

Benchmark Dose of Lead Inducing Anemia at the Workplace

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To estimate the critical dose of lead inducing anemia in humans, the effects of lead on hemoglobin (Hb) and hematocrit (Hct) levels and red blood cell (RBC) count were examined in 388 male lead-exposed workers with blood lead (BPb) levels of 0.05–5.5 (mean 1.3) $\mu\text{mol/L}$ by using the benchmark dose (BMD) approach. The BPb level was significantly related to Hb (regression coefficient $\beta = -0.276$), RBC ($\beta = -11.35$), and Hct ($\beta = -0.563$) among the workers ($p < 0.001$) when controlling for age and working status. The average BPb levels were significantly higher in the workers with anemia (1.85 $\mu\text{mol/L}$), based on the WHO criteria, than in those without anemia (1.26 $\mu\text{mol/L}$). The benchmark dose levels of BPb (i.e., lower 95% confidence limits of BMD), calculated from the K -power model set at an abnormal probability of 5% in unexposed workers and an excess risk of 5% in exposed workers were estimated to be 0.94 $\mu\text{mol/L}$ (19.5 $\mu\text{g/dl}$) for Hb, 0.94 $\mu\text{mol/L}$ (19.4 $\mu\text{g/dl}$) for RBC, and 1.43 $\mu\text{mol/L}$ (29.6 $\mu\text{g/dl}$) for Hct. These findings suggest that reduction in hematopoietic indicators may be initiated at BPbs below the level currently considered without effect.

KEY WORDS: Benchmark dose; hemoglobin; hematocrit; lead; red blood cell

1. INTRODUCTION

The threshold blood lead (BPb) level for a decrease in hemoglobin (Hb) in occupationally exposed workers has been estimated to be 2.4 $\mu\text{mol/L}$ (50 $\mu\text{g/dl}$, U.S. EPA, 1986), based on evaluations of the data of several reports published about 25 years ago (Tola *et al.*, 1973; Lilis *et al.*, 1978; Grandjean, 1979; Baker *et al.*, 1979). Similarly, reduction in hematocrit (Hct) has been described to be greater than proportional to the increase in BPb concentrations between 0.97 and 4.8 $\mu\text{mol/L}$ (ATSDR, 1999). On the other hand, a couple of recent studies failed to observe any association between the BPb and Hb levels (Makino

et al., 1997; Fromm *et al.*, 1999); some researches have suggested that the critical dose of lead toxicity may be extremely low or even nonexistent (Piomelli *et al.*, 1982; Poulos *et al.*, 1986; Murata *et al.*, 2003). Thus, the critical dose at which lead can induce anemia in exposed workers remains controversial (IPCS, 1995; ATSDR, 1999; Fromm *et al.*, 1999). For a measure of the acceptability of occupational exposure levels, it would be crucial to confirm such a discernible critical dose, if it exists.

Concerning the estimation of the critical dose, the no-observed-adverse-effect level (NOAEL) is the highest dose at which no statistically or biologically significant adverse effects in an exposed group are identified (National Research Council, 2000). However, the NOAEL has many shortcomings, e.g., not adequately reflecting the shape of the dose response and not appropriately accounting for study size (Crump, 2002). As an alternative to the NOAEL, the benchmark dose (BMD) approach has been applied in environmental health sciences to provide a point of departure for low dose extrapolation (National Research

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Council, 2000). In this study, the critical dose of lead inducing anemia, characterized by decreased levels of Hb, Hct, and red blood cell (RBC) count, was examined in Japanese lead-exposed workers by introducing the BMD method (Budtz-Jørgensen *et al.*, 2001) for the first time.

2. MATERIALS AND METHODS

2.1. Subjects

A total of 388 male lead-exposed workers on the active list were examined for BPb, Hb, Hct, and RBC at the time of the specific health examination for the prevention of lead poisoning, conducted under the Industrial Safety and Health Law in Japan. Their lead-exposed periods ranged from 1 to 45 years. The subjects were employed in three smelters, in a glass factory, or in an electrical appliance manufacturing (soldering) unit in Japan, including managers and superintendents in the workplace. Of them, 104 had worked as shift workers (i.e., smelter workers in a three-shift system of 8 hours). The nature of the procedure used in the present study was fully explained to all workers, and the study was carried out with their informed consent.

2.2. Laboratory Analysis

Cubital venous blood was obtained from each worker and sodium heparin was used as anticoagulant. BPb was analyzed by graphite furnace atomic absorption spectrophotometry (Hitachi 6100, Tokyo, Japan), as described previously (Karita *et al.*, 1997). The detection limit was $0.05 \mu\text{mol/L}$ blood. The BPb is thought to be the most reliable index of an internal dose of lead, reflecting absorbed doses and body burden (U.S. EPA, 1986; IPCS, 1995; ATSDR, 1999; Araki *et al.*, 2000), although there is more than 99% in the erythrocyte for BPb levels of up to $4.8 \mu\text{mol/L}$ (IPCS, 1995) and the BPb may therefore be affected in a degree by Hct. Hb was measured by the cyanmethemoglobin method by using a hematology analyzer, and Hct and RBC were quantified using an automatic blood cell counter. Quality control was assessed by measuring the reference materials simultaneously and confirmed the mean values within the certified limits (Karita *et al.*, 1997).

2.3. Statistical Analysis

The significance of the relationships between the BPb and hematological indicators (Hb, Hct, and

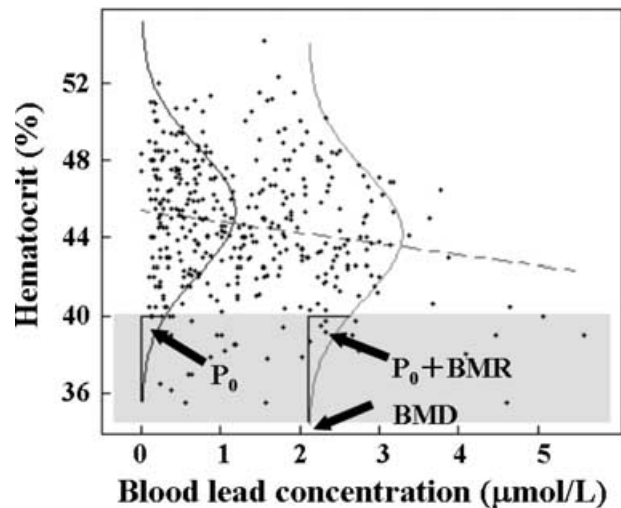


Fig. 1. Dose-effect relation of the blood lead concentration ($1 \mu\text{mol/L} = 20.7 \mu\text{g/dl}$) to hematocrit in lead-exposed workers for benchmark dose calculation. The P_0 and benchmark response (BMR) indicate an abnormal probability (5%) in unexposed workers and an excess risk (5%) above P_0 in exposed workers, respectively. The power parameter of $K = 1$ was used in this figure, after controlling for age and working status.

RBC) was tested by the Pearson's product moment correlation coefficient (r). Working status was scored as "day worker" = 0 and "shift worker" = 1 (mean 0.27, standard deviation (SD) 0.44). The multiple regression analysis was performed to examine the relations of BPb and confounders (age and working status) to Hb, Hct, and RBC.

As shown in Fig. 1, the BMD was defined as the BPb that resulted in an increased probability of abnormal Hct (or Hb or RBC) by a benchmark response (BMR), i.e., from P_0 to $P_0 + \text{BMR}$ at the BMD, when the P_0 and BMR represented an abnormal probability of the endpoint in unexposed subjects and an excess risk in exposed subjects, respectively (National Research Council, 2000; Crump, 2002). Although an observational study has not included an unexposed group completely free of exposure, data of the group could be extrapolated from those of low-exposed subjects (Budtz-Jørgensen *et al.*, 2001; Murata *et al.*, 2003). Using a statistical dose-effect model based on power functions for the dependence $[\mu(d)]$ of Hct on BPb $[g(d) = d^K]$; d representing the BPb level], age, and working status, the BMD and the cutoff value (C) of P_0 were calculated from the following equations (Budtz-Jørgensen *et al.*, 2001; Crump, 2002): $\mu(d) = \beta_0 + \beta \cdot g(d) + \beta_1 \cdot [\text{age}] + \beta_2 \cdot [\text{working status}]$; $P_0 = \Phi([C - \beta_0]/\sigma)$; and $\text{BMD} = g^{-1}\{[\Phi^{-1}(P_0) - \Phi^{-1}(P_0 + \text{BMR})]\sigma/\beta\}$. The Φ and

Table I. Means, Standard Deviations (*SD*), Ranges of Blood Lead Concentration (BPb), Hemoglobin, Hematocrit, and Red Blood Cell Count in 388 Japanese Lead-Exposed Workers

	Mean ± <i>SD</i>	Min – max
BPb (μmol/L)	1.3 ± 1.0	0.05–5.5
Hemoglobin (g/L)	150 ± 11	119–176
Hematocrit (%)	44.7 ± 3.3	35.5–54.2
Red blood cell count (10 ⁴ /μl)	487 ± 45	377–593
Confounders		
Age (years)	44 ± 11	18–67
Work status (% of shift workers)	26.8%	

σ indicated the normal cumulative distribution function and the *SD* of Hct in unexposed subjects, respectively. Since the normalized values ($[X_i - X_{\text{mean}}]/SD$) for age and working status were employed in the regression model (Table I), the cutoff value would be valid for subjects with covariates equal to average values in this study population. The benchmark dose level (BMDL) was calculated as the statistical 95% lower confidence limit of the BMD (National Research Council, 2000; Budtz-Jørgensen *et al.*, 2001). The power parameter *K* has been restricted to values equal to 1 or over, thus allowing the dose-effect curve to be nonlinear (Budtz-Jørgensen *et al.*, 2001). We used the *P*₀ of 5% and the BMR of 5% (and 10%) according to previous applications of this method (National Research Council, 2000; Budtz-Jørgensen *et al.*, 2001; Murata *et al.*, 2002, 2003, 2004; Dakeishi *et al.*, 2004). All analyses, with two-sided *p* values, were performed by using the Statistical Package for the Biosciences (SPBS V9.51) with the BMD program (Murata and Yano, 2002).

3. RESULTS

The summarized data in the 388 Japanese lead-exposed workers are shown in Table I. The BPb was significantly correlated with Hb (*r* = -0.240), Hct (*r* = -0.201), and RBC (*r* = -0.237); these linear relations were statistically significant even when controlling for age and working status (Table II). According to the WHO criteria (IPCS, 1995), anemia in human males was defined either by the Hb level of less than 130 g/L or the Hct level below 39%. The number of workers with anemia was 23. Using the analysis of covariance after adjusting for age, the average BPb level was significantly higher in the 23 workers with anemia (1.86 μmol/L) than in the remaining workers without anemia (1.27 μmol/L) (*p* = 0.014).

The BMDs and BMDLs of BPb for Hb, Hct, and RBC are shown in Table III. The *K*-power model

Table II. Relations of Blood Lead Concentrations (BPb), Age, and Work Status to Hematological Indicators in 388 Lead-Exposed Workers: Results of Multiple Regression Analysis

	Regression Coefficients β		
	BPb	Age	Work Status
Hemoglobin	-0.276**	-0.022**	-0.016
Hematocrit	-0.563**	-0.057**	1.242**
Red blood cell count	-11.35**	-1.046**	1.776

p* < 0.05, *p* < 0.001.

Note: All multiple correlation coefficients (*R*) were significant (*p* < 0.001).

showed the best fit at *K* = 1 or slightly above 1. The BMDLs of BPb were calculated to be 0.94 μmol/L (19.5 μg/dl) for Hb, 1.43 μmol/L (29.6 μg/dl) for Hct, and 0.94 μmol/L (19.4 μg/dl) for RBC (Fig. 1 and Table III). When a logarithmic or square root curve model (i.e., log[*d* + 1] or √*d*) was used for analysis, the BMD and BMDL became substantially lower but these models did not provide a better fit.

4. DISCUSSION

In the present study, the BPb level was significantly higher in the exposed workers with anemia defined by the WHO criteria (IPCS, 1995) than in those without anemia, and lead exposure (i.e., BPb) in all the workers was negatively associated with Hb, Hct, and RBC, after controlling for age and working status. These findings agree with many previous research data (Tola *et al.*, 1973; Lilis *et al.*, 1978; Grandjean, 1979; Baker *et al.*, 1979; Hammond *et al.*, 1980; Khan *et al.*, 1995; Potula & Hu, 1996). A significantly lower RBC count also has been observed in 34 lead-exposed

Table III. Benchmark Doses (BMD, μmol/L) and the Lower 95% Confidence Limits of BMD (BMDL, μmol/L) of Blood Lead Concentrations, Set at the *P*₀ of 5% When Controlling for Age and Working Status, in 388 Lead-Exposed Workers

	<i>K</i> Value	(BMR = 0.05)		(BMR = 0.1)	
		BMD	BMDL	BMD	BMDL
Hemoglobin	1.012	1.38	0.94	2.30	1.57
Hematocrit	1.012	2.12	1.43	3.52	2.38
Red blood cell count	1	1.39	0.94	2.32	1.57

Note: *P*₀ and BMR indicate an abnormal probability in unexposed workers and an excess risk in exposed workers, respectively (see Fig. 1). Cutoff values of hemoglobin (137 g/L), hematocrit (40.0%), and red blood cell count (432 × 10⁴ /μl) were calculated from the *K*-power model of the BMD approach.

workers (mean \pm SD of BPb, $1.97 \pm 0.47 \mu\text{mol/L}$) (Solliway *et al.*, 1996). Recently, Kim *et al.* (2003) reported that 118 lead workers ($1.5 \pm 0.72 \mu\text{mol/L}$) had significantly lower Hb, Hct, serum iron levels, percentage of transferrin saturation, and dietary iron intake than did 42 nonlead workers ($0.24 \pm 0.05 \mu\text{mol/L}$). Thus, Hb, Hct, and RBC may be recognized as non-specific but useful markers of lead toxicity.

By contrast, there are some reports implying that lead exposure did not negatively correlate with Hb levels (Tola, 1975; Valentine *et al.*, 1982; Grandjean *et al.*, 1989; Romeo *et al.*, 1996; Makino *et al.*, 1997; Fromm *et al.*, 1999). Makino *et al.* (1997) found a significant positive relationship between Hb and BPb among 1,573 workers with BPbs of 0.05–1.88 $\mu\text{mol/L}$. Also, Hb tended to increase with the elevated BPb in Israeli industrial workers with BPbs of less than 2.9 $\mu\text{mol/L}$ (Fromm *et al.*, 1999). Three explanations for this discrepancy are possible. (1) The Hb level has been reported to correlate with bone lead levels even in the presence of low BPb levels (Hu *et al.*, 1994). (2) The prevalence of iron-deficiency cases was associated with high blood lead levels (Kim *et al.*, 2003). (3) The Hb level may have been influenced by confounders such as working status or smoking (Pollini *et al.*, 1989; Nordenberg *et al.*, 1990), other than lead and age (Salive *et al.*, 1992; Yamada *et al.*, 2003). We could not adjust for iron-metabolic parameters because such data as ferritin and transferrin were not available in our study conducted under the Industrial Safety and Health Law in Japan; which should be justified in order to avoid overmatching regarding the relation between lead exposure and hematological effects (Brugnara *et al.*, 1999; Rothman and Greenland, 1998). Concerning the smoking status, we were able to obtain data only from one-half of the subjects ($n = 215$). Given the data adjusted by working and smoking status in the restricted subjects, the results showed consistency with the overall present BMDs (data not shown). Though the increase of Hb among smokers has been suggested to be related to increased levels of CO-Hb, an inactive form of Hb resulting from exposure to carbon monoxide (Nordenberg *et al.*, 1990), there is insufficient evidence suggesting that RBC can be affected by smoking (Okuno, 1973; Pollini *et al.*, 1989). In our study, the RBC, as well as Hb and Hct, had a close relation to BPb, implying that our findings represented a robust internal consistency in spite of the limitations.

The BMDs of BPb for Hb and RBC, calculated at the P_0 of 5% and BMR of 5% in this study, were 1.38 and 1.39 $\mu\text{mol/L}$, respectively. These values indi-

cate the BPb level at which 10% ($P_0 + \text{BMR}$) of the exposed workers showed the abnormal Hb or RBC on the dose-effect curve, and are coincidentally in close agreement with the biological exposure index (BEI) of BPb (30 $\mu\text{g/dl}$; i.e., 1.45 $\mu\text{mol/L}$) recommended by the American Conference of Governmental Industrial Hygienists (ACGIH, 2003). This BEI has been designed to minimize the potential mainly for the neurophysiological and psychological effects of lead. Also, Rosenman *et al.* (2003) have reported that nervous system symptoms possibly began to be increased in individuals with BPb levels between 1.21 and 1.45 $\mu\text{mol/L}$, using standardized telephone interviews. On the other hand, the BMDLs, conceptually corresponding to the BMD₁₀ (lower confidence limit of the BMD yielding a dichotomous response with 10% extra risk) in animal experiments, of BPb in this study were estimated to be 0.94 $\mu\text{mol/L}$ for Hb, 0.94 $\mu\text{mol/L}$ for RBC, and 1.43 $\mu\text{mol/L}$ for Hct, and these were considerably higher than those for δ -aminolevulinic acid levels in plasma, blood, and urine (0.14, 0.17, and 0.33 $\mu\text{mol/L}$ in that order) (Murata *et al.*, 2003). If the sample number is smaller, the BMDL would become smaller (Crump, 2002) and the *true* critical dose for each of Hb, RBC, and Hct would be placed somewhere between the BMDL and BMD calculated from our study. In either case, our findings suggest that reduction in hematopoietic indicators can be initiated at BPbs below the level generally accepted as effectless (U.S. EPA, 1986; IPCS, 1995; ATSDR, 1999), despite some uncertainties in the calculation and confounding factors. Additional study with the adjustment for smoking status and other hematological status is needed to reconfirm our results.

The BMD and BMDL of BPb for Hb or RBC were lower than those for Hct in the current study. The order of these BMDs and BMDLs is biologically reasonable, because lead affects the heme synthetic pathway directly (IPCS, 1995; Murata *et al.*, 2003) and causes a reduction in Hb, RBC, or Hct as a consequence. But, Hct can be readily affected by several factors such as heat in the work environment and renal excretion rate other than lead; actually, shift workers (i.e., smelter workers) may have been exposed to heat, because working status was significantly associated with only Hct in the regression model (Table II). The cutoff values of Hb and Hct, calculated from the normal cumulative distribution function of the BMD method (Budtz-Jørgensen *et al.*, 2001), are almost concordant with the standard values of anemia defined by the WHO criteria (IPCS, 1995), whereas

they may depend on the study population to some extent. The slightly high cutoff value of Hb may have been due to the increase of CO-Hb in some smokers, which we could not prove in the present study. In conclusion, it is suggested that BMD calculations provide a promising approach for estimating the threshold of occupational hazardous substances such as lead at low doses of exposure. For risk management of lead, further study is required to reevaluate such critical doses of lead affecting other target organs such as brain, nerves, and kidneys, possibly by using the same method.

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