

An Overview of CIIT's Manganese Research Program

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ABSTRACT

There is adequate published research to document that high-dose manganese exposure is neurotoxic; however, there is a need to further characterize the risk that may be posed by chronic, low-level inhalation exposure to manganese associated with the use of methylcyclopentadienyl manganese tricarbonyl (MMT). A critical issue in assessing the risks of chronic low-level manganese exposure is the ability to develop a predictive physiologically-based pharmacokinetic (PBPK) model for inhaled manganese to relate lung, brain, and other tissue manganese concentrations with exposure concentrations of MMT combustion products during inhalation. Ideally, the PBPK model will also account for differences in the chemical species of manganese, route of exposure, and potentially susceptible human subpopulations. The overall goal of this research program funded Ethyl Corporation is to develop experimental data needed for PBPK model development and validation and to support future manganese risk assessments. Completed projects include studies designed to understand the pharmacokinetics of manganese following 14-day inhalation exposure of rats to low airborne concentrations of manganese phosphate, sulfate, and tetroxide. Other research efforts have examined the role the olfactory nerve plays in the direct delivery of inhaled manganese to the rat brain. Previous research has also evaluated whether individuals with relative manganese deficiency or excess may be at increased risk for manganese toxicity following inhalation exposure. Research examining the role of oxidative stress in manganese developmental neurotoxicity has been recently published. Ongoing projects are examining the pharmacokinetics of inhaled manganese phosphate and manganese sulfate in rats following subchronic inhalation. Future research will include subchronic inhalation studies in monkeys and experiments designed to examine manganese pharmacokinetics in pregnant and lactating rats following inhalation exposure.