

Reproduction

Any need to revisit the male reproductive toxicity of lead?

J P Bonde, P Apostoli

Commentary on the paper by Shiau *et al*
(*Occup Environ Med*, November 2004)*

The toxicity of lead has been known for millennia and has served as a template for toxicology studies.¹ According to some 45 000 measurements in European industrial settings spanning smelters, battery manufacturing, and foundries, the average concentration of lead in blood steadily declined from 68 µg/dl in 1970 to 35 µg/dl in 1995.² In parallel with this development the introduction of non-lead gasoline in the late 1970s was followed by a dramatic decline in body burden of lead in the general population.³ However, unlike many other metals such as zinc, chromium, manganese, copper, and iron, lead has no known essential effects for living organisms, and current exposure levels are still high compared to pre-industrial populations. Therefore it is important to continue to control lead exposure and to unravel effects of the low and very low doses of the metal.

Lead has long been known to be toxic to male fertility. Several studies in rats and other rodents indicate that blood lead concentrations above 30–40 µg/dl are associated with impairment of spermatogenesis and reduced concentrations of androgens—although some rat species and strains seem quite resistant.⁴ The latter could be due to differences in tissue distribution. Contrary to findings in small rodents, a comprehensive study in rabbits estimated a threshold for reduced sperm count of 24 µg/dl and even lower for a range of other semen characteristics.⁵ Male reproductive toxicity studies in humans have addressed effects on sex hormone levels,^{6,7} birth rates,^{8–10} time taken to conceive in couples not using contraception,^{11–13} and semen characteristics.^{14–19} Although findings across studies and endpoints are not entirely consistent, the main body of evidence points to current blood lead concentrations of about 40–50 µg/dl as a most likely no adverse effect threshold. This applies to semen characteristics such as sperm count, sperm

motility, and abnormal sperm forms, as well as to fertility rate and time taken to conceive, whereas primary effects on the hormonal regulation of the male reproductive system at these exposure levels are questionable.

This view on male reproductive toxicity of lead is challenged by the findings on decreased fecundity among male lead workers published by Shiau *et al* in the November 2004 issue of this journal.²⁰ Using the time to pregnancy methodology, they observed an astonishing clear exposure response relation between current blood lead level and time taken to conceive among male battery workers in Taiwan. The fecundability ratio, which estimates the probability of conception in a menstrual cycle in exposed compared to non-exposed, declined steadily from 0.9 in men with blood lead levels below 20 µg/dl to 0.4 among men with a blood level above 40 µg/dl. These findings are divergent from the results in a few earlier time to pregnancy studies in lead exposed workers.^{13,21,22} Close scrutiny does not reveal artifacts of design or research methodology, although a rather small sample size, few men in each exposure category, and time varying fecundability ratios adds to the limitations of this study. We must acknowledge several inherent limitations of retrospective time to pregnancy studies based on samples of women with recognised pregnancies. For instance, the time or the number of menstrual cycles taken to conceive is only defined for planned pregnancies. Accidental (unplanned) pregnancies are related to fecundity and could be associated with behavioural and lifestyle factors, and indirectly with occupational exposure. Various contraceptive methods are not equally effective and may not be used rigorously over time, which may blur the distinction between protected and unprotected cycles. Similarly, fecundability is strongly dependent on frequency and timing of sexual intercourse, which cannot reliably be determined in retrospective studies. However, many of these uncertainties most likely

will result in failure to detect true effects. The fact that a large European study failed to show effects of lead on time to pregnancy in any of three independent study populations¹² is not reassuring if the consistency of findings across countries reflects repetition of errors inherent in the study design. The divergent findings in Europe and Taiwan could of course also be due to differences in susceptibility to the toxic effects of lead, such as the well known higher toxicity of several organic solvents in Asian workers.

But are the findings of Shiau *et al* not in conflict with the semen studies? Several cross sectional studies of worker populations do not reveal effects of blood lead at levels below 40–50 µg/dl on sperm concentration or sperm count. And semen characteristics are considered more sensitive indicators of male fecundity than functional measures such as time to pregnancy.²³ Obviously the answer to this question depends on the site of action and the mechanism of the reproductive toxicity of lead. Reproductive effects at low exposure levels could bypass detection by crude semen characteristics. During recent years it has been shown that lead may interfere with the reorganisation and tight packaging of sperm DNA during spermatogenesis—the chromatin condensation—by competition with zinc on protamin binding sites.^{24,25} This results in reduced stability of the chromatin, and abnormal chromatin structure is strongly related to reduced fertility in humans.²⁶ And there is indeed limited evidence that chromatin structure abnormalities are related to lead exposures in the lower range of blood lead values in men with high concentrations of lead within spermatozoa.¹⁶ Other mechanisms might be of significance as well. Thus it was recently found that lead at environmental levels strongly interferes with the sperm acrosome reaction, which is essential for fertilisation and negatively affects outcomes of artificial insemination.²⁷

If the findings of Shiau and co-workers are corroborated in independent studies, it may have profound implications for worker safety programmes, even at present day lower exposure levels. In addition to studies using functional measures of fertility, it is warranted to undertake semen studies with assessment of lead close to the target organ—firstly in spermatozoa—and to include measurements of chromatin structure and acrosome reactions as endpoints. In our opinion the study from Taiwan does not present data sufficient to modify the main conclusions from the European studies on effects of lead on male fertility, but

*Shiau C-Y, Wang J-D, Chen P-C. Decreased fecundity among male lead workers. *Occup Environ Med* 2004;**61**:915–23.

there is definitely a need to keep open this line of research.

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OEM EDITORIAL BOARD MEETING

10 November 2004

The 2004 meeting of the OEM Editorial Board was held on Wednesday, 10 November 2004 at BMA House, London. The photo shows some of the Board Members and Editorial Staff.

Other Editorial Board Members are: Anders Ahlbom, Harvey Checkoway, Francesco Forastiere, Timo Kauppinen, Robert Maynard, Laura Punnett, Stephen Rappaport, and David Snashall.

Front row, left to right: David Koh, Andy Fosberry, Manolis Kogevinas, Peter Westerholm, Dana Loomis, Keith Palmer, Harry Roels, Kathryn Walsh.
Back row, left to right: Craig Jackson, Malcolm Sim, Roseanne McNamee, Dick Heederik, Mark Neuwenhuijsen, Harry Shannon, Hans Kromhout, Rachel Harvey.





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