Manganese – reassuring evidence about male reproductive health effects

This fact sheet summarises important new experimental information about the possible risk to male reproductive performance from inhalation exposures to Manganese.

Recently, in proposing occupation exposure limits for manganese in workplace air, the European Commission’s Scientific Committee on Occupational Exposure Limits (SCOEL) commented that there was little evidence for reproductive or developmental toxicity of inhaled manganese\(^1\). However, other available evidence, particularly on neurological effects, was considered in setting the occupational exposure limits (OEL) for both inhalable and respirable manganese dusts (see IMnI Fact Sheet 7).

To help address this data gap, a study was commissioned by the IMnI under its Worker’s Safety Programme to investigate the effect of the inhalation of respirable manganese dust on the reproductive performance and sexual maturation of male rats.

At all target dose levels investigated, (the highest target concentration was 20 mg/m\(^3\)) the inhalation of respirable manganese dichloride dust for 10 weeks during the post pubertal phase did not affect reproductive performance by all the parameters measured (relevant organ weight and histology, sperm quality and quantity). Nor did it affect the sexual development of the subsequent generation of male pups fathered by the exposed males; the pups were exposed to manganese dust, \textit{in utero}, and also from weaning up to their sexual maturation.

This is the first experimental toxicity study that specifically investigates male reproductive performance by the inhalation route with manganese. A No Observed Adverse Effect Level (NOAEL) of 20mg/m\(^2\) was identified. This exposure is more than a hundred times higher than the OEL of 0.05 mg/m\(^3\) set by SCOEL on the basis of neurological effects of respirable manganese dust and provides reassurance that the current OEL is also highly protective against possible adverse reproductive effects in male workers.

1. The Study
An experimental study designed specifically to investigate male reproductive function has recently been reported\(^2\). Groups of male Sprague-Dawley rats were exposed to very fine dusts of manganese dichloride in the respirable range (particle size averaging 2.5 microns) at target concentrations of 5, 10 or 20 mg/m\(^3\) for 6 hours per day, 7 days per week.

Groups of 24 to 28 male rats (called the F0 generation) were exposed from the age of 7 weeks (i.e. pre-puberty) for 10 weeks, during which time their mating performance with manganese-exposed female rats was evaluated. The male pups (the F1 generation) delivered from the subsequently pregnant females, were then additionally exposed (i.e. in addition to exposure \textit{in utero}, shortly after weaning, for a further 11 weeks (6 hours per day, 7 days per week) until sexual maturation. Investigations of both generations of male rats included assessment of their fertility, development of sexual organs, and various investigations of semen quality and motility. The protocol and investigations were in line with OECD protocol 416\(^3\).

There were no indications of any effects on male reproductive performance in either the parent (F0 generation) or in their male offspring (F1 generation) as measured by behaviour, mating performance and sexual development. There were no changes noted in the organ weights of the male reproductive system and no microscopic findings observed in the seminal vesicles or testes. Assessment of the number of sperm, sperm mobility, straight-line velocity and sperm morphology in the F0 or F1 generations did not reveal any effect of exposure to manganese dichloride at these exposure levels.

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\(^1\)SCOEL(2011) Recommendation from the Scientific Committee on Occupational Exposure Limits for manganese and inorganic manganese compounds. SCOEL/SUM/127. Published June 2011

\(^2\)International symposium on biological monitoring (ISBM) 9-11th Sept 2013; Manchester, UK

\(^3\)OECD GUIDELINE FOR TESTING OF CHEMICALS Two-Generation Reproduction Toxicity Study Guideline 416 dated January 2001

2. Conclusion and interpretation

This is the first study to specifically investigate the effects of inhaled manganese dust on male reproductive performance in controlled animal studies. A No Observed Adverse Effect Level (NOAEL) for the reproductive performance in male rats of 20mg/m$^3$ was identified.

The study provides evidence that the SCOEL occupational exposure limit (OEL) for respirable manganese dust of 0.05mg Mn/m$^3$ (8-hour time-weighted average) offers a high degree of protection for male workers from any potential adverse reproductive effects. The SCOEL OEL is set at an exposure level which is around 100 times lower than a level at which no adverse reproductive effects were observed in two generations of male rats who were exposed from pre-puberty to sexual maturation, in utero and during their early life stages leading up to puberty.

The study complements an earlier reported smaller scale study\(^4\) which showed that respirable manganese chloride dusts inhaled by male and female Sprague-Dawley rats for 9 weeks, at target dose level of up to 10mg/m$^3$, prior to and during mating and weaning did not have any adverse effect on mating performance, fertility, gestation time, litter size, or survival.

On the basis of this evidence, occupational exposures, even if they were well above the SCOEL OEL, would be protective of reproductive effects in exposed workers.

3. Contribution to the evidence database

A recent toxicity profile document for manganese by the US Agency for Toxic Substances and Disease Registry (ATSDR)\(^5\) has reported that, in male workers who had clinically identifiable signs of manganism, impotence and loss of libido were common symptoms. These neurological effects could affect male reproductive function. Additionally, male workers exposed for up to 21 years to high levels of manganese dust (approximately 1mg/m$^3$) but who were without clinical signs of manganism did show signs of impaired fertility. The ATSDR report suggests that impaired sexual function in men may be one of the earliest clinical manifestations of manganese toxicity. Health Canada’s website\(^6\) states that a number of experimental studies have shown that exposure to manganese can cause deleterious effects on the male reproductive system. It also quotes an epidemiological fertility study conducted in 1985 of Belgian workers exposed to manganese which concluded that the number of children born to exposed male workers (aged 16-35) was half that in a control group.

However, the dose-response information for these effects from the older studies is poor and it was not possible at the time to define a threshold for the effects.

This study therefore provides the first reliable evidence of a threshold for reproductive outcomes in a controlled animal study conducted to an internationally agreed protocol and by a route relevant to workplace exposures. This new piece of information offers reassurance that where workplace exposures to manganese dust are well controlled, adverse effects on male reproductive performance would not be expected to arise.

Further information:


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\(^5\) TOXICOLOGICAL PROFILE FOR MANGANESE U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES