Inhalational exposure to Manganese fumes and the associated hearing loss

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Introduction

- Workers in many industries such as mining, welding, smelting, and ceramic industry are chronically exposed to Manganese (Mn) fumes, with a risk of Mn toxicity by inhalation leading to hearing loss.
- The minimal risk level (MRL) for Mn has been estimated as 0.3 µg/m3 in respirable dust based on health effects resulting from chronic inhalation exposure to Mn.
- Based on LOAEL, EPA estimated the chronic inhalation reference concentration (RfC) for Mn as 5 x 10^{-5} mg/m^3. Further, due to the serious health effects resulting from chronic occupational inhalation exposure of Mn, the American Conference on Governmental Industrial Hygienists sets the Threshold Limit Value (TLV) as 0.02 mg/m^3 in the respiratory fraction of factory workers.
- Though most of the reported cases of Manganese toxicity occurred in individuals exposed to the high concentration of airborne Mn (> 5 mg m^{-3}), individuals exposed to Mn less than 1 mg m^{-3} manifested subtle signs of Mn toxicity.

Objective

- Despite the reports of Mn-induced neurotoxicity in humans, such as welding-related Parkinsonism, there is not much clinical evidence about manganese-induced ototoxicity.
- In an earlier invitro study Mn Concentration as low as 0.01 mM caused damage to the synapses of sensory hair cells. Mn preferentially damages inner hair cells (IHCs) more than outer hair cells (OHCs) of the cochlea and the damage increases in a dose-dependent manner. To date, evidence of hearing loss as a result of exposure to Mn fumes is lacking.
- Hence, in this study, the objective is to characterize the hearing loss associated with the inhalational exposure of Mn fumes for 90 days.

Methods

- The Long-Evans rats (n=4) were exposed to Mn fumes (respirable Mn) for **three months** using CH Technologies Electronic Cigarette Aerosol Generator and controller (Fig 1). The general population manifesting sub-clinical signs of Mn toxicity had environmental air exposures >0.1 µg/m^3. Therefore, our 5 mg/m3 of Mn fumes exceeds the threshold limit value (TLV) of 0.02 mg/m^3.
- The Mn particles were aerosolized from the Manganese Chloride solution at a 2.5 L/min flow rate to achieve **5mg/m^3** with ten puffs of Mn fumes every 5 mins, which repeats every 25 mins up to 6 h (90 days). In this study, we measured the particle concentrations of manganese using an ultrasonic personal air sampler (UPAS) and condensation particle counter (CPC).

Fig 1. A: Experiment's setup
B: MyUwell. (n.d.). Valyrian III. Retrieved April 22, 2023, from https://www.myuwell.com/products/mod&kit/valyrian-III.html

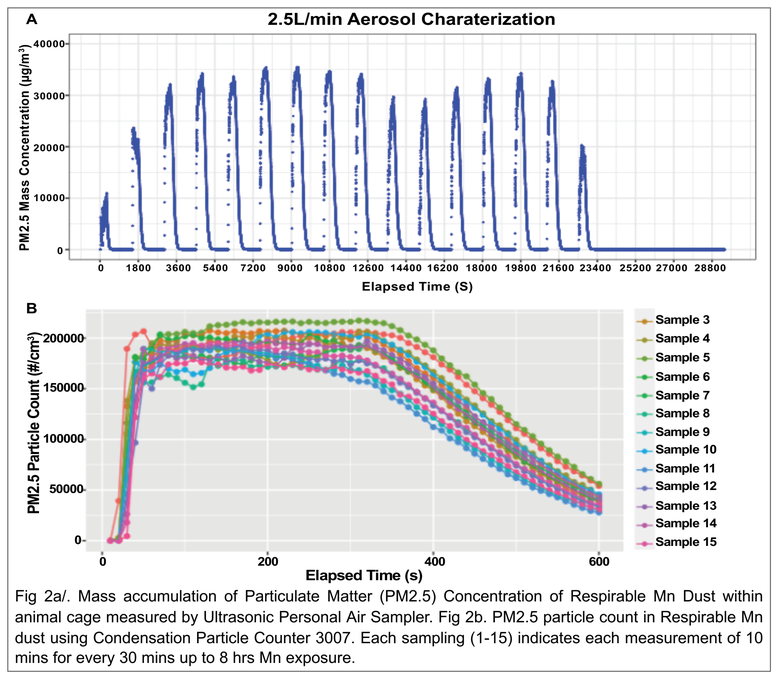

Fig 2a/. Mass accumulation of Particulate Matter (PM2.5) Concentration of Respirable Mn Dust within animal cage measured by Ultrasonic Personal Air Sampler. Fig 2b. PM2.5 particle count in Respirable Mn dust using Condensation Particle Counter 3007. Each sampling (1-15) indicates each measurement of 10 mins for every 30 mins up to 8 hrs Mn exposure.

Minimally invasive assessments of auditory function

Pre- and post-manganese exposure (post 3 months), minimally invasive measurements of auditory function were performed to characterize cochlear and neural responses.

Auditory Brainstem Response (ABR): Using subdermal needle electrodes and foam-tipped insert earphones, auditory brainstem responses (ABRs) were measured to determine thresholds and amplitude/latency growth functions.

Distortion-product otoacoustic emissions (DPOAEs): DPOAEs were measured in the same session to obtain functional measures of outer-hair-cell (OHC) status.

Audiogram

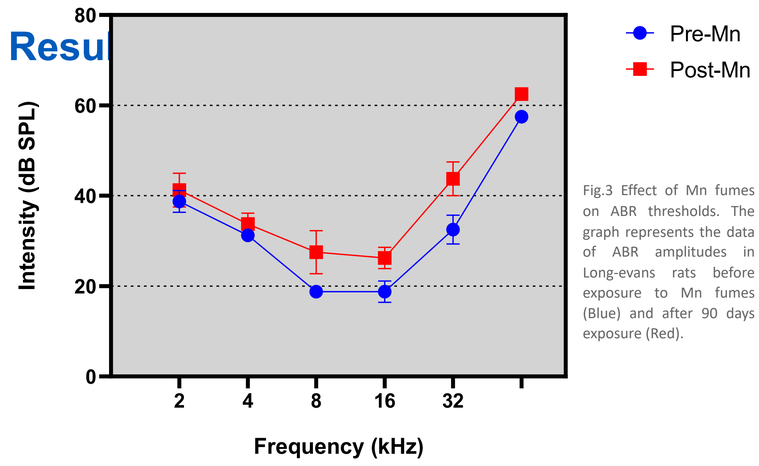

Fig.3 Effect of Mn fumes on ABR thresholds. The graph represents the data of ABR amplitudes in Long-evans rats before exposure to Mn fumes (Blue) and after 90 days exposure (Red).

The paired t-test (normality assumptions hold) indicates that the ABR thresholds were significantly elevated across frequencies (2, 4, 8, 16, 32, and 64 kHz) in Long-Evans (n=4) that were exposed to 90 days of Mn fumes when compared to the ABR threshold levels before Mn fumes exposure (Fig 3).

The mean of differences was 6.25 ± SEM 1.44 (Paired t (5) = 4.330, p=0.0075) with a 95% CI of 2.54 to 9.96. This indicates that Mn fumes exposure in rats reduces auditory sensitivity across frequencies.

Fig.4 Effect of Mn fumes on ABR Wave I Latency. The graph represents the data of ABR wave I latencies in 2, 4, 8, 16, 32, and 64 kHz in Long-Evans rats before exposure to Mn fumes (Blue) and after 90 days of exposure (Red).

The wave I latency was increased significantly in Mn-exposed rats (Fig 4).
The significant changes were consistently at an alpha level of 0.001 i.e 2 kHz (t=12.98, df=7, p<0.0001), 4 kHz (18.36, df=8, p<0.0001), 8 kHz (t=7.3, df=11, p<0.0001), 16 kHz (t=21.96, df=9, p<0.0001) and 32 kHz (t=15.24, df=8, p<0.0001).

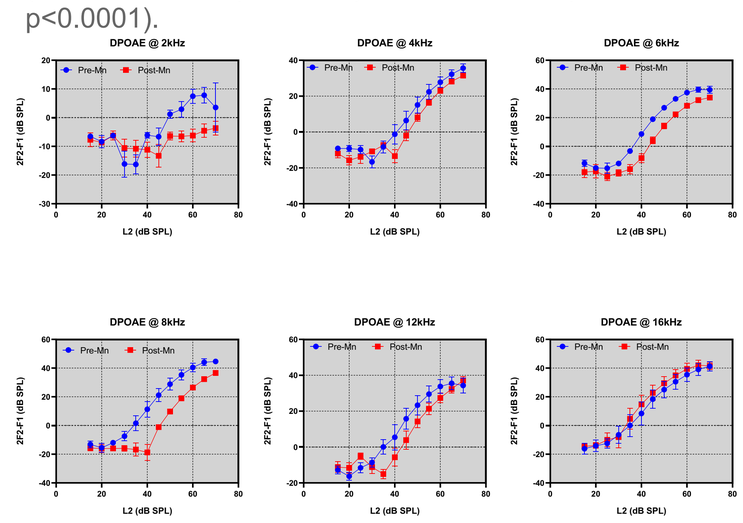

Fig. 5. Effect of Mn fumes exposure on the integrity of Outer Hair Cells. The graphs A-F represents the DPOAE amplitudes (2F2-F1) in 2, 4, 6, 8, 12 and 16 kHz as a function of L2 intensities.

In Low frequencies, the Mn fumes induced decrease of otoacoustic emission was significant at an alpha level of 0.05 at 2 kHz, at 0.005 at 4 and 16 kHz, and at 0.001 in 6, 8, and 20 kHz.

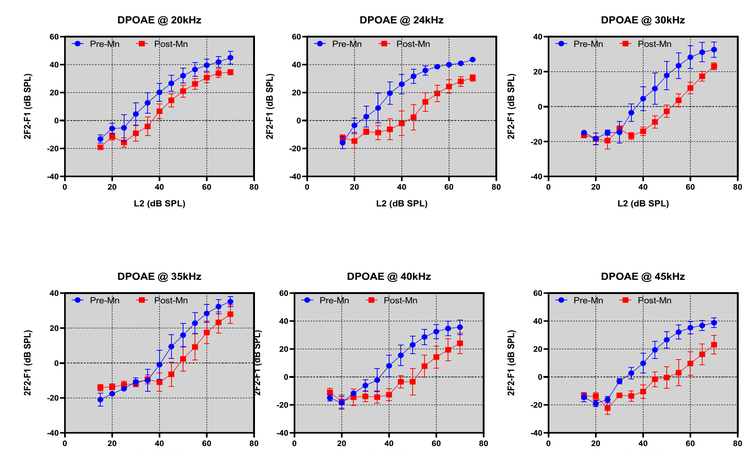

Fig. 6. Effect of Mn fumes exposure on the integrity of Outer Hair Cells. The graphs A-F represents the DPOAE amplitudes (2F2-F1) in 20, 24, 30, 35, 40 and 45 kHz as a function of L2 intensities.

In higher frequencies, DPOAE amplitudes were reduced at the following frequencies 20 kHz (t=11.23, df=11, p=0.0001), 24 kHz (t=6.42, df=11, p=0.0001), 30 kHz (t=4.71, df=11, p=0.0006), 35 kHz (t=2.50, df=11, p=0.029), 40 kHz (t=4.58, df=11, p=0.0008), 45 kHz (t=4.90, df=11, p=0.0005).
In high frequencies, the Mn fumes induced decrease of otoacoustic emission was significant at an alpha level of 0.05 at 35 kHz, and at 0.001 in 20, 24, 30, 40, and 45 kHz.

Conclusion

- Mn fumes exposure in rats reduces auditory sensitivity across frequencies.
- Mn exposure results in abnormal action potential propagation along AN and demyelination and/or degeneration of AN fibers.
- The 90 days of exposure to Mn fumes alone reduced the integrity of outer hair cells and reduced the amplification function.

References

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