Review of occupational exposure to manganese and the potential health effects of such exposure

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The objective of the project is to summarise and assess the evidence on potential negative health effects of manganese for workers. The goal is to give a descriptive summary of the available evidence about the exposure, its consequences and possible competing factors, as well as to quantify the evidence in a dose-response relationship and to judge the quality of the evidence.

Background

Manganese is an essential mineral that occurs naturally in the earth. As a micronutrient Manganese (Mn) helps the body form connective tissue, bones, clotting factors, and helps maintain normal brain and nerve activity. It serves as co-factor for important enzyme activities within human cells such as manganese superoxide dismutase (MnSOD) which is an important antioxidant. While Mn deficiency can lead to illnesses related to bone, joint and collagen functions, its excess can also be poisonous leading to disorders of the nervous system. The adequate dietary intake for adult men and women is 2.3 and 1.8 mg/day, respectively. A Tolerable Upper Intake Level (UL) of 11 mg/day was set for adults based on a no-observed-adverse-effect level for Western diets. (1)
Exposure to manganese can occur from various sources. These include diet, where it occurs naturally in water, grains and green leafy vegetables, and air, where it reaches from both natural and manmade sources. The manmade sources associated to Mn are industries of ferroalloy production, iron and steel foundries, welding, battery production and power plants. Mn is also found in some unleaded gasoline as methylcyclopentadienyl manganese tricarbonyl (MMT) and high traffic levels have been found associated with higher Mn levels in the air.(2) Furthermore, plant fertilizers often contain manganese along with other metals, and the making of pigments, dyes, inks and incendiary devices also involves manganese. Long term parenteral nutrition can also lead to manganese toxicity.(3) Manganese could thus enter the body via the enteral, parenteral or inhalation route, although occupational relevance is for ingestion and inhalation routes alone. NIOSH lists the potentially affected organs to be respiratory system, central nervous system, liver and kidneys.(4)

There is a safety margin between daily retirement levels and those causing damage. When ingested or inhaled in amounts much greater than the daily requirements manganese can also damage cells. The various mechanisms of action based on current evidence suggest that manganese in large amounts increases oxidative stress within cells. This can cause mitochondrial dysfunction, glutamate mediated excitotoxity and aggregation of proteins in the cell.(5-7) The neurodegenerative effects called manganism - a condition with Parkinsonism. The central nervous system effects may be explained by the accumulation of Manganese in the brain especially in the basal ganglia region.(8) Besides neuronal damage, the extensive exposure to large amounts of manganese has been shown to damage liver and kidneys. This is because both these organs are involved in its metabolism and excretion.
After stopping exposure some cognitive function may improve, although some motor and sensory functions and mood disturbances may remain or progress.(9-12) Thus, the prevention and cure lies in the minimization or cease of exposure. The NIOSH recommendations for occupational exposure limit is 1 mg/m3 (Time weighted average: 8 hrs) and 3 mg/m3 (short term exposure limit: -> 15min). Agency for Toxic Substances and Disease Registry (ATSDR) recommends an Inhalation Minimal Risk Level (MRL) of 0.04 μg/m3 (chronic exposure). The US department of labor indicated the lowest observed adverse effect limit (LOAEL) to be 0.05mg/m^3. The same threshold for neurological deficits related to Mn exposure was found by a recent meta-analysis based on individual participant data.(13) The exposure assessment however is difficult with Mn, because the particles size and shape varies very much. Thus, the adverse effects may relate to lower

levels in welding (small particles) than higher ones in mining with dusts (bigger particles). Also, in the literature there are many descriptions of exposure: total Mn, soluble Mn, inhalable Mn and respirable Mn. And these issues have not always been taken into account in previous meta-analyses.

Studies showing severe health effects from very high exposure to manganese have been conducted as early as the 1970s.(14-16) The earliest adverse effects in the nervous system, before manganism with parkinsonistic features appears, seem to be in the neuropsychological functions e.g. reduced psychomotor performance. This was shown in a meta-analysis based on individual patient data from eight studies comparing occupationally exposed workers to unexposed workers. Motor deficits were related to exposures at mean concentrations of inhalable Mn ranging from 0.05 mg/m3 to 0.30 mg/m3. However, a dose response relationship between the level of biomarkers in the blood- a poor proxy for actual exposure- and health effects could not be established.(13)

European countries enforce low occupational and environmental exposure to manganese by policies stating that the employer should ensure the work (exposure) does not cause illness to the employees. However, exposure-work still exists and thus harmful exposure may still occur in many occupations. Inhalation of Mn fumes, common in occupational settings, may be more difficult to control compared to ingestion and is therefore more problematic. Manganese exposure therefore still remains a risk factor for occupational adverse health effects and disease. As evident from the description above, some industries and occupations are more at risk than others where the use of manganese cannot be completely replaced or avoided.

Since exposure-related effects are dose-dependent, low-levels may not be harmful. Therefore the knowledge of exposure levels without health effects is essential both to the work places and to the workers. In order to protect workers adequately, it is necessary to collect and assess the available evidence. Despite extensive research there are still unanswered questions such as at what exposure level and after what duration which types of health effects may occur. Furthermore, dose response relationships are still unclear. There are many individual factors that determine the outcome and prognosis of the toxic effects including but not limited to genetic profiles. Last but not least, many times the exposure is not to Mn alone and the effects of other exposures in the same industries or non-occupational factors such as liver disease or iron deficiency are difficult to rule out.

This review will build on the previous work in this area. We will follow an apriori protocol so that data driven analysis is avoided and we can answer the questions of interest reliably.

In order to prevent the exposure to manganese and protect workers from resultant occupational disease and disability it is important to find out risk levels and competing factors. A systematic appraisal of the literature should hence result in clear findings about:

- Exposure: Nature of exposure, workers most or least exposed to Mn- variance in exposure intensity, thresholds of exposure allowed- occupational exposure limits, duration, intensity and quality of exposure in various industries or jobs
- Effect of exposure: Nature of effect (quality) and magnitude of the effect (quantity) attributable to this exposure, taking into account any confounding factors, type, size and direction of effect, any lag period from exposure to onset of disease, and dose response analysis.
- Prognosis: if exposure is stopped, development and prognosis of the exposure related condition. Other factors besides exposure on the adverse health effect.

Methods

Inclusion criteria:

Study type

Experimental studies of manganese exposure at the workplace are unlikely due to ethical issues.

We will thus primarily include cohort studies (prospective and retrospective) and systematic reviews of manganese exposed workers to answer these questions about exposure-related harmful effects, dose-response relationships, prognosis, preventing factors or other risk factors, and risk estimates. We will additionally

include case-control studies to summarise other factors that limit, delay or prevent the development of the disease (confounders).

Participants

Workers of both sexes and any age

Exposure

Manganese exposure by inhalation or ingestion at work at any dose

Comparison

Occupationally exposed to manganese compared to unexposed workers

Workers exposed to high levels of manganese compared to those exposed to low levels

Outcome

We will include outcome measures only if the study reports or indicates diagnoses of a condition made by a physician using valid methods. Biomarkers and proxy measures will not be considered as these cannot represent the actual outcome and may limit interpretation of results.(13)

Outcome must be measured as the incidence or severity of an exposure related condition at final follow up.

Searching and including studies:

We will search multiple databases and non-electronic sources (reference searching, expert contact) for finding studies. We have developed a sensitive search in PubMed and then translate it to the other databases (ToxNet, Inchem, EMBASE, and OSHUpdate) to locate all relevant systematic reviews on the topic to date and all empirical studies since the publication of systematic reviews. Appendix A.

Two reviewers will independently check fulfilment of the inclusion criteria first via titles and abstracts that come up from the search and then via full text. Disagreements will be resolved by discussion or by a third reviewer.

Data extraction and management:

Two reviewers will independently extract data from the articles that are included in the review. The following data will be extracted from the included studies and used for the risk of bias assessment:

- study design,
- participants (age, gender, type of work, number of participants),
- type of exposure (quality, quantity, and duration of the exposure) and exposure measurement,
- type of health outcome (type of disease, severity, prognosis) and outcome measurement (diagnostic tests used),
- adjustment for most important confounders (competitive factors like pre-existing diseases or age of the study participants),
- country of origin, year of study, funding and conflict of interests

We will assess the risk of bias in the included primary studies by adapting a check list for assessing the quality of observational studies as proposed by Shamliyan.(17, 18) For included systematic reviews will use the AMSTAR tool. (19-21) We will distinguish between studies with a high risk of bias and studies with a low risk of bias. We will use the better quality studies (low risk of bias) to inform our conclusions.

Analysis:

First an overview of the included systematic reviews will be conducted.

The results from any additional primary studies will be added to the findings of the overview. If this is not possible an additional random effects meta-analysis will be conducted on the empirical studies if suitable data is available.

Alternatively the findings will be tabulated with narrative analysis. In meta-analysis we will present risk ratios as estimates of the effect of the exposure. We will analyse each disease outcome separately, or if suitable, in subgroups.

Adjustment for confounding

If studies have not adjusted for competitive risk factors and data are available on the influence of these risk factors we will adjust the effect estimates for these risk factors following the methods described by Greenland. (22, 23)

Dealing with missing data

We will contact study authors for additional information, if necessary data for the analysis are missing from the articles. If they cannot be reached we will try to calculate the missing data from the available statistics. This is possible for example for standard errors where only p-values are available.
Previous clinical research indicates no clear pattern between increasing exposure and the development of symptoms due to manganese. Therefore we will assume and test a linear relationship between the natural logarithm of RR and increasing exposure. Based on published evidence, we will use the exposure to 0.05 mg/m3 as threshold and 0.01 as the incremental step of increased exposure for inhalation, and 11 mg/day and 1mg/ day as the incremental step of increase in exposure for ingestion.

Data synthesis

We will combine the RRs per unit increase in exposure for each important disease outcome. We will use the most adjusted natural logarithms of the relative risk as input for a random effects meta-analysis.

At first, studies will be assessed for similarity of participants, exposure (route, duration and intensity) and outcome measurement and grouped for analysis accordingly. Exposures will be sub grouped by job/occupation/industry and different disease outcomes will be analysed separately.
Next we will assess statistical heterogeneity by means of the I^2 statistic. We will take an I^2 value of up to 25% as low, values between 25% and 75% as moderate, and values over 75% as high degrees of heterogeneity respectively.

Assessment of reporting biases

We will avoid language and publication bias by including studies in any language and of any publication status. Later we will assess publication bias by using a funnel plot and applying Egger's test to the included studies.

Subgroup analysis and investigation of heterogeneity

We will evaluate if the outcomes vary according to:

- the types of occupation, where we will analyze workers by industry.
- the year of the study, where we will separate studies that are carried out before and after the year 2000.
- the country of the study, where we will especially differentiate between study participants from Western Europe and the US versus study participants from Asia.

If more than 10 studies are available we will perform a meta-regression analysis to evaluate which study factors are related to the effect size.

Sensitivity analysis

We will evaluate if our results are sensitive to the inclusion of low quality studies with a high risk of bias, by excluding high risk studies from the meta-analysis. We will also evaluate how sensitive our results are to assumptions made about the level of exposure to manganese. We will use fixed-effect meta-analysis to check how sensitive the results are to the model assumptions.

We have identified the most relevant competitive (confounding) factors already based on existing evidence. These are: pre-existing diseases that can affect Mn metabolism such as liver disease, or non-occupational exposures to manganese.

We will try to analyse the confounding effect of these factors in our analysis or present sensitivity analyses to remove their effect from our findings.

Grading and Strength of causality of the evidence

We will use the approach of the Danish Occupational Medicine Association to grade the strength of causality. In addition, we will use the GRADE approach to assess the overall quality of evidence.

Appendix A

Search	Add to builder	Query	Items found	Time
#8	Add	Search **(((((((("Manganese"[Mesh] OR "Manganese Compounds"[Mesh] OR manganese[tw]))) OR (("Manganese Poisoning"[Mesh] OR manganism* OR "Manganese/adverse effects"[Mesh] OR "Manganese/toxicity"[Mesh] OR "Manganese Compounds/adverse effects"[Mesh] OR "Manganese Compounds/poisoning"[Mesh] OR "Manganese Compounds/toxicity"[Mesh]))))) AND (((work[tw] OR works*[tw] OR work'*[tw] OR worka*[tw] OR worke*[tw] OR workg*[tw] OR worki*[tw] OR workl*[tw] OR workp*[tw] OR occupation*[tw]) OR welder OR welders OR welding OR "steel industry" OR mining OR miners)))) NOT ((Animals[Mesh] NOT Humans[Mesh]))**	2272	03:16:10
#7	Add	Search **(Animals[Mesh] NOT Humans[Mesh])**	3875032	03:15:47
#6	Add	Search **((((((("Manganese"[Mesh] OR "Manganese Compounds"[Mesh] OR manganese[tw]))) OR (("Manganese Poisoning"[Mesh] OR manganism* OR "Manganese/adverse effects"[Mesh] OR "Manganese/toxicity"[Mesh] OR "Manganese Compounds/adverse effects"[Mesh] OR "Manganese Compounds/poisoning"[Mesh] OR "Manganese Compounds/toxicity"[Mesh]))))) AND (((work[tw] OR works*[tw] OR work'*[tw] OR worka*[tw] OR worke*[tw] OR workg*[tw] OR worki*[tw] OR workl*[tw] OR workp*[tw] OR occupation*[tw]) OR welder OR welders OR welding OR "steel industry" OR mining OR miners))**	2671	03:15:30
#5	Add	Search **((work[tw] OR works*[tw] OR work'*[tw] OR worka*[tw] OR worke*[tw] OR workg*[tw] OR worki*[tw] OR workl*[tw] OR workp*[tw] OR occupation*[tw]) OR welder OR welders OR welding OR "steel industry" OR mining OR miners)**	1118429	03:15:16
#4	Add	Search **((((((("Manganese"[Mesh] OR "Manganese Compounds"[Mesh] OR manganese[tw]))) OR (("Manganese Poisoning"[Mesh] OR manganism* OR "Manganese/adverse effects"[Mesh] OR "Manganese/toxicity"[Mesh] OR "Manganese Compounds/adverse effects"[Mesh] OR "Manganese Compounds/poisoning"[Mesh] OR "Manganese Compounds/toxicity"[Mesh]))))) NOT (("Manganese"[Mesh] OR "Manganese Compounds"[Mesh] OR manganese[tw]))**	3	03:14:20
#3	Add	Search **((((("Manganese"[Mesh] OR "Manganese Compounds"[Mesh] OR manganese[tw]))) OR (("Manganese Poisoning"[Mesh] OR manganism* OR "Manganese/adverse effects"[Mesh] OR "Manganese/toxicity"[Mesh] OR "Manganese Compounds/adverse effects"[Mesh] OR "Manganese Compounds/poisoning"[Mesh] OR "Manganese Compounds/toxicity"[Mesh]))**	37606	03:13:52
#2	Add	Search **("Manganese Poisoning"[Mesh] OR manganism* OR "Manganese/adverse effects"[Mesh] OR "Manganese/toxicity"[Mesh] OR "Manganese Compounds/adverse effects"[Mesh] OR "Manganese Compounds/poisoning"[Mesh] OR "Manganese Compounds/toxicity"[Mesh])**	1784	03:13:43
#1	Add	Search **(("Manganese"[Mesh] OR "Manganese Compounds"[Mesh] OR manganese[tw])**	37603	03:13:13

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