normal distribution; their central tendency is shown as geometric mean (GM) and the dispersion as geometric standard deviation (GSD). After stratification of workers by PbB quartiles, comparisons between the worker and the control group, as well as correlations between variables were evaluated by parametric (Student's *t*-test for independent samples, one-way ANOVA followed by the Bonferroni's *post-hoc* test test, Pearson's correlation analysis) or non-parametric tests (Mann–Whitney *U* test, Kruskall–Wallis test, Spearman's correlation analysis) according to data distribution. A stepwise multivariate linear regression analysis was finally run to assess the contribution of PbB levels, age, BMI, exposure duration, smoking habits and alcohol drinking to the variability of S-PRL, set as dependent variable. The significance level for all tests was $p \leq 0.05$ (two-tailed). Stepwise regression analysis was run using a significance level of 0.05 for entry and 0.10 for removal from the model.

To evaluate our results together with those of previous similar case–control studies, we performed a meta-analysis, with the aim of evaluating the means and 95% CI of S-PRL concentrations in different studies by the Comprehensive Meta-Analysis software (Biostat, NJ, USA), taking into account the guidelines of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) Group (Stroup et al. 2000). Relevant studies were retrieved from the PubMed® database (US National Library of Medicine, National Institute of Health) after identification of the MeSH terms relevant for our purposes. A first research was performed using the following MeSH restricted search string: "lead" [MeSH] AND "prolactin" [MeSH] AND "dopaminergic system" [MeSH] AND ("occupational exposure [MeSH] OR environmental exposure" [MeSH]), that gave rise to nine citations. A further not MeSH restricted research was thereafter performed using the search terms "prolactin AND lead", in order to include recent papers not yet indexed for Medline. The research was limited by species (humans) and gender (male). Nine papers (Assennato et al. 1986; Govoni et al. 1987; Roses et al. 1989; Ng et al. 1991; Bergamaschi et al. 1993; Telisman et al. 2000; Lucchini et al. 2000; Telisman et al. 2007; Meeker et al. 2009) were retrieved and evaluated by two independent investigators (GDP and SC). Only case–control studies reporting necessary descriptive data [sample size, means and standard deviations (SD) of S-PRL] were selected, this leading to the exclusion of two recent studies (Telisman et al. 2007; Meeker et al. 2009). As the number of selected papers was low, we decided to further limit the selection process, omitting any evaluation about the quality of studies. The Comprehensive Meta-Analysis software calculated the effective weight and the range of interval of each study for an effect size estimate. Heterogeneity of results in evaluated studies was measured using the χ^2 test for heterogeneity and a random effect model was used depending on the presence of statistical significance ($p < 0.05$). The evaluation regarded S-PRL levels in lead exposed and unexposed men. As reference upper limit, we used the median of the upper limit values reported in the studies considered (13 ng/mL).

Results

Table 2 summarizes the distributions of individual characteristics and lifestyle habits in the exposed and unexposed group, the latter also stratified by PbB quartiles. The groups were comparable as to age, body mass index, alcohol intake and drug assumption (data not shown), whereas current smokers prevailed among smokers.

Among exposed subjects, PbB values ranged from 60 to 800 μg/L, 96.7% of the cases showing values higher than 100 μg/L and 25 cases exceeding 500 μg/L. In the control group, PbB values were invariably lower than 100 μg/L and ranging between 5 and 88 μg/L.

Table 3 shows the distribution of S-PRL values in the control and exposed group, in the latter case also after stratification by PbB quartiles (PbB; 60 ≥ PbB ≤ 191.9 μg/L; 192.1 ≥ PbB ≤ 270.9 μg/L; 271 ≥ PbB ≤ 402.50 μg/L; PbB ≥ 402.51 μg/L). The prevalences of people with S-PRL values exceeding the upper reference limit is also shown, either in the same groups and in both exposed and unexposed subjects.

The distributions of S-PRL levels were not significantly different between groups of unexposed and exposed people, the latter also after stratification by PbB quartiles. The prevalence of controls exceeding the upper reference limit of S-PRL values was almost double than exposed subjects [Odds ratio (95% confidence interval) 2.06 (1.00–4.24); $p = 0.072$]. The distribution of subjects with abnormal S-PRL values in the exposed group failed to show significant differences among PbB quartiles (chi square analysis was not significant).

No significant relationship between PbB and S-PRL values was found at the Pearson's correlation analysis either in the whole sample ($r = 0.101$, $p = 0.062$) or in

Table 2. General characteristics of exposed and unexposed people. For the exposed group, data are shown for the whole group and for quartiles of lead blood levels levels (PbB; 60 ≥ PbB ≤ 191.9 μg/L; 192.1 ≥ PbB ≤270.9 μg/L; 271 ≥ PbB ≤ 402.50 μg/L; PbB ≥ 402.51 μg/L).

		Exposed					
	Unexposed (N = 102)	Total (N = 241)	1st Quartile (N = 59)	2nd Quartile (N = 61)	3rd Quartile (N = 61)	4th Quartile (N = 60)	p
Age, years, mean (SD)	43.7 (7.2)	40.8 (8.2)	40.0 (8.5)	40.3 (8.6)	40.6 (8.6)	42.2 (7.0)	0.001[a]
Body mass index, mean (SD)	25.8 (3.0)	26.2 (3.2)	26.2 (2.8)	25.9 (3.3)	26.3 (3.4)	26,5 (3.3)	0.262 [a]
Exposure (years), median, range	/	13.0 (1.0–33.0)	14.0 (1.0–31.0)	12.0 (1.0–29.0)	13.0 (1.0–33.0)	11 (1.0–25.0)	
Alcohol, (g/ day), median, range	19.9 (8.0–66.5)	30.8 (7.0–111.4)	21.3 (7.1–54.5)	32.3 (7.1–104.3)	30.8 (7.1–111.4)	30.8 (7.1–86.9)	0.036[b]
Current smokers (yes/no)	22/80	100/141	18/41	22/39	30/31	30/30	0.001[c]

[a]Student's *t*-test, unexposed vs. exposed people.
[b]Mann–Whitney *U* test, unexposed versus exposed people.
[c]Chi square test, unexposed versus exposed people.

Table 3. Geometric means [geometric standard deviations] of lead blood (PbB) and serum prolactin (S-PRL) values in exposed and unexposed males. Among exposed, values are shown for the whole sample and for quartiles of lead blood levels (PbB; 60 ≥ PbB ≤ 191.9 μg/L; 192.1 ≥ PbB ≤ 270.9 μg/L; 271 ≥ PbB ≤ 402.50 μg/L; PbB ≥ 402.51 μg/L). The prevalence of subjects exceeding the upper reference limit of our assay is also shown (males <45years, 14.2 ng/mL; males ≥45 years, 16.2 ng/mL).

		Exposed					
	Unexposed (N = 100)	Total (N = 241)	1st Quartile (N = 59)	2nd Quartile (N = 61)	3rd Quartile (N = 61)	4th Quartile (N = 60)	p
PbB (μg/L)	31.62 [1.85]	274.52 [1.43]	137.36 [1.29]	232.72 [1.10]	325.51 [1.13]	491.15 [1.17]	0.0001[a]
S-PRL (ng/mL)	6.69 [2.04]	7.74 [1.68]	7.48 [1.73]	7.90 [1.76]	7.16 [1.65]	8.47 [1.59]	0.067[a] 0.323[b]
No. (%) with abnormal S-PRL	15 (15)	19 (7.8)	4 (6.8)	7 (11.5)	1 (1.6)	7 (11.7)	0.072[c] 0.131[d]

S-PRL, serum prolactin; PbB, lead blood.
[a]Student's t test, exposed versus unexposed people.
[b]One-way ANOVA followed by Bonferroni's *post-hoc* test, among PbB quartiles.
[c]Chi square test, exposed versus unexposed.
[d]Chi square test, exposed people stratified by PbB quartiles.

exposed (r = 0.081, p = 0.21) or control group (r = 0.072, p = 0.48).

In the exposed group, both age and duration of exposure were negatively correlated with S-PRL (r = –0.24 and ρ = –0.30, respectively, $p \leq 0.0001$ for both) but unrelated to PbB levels. The distribution of S-PRL levels among workers stratified by quartiles of duration of exposure confirmed the negative association observed in the correlation analysis, with median values of S-PRL of 10.2, 8.7, 7.0 and 6.5 ng/mL in the 1st to the 4th quartile, respectively ($p \leq 0.0001$, Kruskall–Wallis Test).

A stepwise multivariate linear regression model including S-PRL as dependent variable and PbB levels, age, smoking habits, alcohol drinking, BMI and duration of exposures as independent variables, showed only a significant effect of duration of exposure on S-PRL levels (adjusted r^2 = 0.081, standardized beta coefficient = –0.285, $p \leq 0.0001$).

Figure 1 shows the frequency distribution of the values in both the exposed and unexposed groups. There was a clear overlap between both the distributions.

The weighed means of S-PRL levels in men exposed (8.36 ng/mL) or unexposed (6.06 ng/mL) to lead reported by studies evaluated by the meta-analysis and including also our results are shown in Figure 2. The standardized mean difference between exposed and unexposed males was 2.38 ± 0.17 ng/mL ($p < 0.0001$), and the mean S-PRL values falling in any case within the above mentioned reference range.

Discussion

Serum prolactin has been proposed as a biomarker of neuroendocrine effect in people exposed to pollutants targeting the central dopaminergic function. An elevation of S-PRL levels has been observed in subjects exposed to manganese (Alessio et al. 1989a; Mutti et al. 1996; Montes et al. 2011), aluminum (Alessio et al. 1989b), styrene (Mutti et al. 1984; Bergamaschi et al. 1996, Luderer et al. 2004), anesthetic gases (Lucchini et al. 1996) and lead (Govoni et al. 1984; Bergamaschi et al. 1993; Lucchini et al. 2000).

Raised S-PRL levels are generally considered to provide indirect evidence of reduced dopaminergic tuberoinfundibular (TIDA) activity, since PRL secretion is tonically inhibited by dopamine released by TIDA which in turn is stimulated by PRL in a feedback loop (Mutti et al. 1996).

A lead blood concentration of 100 μg/L has been established as a "level of concern" to avoid detectable deficits on neurobehavioral functions and cognitive development; however, neurotoxic effects have been observed also at lower PbB levels (Lanphear et al. 2000; Schwartz 1994). The neurotoxic effects of lead may, at least in part, be mediated in selected brain areas through its interferences with the dopamine (DA) pathway, including (i) interference with activities involved in DA metabolism, (ii) modification of the affinity of DA and tyrosine with their carriers, (iii) reduction of the number and density of DA receptors, and (iv) alteration of DA turnover and release through lead's ability to substitute for calcium and interact in calcium homeostasis (Cory-Slechta 1995; Goldstein 1993; Simons 1993).

Most of the studies investigating the association between lead exposure and S-PRL levels are cross-sectional case–control studies, generally limited in size (samples ranging between 122 and 21 cases and 21 and 86 controls) and thus particularly prone to type I (selection) bias, especially affecting the unexposed (control) group. Moreover, the upper reference limit of S-PRL values ranges from 11.5 to 20 μg/L in different studies, depending on the variability of the assay.

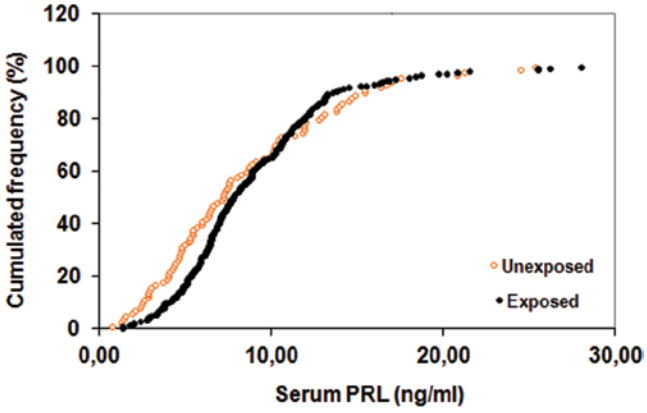

Figure 1. Cumulative frequency distribution of serum prolactin (S-PRL) among lead exposed and unexposed males.

All the studies suffer a generally poor control of potential confounding factors, an issue that is particularly relevant for prolactin, whose secretion is influenced by a lot of external and endogenous factors, including anxiety and other psychological disorders, stress, invasive procedures (even the simple venopuncture to achieve the blood sample) and hypoglycaemia (Ohlson et al., 2001). Raised S-PRL concentrations have been, moreover, reported in the active phases of several inflammatory-immunological disorders, including celiac disease, uveitis, rejection of heart transplantation and other multi-organ and organ specific autoimmune diseases such as systemic lupus erythematosus, diabetes mellitus type I, rheumatoid arthritis, autoimmune thyroiditis, multiple sclerosis (Chikanza 1999; De Bellis et al. 2005; Chuang & Molitch 2007; Orbach & Shoenfeld 2007) and psoriasis (Giasuddin et al. 1998; Dilmé-Carreras et al. 2011).

Probably as a consequence of the above recalled limitations, the available studies have produced conflicting results. Three studies (Assennato et al. 1986; Govoni et al. 1987; Bergamaschi et al. 1993) evaluated S-PRL values in males exposed to high lead levels (PbB between 550 and 603 μg/L). Assennato et al. (1986) failed to find differences between S-PRL measured in battery workers (PbB 500 ± 140 μg/L) and cement workers (PbB 220 ± 40 μg/L). On the other hand, Bergamaschi et al. (1993) reported a dose-response relationship between PbB and S-PRL values, as 8% of controls, 28% of workers with low exposure (PbB < 400 μg/L) and 43% of heavily exposed workers (PbB > 400 μg/L) showed S-PRL values exceeding the

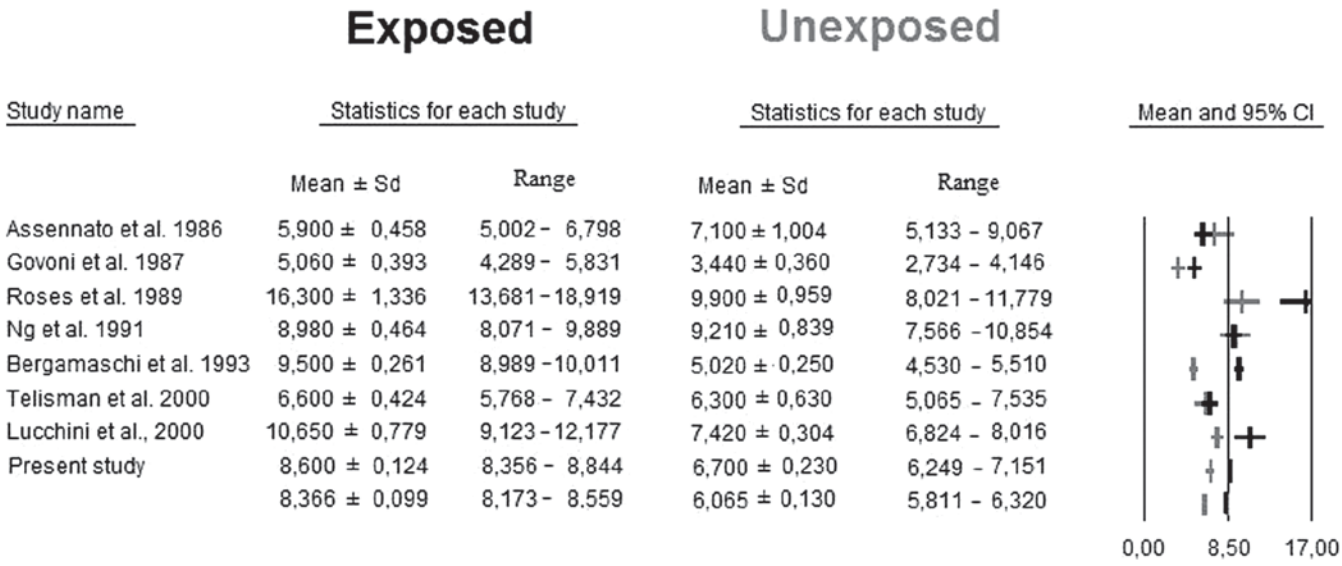

Figure 2. Results of the meta-analysis of serum prolactin (S-PRL) concentrations (ng/L). For each of the studies, the mean S-PRL values are shown for exposed (black) and unexposed (grey) people. Boxes indicate point estimates of effect weighted means in single studies and horizontal lines the confidence intervals.

upper reference limit. As anticipated in the Introduction, Govoni et al. (1987) reported S-PRL higher than controls only among subjects with ZPP values higher than 400 μg/L.

Other studies investigated, the effects of more moderate lead exposure levels (Lucchini et al. 2000; Telisman et al. 2000 and Ng et al. 1991). In the paper by Lucchini et al. (2000), battery workers with mean PbB levels of 275 ± 110 μg/L showed significantly higher S-PRL levels and a higher prevalence of people with S-PRL levels exceeding the upper reference limit (31.6 vs. 2.5%) than the control group. It is noteworthy, however, that the upper reference limits of S-PRL both in this study and that by Bergamaschi et al. (1993) were the lowest. The studies by Telisman et al. (2000) and Ng et al. (1991) failed to find any significant difference of S-PRL concentration between the exposed and the control group, or between workers classified by work seniority (duration of exposure <10 years and ≥10 years) (Ng et al. 1991).

At environmental exposure levels, a weak positive correlation between S-PRL and PbB levels has been reported by Leite et al. (2002), only in children with PbB levels higher than 100 μg/L. More recently, however, a negative association between S-PRL and low PbB levels (<50 μg/L) has been reported by two independent studies in men not occupationally exposed to metals and/or other factors known or suspected of influencing the male reproductive function or metal metabolism (Telisman et al. 2007; Meeker et al. 2009).

Our findings confirm the results of previous studies (Assennato et al. 1986; Ng et al. 1991; Telisman et al. 2000) failing to demonstrate an association between PbB and S-PRL values. A somewhat unexpected finding was an odds ratio of abnormal S-PRL almost double among controls, as compared to exposed workers.

A biomarker of effect is defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (National Research Council, NRC 1989). The effectiveness of such a biomarker for diagnostic/preventive purposes relies on its ability to identify always (sensitivity) and only (specificity), at individual level, the subjects bearing the biochemical-functional alteration which is causally related to the internal dose of the xenobiotic. This implies the demonstration of both a dose-effect (i.e. the extent of the effect as a function of the dose) and dose-response (i.e. the prevalence of subjects with abnormal values as a function of the dose) relationships. The meta-analysis shows that, on a group basis, lead exposed workers display significantly higher S-PRL levels than unexposed men. Thus, a dose-effect relationship is probably demonstrable, although average values fall in any case within the range of physiological variability of the biomarker and recent environmental studies show a negative relationship between PbB and S-PRL levels (Telisman et al. 2007; Meeker et al. 2009). Looking at our results and those of previous similar studies (Govoni et al. 1987; Lucchini et al. 2000; Bergamaschi et al. 1993) reporting the prevalence of abnormal values among exposed and unexposed men, we find that two studies (Lucchini et al. 2000; Bergamaschi et al. 1993) show a significant excess of abnormal S-PRL values among exposed workers, whereas both the others do not, actually in our case showing an opposite result. Thus, it seems that a dose–response relationship is hard to be established, as confirmed also by our results in exposed men stratified by PbB quartiles.

No relationship was found between PbB and S-PRL values either in the whole sample or in the sample stratified by occupational exposure. In our study, S-PRL values were significantly affected by duration of occupational exposure but with a negative trend, substantially in agreement with an inconsistency of association between occupational exposure to lead and S-PRL levels.

In our opinion, the overall amount of obtained evidence seriously limits the biomarker's suitability for preventive purposes in occupational health settings, at least for its application at an individual level.

Declaration of interest

The authors report no declarations of interest.

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