Reproduction

Any need to revisit the male reproductive toxicity of lead?

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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. 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. In parallel with this development the introduction of non-leaded gasoline in the late 1970s was followed by a dramatic decline in body burden of lead in the general population. 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. 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. Male reproductive toxicity studies in humans have addressed effects on sex hormone levels, birth rates, time taken to conceive in couples not using contraception, and 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. This results in reduced stability of the chromatin, and abnormal chromatin structure is strongly related to reduced fertility in humans. 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. 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.

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 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 populations 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, as well as 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 fertility than functional measures such as time to pregnancy. 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. This results in reduced stability of the chromatin, and abnormal chromatin structure is strongly related to reduced fertility in humans. 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. 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.

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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.

Front row, left to right: David Kah, Andy Fosberry, Manolis Kogevinas, Peter Westerholm, Dana Loomis, Keith Palmer, Harry Roels, Kathryn Walsh.

Back row, left to right: Craig Jackson, Malcolm Sim, Roseanne McIlvane, Dick Heederik, Mark Neuvonen, Harry Shannon, Hans Kromhout, Rachel Harvey.