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Authors: Bledsoe, Michael L., Pinkerton, Lynne E., Silver, Sharon, Deddens, James A., and Biagini, Raymond E.

ORIGINAL RESEARCH

Thyroxine and Free Thyroxine Levels in Workers Occupationally Exposed to Inorganic Lead

Michael L. Bledsoe[1], Lynne E. Pinkerton[2], Sharon Silver[2], James A. Deddens[2] and Raymond E. Biagini[3]

[1]Occupational Medicine Services, 78th Aerospace Medicine Squadron, 78th Medical Group, United States Air Force, Robins Air Force Base, GA, USA. [2]Division of Surveillance, Hazard Evaluations and Field Studies, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, OH, USA. [3]Division of Applied Research and Technology, National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, Cincinnati, OH, USA. Corresponding author email: michael.bledsoe@us.af.mil

Abstract:
Background: The effects of lead exposure on thyroid function are unclear.
Methods: Serum thyroxine (T4) was evaluated among 137 lead-exposed workers and 83 non-exposed workers. Free thyroxine (FT4) was evaluated among a subset of these workers. Exposure metrics included blood lead level (BLL), which reflects recent exposure, zinc protoporphyrin (ZPP), a marker of intermediate-duration lead exposure, exposure duration, and estimated cumulative exposure. Multiple linear regression results were adjusted for age, race, and current smoking status.
Results: Mean BLLs were 38.9 µg/dL in lead exposed workers and 2.1 µg/dL in non-exposed workers. The adjusted mean T4 and FT4 concentrations among exposed and non-exposed workers were similar. While T4 was not significantly related to any of the exposure metrics, FT4 was inversely related to the logged values of both exposure duration and cumulative exposure, but not to ZPP or BLL.
Conclusions: The findings suggest that FT4 levels may be related to long-term lead exposure.

Keywords: thyroxine, free thyroxine, lead, occupational exposure

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Introduction

Lead is one of the oldest known occupational and environmental poisons, but one whose properties make it a valuable industrial metal. Lead has long been known to affect the neurological, renal, and reproductive systems.[1] Scientific understanding of lead toxicity in other organ systems and at low levels of exposure continues to evolve.[2]

The two primary thyroid hormones are thyroxine (T4) and triiodothyronine (T3). T3 and T4 primarily circulate bound to carrier proteins; less than 1% of each circulates unbound as free T3 (FT3) and free T4 (FT4), respectively. The unbound or "free" fraction is responsible for the biological effects. Thyroid hormone production is regulated by a complex negative feedback system controlled by the hypothalamus through the pituitary gland, with thyroid stimulating hormone (TSH) an important mediator. Thyroid function is primarily evaluated by serum testing of TSH, T4, FT4, T3, and FT3.

Several studies have evaluated the effects of lead on thyroid hormone levels. Moline and Landrigan[3] note that thyroid function is often depressed in lead-exposed workers. However, the findings have been inconsistent. Differences in exposure levels may explain some of the disparity. Decreased thyroid hormone levels have been reported primarily in studies of workers with higher exposure levels, with mean blood lead levels (BLL) above 60 µg/dL (micrograms of lead per deciliter of blood); at lower exposure levels, results have been mixed, with studies reporting increases, decreases, or no change in hormone levels.[4] Moreover, some studies of highly exposed workers observed no association between lead exposure and serum thyroid hormones.[5] Potential reasons for these disparities include small sample sizes, potential confounders, and differences in clinical laboratory assessments.[4] The lack of scientific consensus about the effects of lead exposure on thyroid hormone levels demonstrates the need for additional research.

In 1994, the National Institute for Occupational Safety and Health (NIOSH) performed a cross-sectional study[6] comparing immunologic factors in workers occupationally exposed to lead ("exposed") and manufacturing workers without lead exposure ("non-exposed"). As part of the study, sera from exposed and non-exposed participants were analyzed for T4, BLL, and zinc protoporphyrin (ZPP). Two years later, FT4 was analyzed in stored serum from study participants who gave consent for serum remaining from the study to be used for future research. In order to elucidate the relations between occupational lead exposure and thyroid hormone levels, the current study compared T4 and FT4 levels to several metrics of lead exposure among workers with and without occupational lead exposure.

Materials and Methods
Study population

In the original study, lead-exposed workers were recruited from a large secondary lead smelter (a facility that recycled batteries) in the southeastern US. A non-exposed comparison group was recruited from a nearby hardware manufacturing plant that mainly produced metal door hinges. Male employees on first and second shift who were hired at least six months prior to the study were invited to participate. Women were not invited to participate because of the small number of lead-exposed female employees at the secondary lead smelter. Because the study evaluated immunologic factors, exclusion criteria were developed based on factors known or suspected to alter immune response. Exclusion criteria (at the time data were collected) included use of medications (such as corticosteroids) known to alter immune function, or serious illnesses of the immune system (such as leukemia or acquired immune deficiency syndrome).

The original study examined 145 lead exposed and 84 non-exposed workers. The study protocol was approved by the Human Subjects Review Board of NIOSH. Informed consent was obtained from all participants. Blood was obtained to measure BLL (which provides an estimate of recent exposure), ZPP (which provides an estimate of intermediate duration lead exposure), and serum T4. Numerous measurements of immune function were made and have been reported previously.[6] Many, but not all, participants gave consent for any remaining sera to be used for future research.

Participants were also administered a questionnaire that included personal demographic information, medical history, medication use, smoking and drinking habits, and work history. Self-reported medication use was later reviewed for any use of medications that affect thyroid function. Six exposed and two non-exposed participants reported aspirin use, but below

the 2600 mg daily dose associated with a potential to alter thyroid function.[7] One exposed participant was excluded for daily use of phenytoin, reported to alter thyroid function.[7] No participants reported a history of thyroid disease or a hobby (such as bullet casting) or previous employment which would entail exposure to lead.

At the time of the original study, not all participants consented to allow their remaining sera to be analyzed for future research and not all stored serum samples had sufficient volume remaining for analysis of FT4. For the final analysis, there were 137 lead-exposed participants, of whom 83 also had a FT4 result available, and 83 non-exposed participants, of whom 47 also had a FT4 result available. One exposed participant had a T4 of 16.2 µg/dL (normal range 5.0–12.0 µg/dL), 6.2 standard deviations above the mean of 5.7 µg/dL, but had no available FT4 result. The results presented here omit this participant, giving final analyses of 136 lead-exposed and 83 non-exposed workers.

Exposure characterization

The primary exposure at the secondary lead smelter was lead. According to company air monitoring data, air concentrations of arsenic and other elements were negligible. Areas of the hardware manufacturing plant where exposure to chemicals was negligible were identified based on a review of the Material Safety Data Sheets and a walkthrough survey of the plant. The non-exposed comparison group was limited to workers who were employed in these areas. NIOSH investigators also conducted air sampling for metals and oil mists at the hardware manufacturing plant; air concentrations were negligible.[6]

Sample collection

In 1994, blood was collected for the original study by antecubital venipuncture into trace element tubes for blood lead analysis and serum separator tubes to isolate sera. The sera were separated on site by centrifugation at $1,000 \times g$ for 10 minutes for serum chemistry analyses. All tests were performed by methods consistent with established guidelines for clinical analysis and in compliance with regulations of the Clinical Laboratory Improvement Act.[8] Extra serum remaining from the original study was stored at -70 °C.

Clinical chemistry

Blood lead analyses and ZPP measurements were performed by a commercial laboratory (Smith-Kline Beecham, St. Louis, MO, OSHA certified). T4 measurements were performed at NIOSH (Cincinnati, OH) using a centrifugal chemistry analyzer (COBAS FARA II, Roche, Inc., Nutley, NJ) using reagents and standards supplied by the manufacturer. FT4 measurements were performed on previously stored sera by a commercial laboratory (Corning Hazelton, Inc., Vienna, VA) using a solid-state ^{125}I radioimmunoassay.

Statistical analysis

Participant demographic and biometric characteristics, T4, and FT4 of exposed and non-exposed participants were compared with t-tests for continuous variables, and Chi-square tests for categorical variables. Similarly, characteristics of participants with both T4 and FT4 results available were compared to participants with only T4 results.

Multiple linear regression analyses were used to examine the relations between measures of lead exposure and measures of thyroid function (T4 and FT4). A dichotomous variable indicating whether the subject was occupationally exposed to lead was the initial exposure variable included in the models. These models were used to obtain adjusted ("least squares") mean values in the lead-exposed and non-exposed groups for T4 and FT4. For all regression models, potential confounders and effect modifiers examined included age, race, body mass index, smoking (current status, pack years), and alcohol use.

In order to evaluate exposure-response relations in the group of lead-exposed workers, regression analyses were conducted in which the dichotomous exposure variable was replaced by a continuous exposure biometric (current BLL or current ZPP) or by a continuous non-biological exposure metric (duration of lead exposure or an estimate of cumulative lead exposure). Cumulative lead exposure (in µg/dL•years) was estimated for the lead-exposed participants from historical blood lead monitoring results with the equation

$$\int_0^T B(t)dt = \sum_{i=1}^{n-1} (1/2)(B_i + B_{i+1})\Delta t$$

Table 1. Characteristics of workers exposed to lead at a secondary lead smelter and non-exposed workers.[†]

	Exposed N = 136[‡]	Non-Exposed N = 83
Mean age (yrs)*	32.9 (8.5)	30.2 (9.3)
Mean body mass index (kg/m²)	27.8 (5.4)	27.3 (5.5)
Race*		
Caucasian	54 (39.7%)	51 (61.4%)
African-American	82 (60.3%)	32 (38.6%)
Smoking status		
Never smoker	70 (51.5%)	34 (41.0%)
Former smoker	19 (14.0%)	14 (16.9%)
Current smoker	47 (34.6%)	35 (42.2%)
Mean pack years of smoking	4.8 (9.6)	4.0 (7.5)
Alcohol use (1 drink/wk, on average, during last 6 months)	84 (61.8%)	46 (55.4%)

Notes: [†]Results are presented as mean (standard deviation) or number (%); [‡]A few individual data items were missing for some participants. The total number of exposed and non-exposed participants used in these analyses ranged from 135 to 136 and from 82 to 83, respectively, because of missing data. *$P < 0.05$.

where B_i and B_{i+1} are the ith and (i + 1)th blood lead measurements (in µg/dL), respectively; Δt is the time interval (in years) between measurements; and n is the total number of blood lead measurements. Time-integrated blood lead concentration has been reported to correlate with measurements of bone lead, which is considered a measure of cumulative lead exposure.[9,10]

All analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC). Values of blood lead below the limit of detection (2 µg/dL) were estimated by dividing the limit of detection by two.[11]

Results

Demographic information and exposure measurements for lead-exposed and non-exposed participants are shown in Tables 1 and 2. Lead-exposed participants were older, on average, than non-exposed participants ($P = 0.03$) and more likely to be African-American ($P = 0.002$). The mean body mass index of exposed and non-exposed participants was similar ($P = 0.57$). The mean BLL was 38.9 µg/dL among exposed participants and 2.1 µg/dL among non-exposed participants, while the median ZPP was 48.0 µg/dL in exposed workers and 18.0 µg/dLin the non-exposed. The median duration of lead exposure among exposed participants was 4.8 years (range: 0.5–18.4 years). The group of participants with both T4 and FT4 results and the group of participants with T4 results only were similar in terms of BLL, ZPP, T4, and demographic characteristics.

The unadjusted mean T4 levels of lead-exposed and non-exposed participants (Table 2) were similar ($P = 0.25$), but the unadjusted mean FT4 was marginally lower among lead-exposed participants than non-exposed participants ($P = 0.06$).

Age was a confounder for all of the regression models for FT4, and race and current smoking status (current smoker yes/no) were confounders for some of the exposure metrics in models for FT4 and T4. For consistency, age, race, and current smoking status were included in all of the final models. All models

Table 2. Exposure metric levels and selected thyroid hormone levels for workers exposed to lead at a secondary lead smelter and non-exposed workers.[†]

	Exposed N = 136[‡]	Non-Exposed N = 83	Differences P-value
Mean blood lead level (µg/dL)	38.9 (8.7)	2.1 (1.8)	<0.0001
Median zinc protoporphyrin (µg/dL)	48.0 (2–424)	18.0 (1–59)	<0.0001
Median time-weighted average blood lead level over years of lead exposure (µg/dL)	36.5 (14.2–55.8)	Not applicable	
Median duration of lead exposure (years)	4.8 (0.5–18.4)	Not applicable	
Median estimated cumulative lead exposure (µg/dL•year)	151.6 (7.6–969.2)	Not applicable	
Mean T4 (µg/dL)	5.81 (1.34)	6.01 (1.04)	0.25
Mean FT4 (ng/dL)	1.10 (0.26)	1.18 (0.23)	0.06

Notes: [†]Results are presented as mean (standard deviation) or median (range); [‡]A few individual data items were missing for some participants. The total number of exposed and non-exposed participants used in these analyses ranged from 135 to 136 and from 82 to 83, respectively, because of missing data. 136 exposed and 83 non-exposed workers were included in the analyses of T4. 83 exposed and 47 non-exposed workers were included in the analyses of FT4.

Table 3. Association of measures of lead exposure with the level of thyroxine (T4) and free thyroxine (FT4)[†].

	T4		FT4	
	Coefficient	**P-value**	**Coefficient**	**P-value**
Occupational lead exposure (Yes = 1)	−0.05758	0.74	−0.05172	0.26
Blood lead level (μg/dL)[‡]	−0.00977	0.46	−0.00173	0.65
Natural log (zinc protoporphyrin in μg/dL)[‡]	−0.20430	0.16	−0.05186	0.20
Natural log (duration of exposure in years)[‡]	−0.14911	0.27	−0.06933	0.04
Natural log (estimated cumulative lead exposure in μg/dL•year)[‡]	−0.17595	0.13	−0.05805	0.05

Notes: [†]All multiple linear regression models included age, race, current smoking status, and an exposure variable (occupational lead exposure, blood lead level, or the natural log of zinc protoporphyrin, duration of exposure, or estimated cumulative lead exposure); [‡]The last eight models were restricted to exposed workers.

satisfied the usual assumptions of independent normally distributed errors with equal variance.

In regression analyses conducted for exposed workers, the logged values of ZPP, exposure duration, and estimated cumulative exposure were used, due to the skewed distributions of these variables. BLL was approximately normally distributed, so the unlogged values were used for BLL.

After adjusting for age, race, and current smoking status, exposed and non-exposed participants had similar mean levels of T4 (exposed = 5.86 μg/dL, non-exposed = 5.92 μg/dL, $P > 0.74$) and FT4 (exposed = 1.11 μg/dL, non-exposed = 1.16 μg/dL, $P = 0.26$). In analyses adjusted for age, race, and current smoking, T4 did not show a statistically significant relation with any of the exposure metrics (Table 3). In contrast, FT4 was inversely related to the logged values of both exposure duration ($P = 0.04$) and cumulative exposure ($P = 0.05$), but not to either of the biological exposure metrics. R^2 values for the models were low, but were higher for the models of FT4.

Discussion and Conclusions

This study found no difference in mean T4 or FT4 between exposed and non-exposed workers after adjusting for age, race, and current smoking status. While the concentration of T4 was not associated with any exposure metric in models adjusted for age, race, and current smoking status, the serum concentration of FT4 was negatively associated with both exposure duration and cumulative exposure. The reasons for this are unknown. Other investigators have found that lead decreases thyroid uptake of iodine[12] and may adversely affect the pituitary-thyroid axis.[13,14]

Our findings suggest that lead may affect the equilibrium between protein-bound and free hormone. Free thyroid hormones represent less than 1% of all thyroid hormones but are responsible for biological effects.[15] A process that alters protein binding could disrupt biological effects by dramatically altering the amount of free thyroid hormones while maintaining normal or near normal levels of total T4 and TSH. Although FT4 results were available only for a subset of participants in this study, the groups of participants with and without FT4 results available were similar with respect to demographic characteristics, body mass index, smoking, and exposure metrics, suggesting that differences in the findings are not due to bias in the sample.

Previous research on the effects of lead on thyroid function has had widely varying results. A number of studies have examined the relation between thyroid hormone levels and BLL, which reflects recent lead exposure. Some studies have suggested that BLLs higher than those in the current study are associated with decrements in thyroid hormone levels.[13,14,16] However, similar findings have not generally been observed in studies of workers with BLLs less than 60 μg/dL. Refowitz[17] and Schumacher and colleagues[18] found no association with BLL and thyroid hormone levels among groups of workers with mean BLLs less than ~60 μg/dL. In contrast, Gustafson and colleagues[19] and Dursun and Tutus[20] found higher levels of T4, on average, among exposed workers with mean BLLs of 39.4 μg/dL and 17.07 μg/dL, respectively, than among non-exposed workers. Dursun and Tutus[20] also found higher levels of FT4 and FT3, on average, among exposed workers. Singh et al[21] found no difference in T3 and T4 between controls and a group of exposed workers with a mean BLL of 51.9; however, mean TSH

was significantly higher in the exposed group. Lopez and colleagues[16] found a positive correlation between BLL and T3, T4, FT4, and TSH at BLLs below 50 μg/dL and a negative correlation between BLL and T3, T4, and FT4 at BLLs above 50 μg/dL, suggesting the existence of a threshold effect. In the current study of workers with current BLLs below 60 μg/dL, no association was observed between T4 or FT4 and occupational lead exposure (yes/no) or BLL.

Relatively few studies have evaluated the effect of chronic or cumulative lead exposure on thyroid function; most have used duration of exposure as a surrogate of chronic lead exposure. Tuppurainen and colleagues[22] found negative correlations between duration of exposure and both T4 and FT4, especially among workers with individual average BLLs above 56.6 μg/dL, suggesting that chronic, intense lead exposure may depress thyroid function. Dursun and Tutus[20] found a negative association between duration of exposure and T4 but not FT4. In contrast, Gennart and colleagues[23] found no relationship between duration of exposure and T3, T4, FT4 index, or TSH. Erfurth and colleagues[24] found no relationship for FT4, FT3, and TSH with two metrics designed to estimate long-term exposure: a cumulative blood lead index and finger bone lead. The current study found negative associations between concentrations of FT4, but not T4, and long-term exposure (as measured by either exposure duration or estimated cumulative lead exposure).

The disparity in findings among studies of lead exposure and thyroid function may be related to study limitations such as sample size, or to non-comparability between studies. Other limitations include absence of a non-exposed referent group,[13,14,17,18,22] relatively high BLLs in the "non-exposed" referent group,[23,16] and lack of data on potential confounders such as age, race, alcohol use, and/or smoking.[13,16–24] For studies examining the effects of exposure duration, disparities in the results may be related to between-study differences in the relations between exposure duration and cumulative lead exposure.

The current study has several limitations. T4 and FT4 were evaluated, but TSH, T3, and FT3 measurements were not available. In addition, FT4 could be evaluated only for a subset of participants. A more comprehensive laboratory battery would have been desirable. As with any cross-sectional study, it is impossible to detect temporal associations between exposure and outcome variables; moreover, numerous associations were evaluated, and some of the findings may have attained statistical significance by chance. The R^2 values for the relations between blood lead levels and thyroid hormones were low in this study, as in other studies of this topic. This suggests that other factors not taken into account by these studies, such as genetic polymorphisms[25] may have substantial explanatory value. Another limitation is that information on potential confounders was from self reports; there was no validation of reports of personal habits, medical history or medication use.

Strengths of the study include having participants with significant lead exposure but BLLs allowable under the current lead standard (29 CFR Part 1910.1025)[26] and a large number of participants in exposed as well as non-exposed groups. Some previous studies reported relatively high BLLs for non-exposed comparison groups, suggesting that those participants had significant environmental lead exposure from some source, whether occupational or not. The low mean BLL for non-exposed participants in this study suggests that non-exposed participants had little recent lead exposure.

Another strength of this study is the use of multiple measurements of lead exposure. The complexity of lead metabolism limits the value of a single variable in estimating the biological burden on people chronically exposed.[27] This study used multiple variables to seek insight into whether short, medium, or long-term exposure is potentially most damaging to thyroid metabolism. BLL provides the best measurement for recent lead exposure. ZPP reflects intermediate lead exposure over the previous three to four months.[27] Duration of exposure and estimates of cumulative lead exposure (the calculation of which is described above) provided two different but related ways of considering long-term lead exposure.

In summary, the findings suggest that the concentration of FT4 may be inversely related to long-term lead exposure. In contrast, T4 was not associated with metrics of lead exposure (BLL, ZPP, exposure duration, or estimated cumulative exposure).

Acknowledgments

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