Spacecraft Maximum Allowable Concentrations for Manganese Compounds in Mars Dust

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INTRODUCTION: Exposure to excess manganese (Mn) can cause multiple toxicological outcomes in humans, most notably neurotoxicity. Ample epidemiological evidence suggests that chronic, low-level exposure causes subclinical cognitive effects. Because NASA astronauts will be exposed to Mars regolith, Spacecraft Maximum Allowable Concentrations (SMACs) were developed following an extensive literature review.

METHODS: Multiple databases were searched for information relevant to derivation of Mn SMAC values. An additional search for Mars dust data was performed. Risk assessment approaches were applied, including adjustments for space-relevant susceptibility to Mn effects, to develop limits for 1-h to 1000-d exposures. Rover data informed the assessment and enabled calculation of allowable total dust exposure based on Mn content.

RESULTS: Over 400 relevant sources were identified. Applicability of exposure characteristics and data collection methods influenced key study choice. SMACs ranging from 3 mg · m^{-3} (1 h) – 0.0079 mg · m^{-3} (1000 d) were set to protect primarily against neurocognitive and respiratory effects. Considering 0.38 wt% total Mn presence in the dust, maximum recommended total dust exposure should not exceed 790 mg · m^{-3} (1 h) – 2 mg · m^{-3} (1000 d).

DISCUSSION: This literature review allowed for identification of relevant studies to inform SMAC development. Manganese is one of several components to consider when developing an appropriate total dust limit for Martian dust; other dust elements may alter Mn bioavailability. Mission-specific activities may require alteration of assumptions regarding Mn dust concentration and exposure duration. However, based on expected toxicity of particulate matter itself, the acute SMACs are protective, even with transient exposure during activities that could produce higher concentrations.

KEYWORDS: Mars dust, manganese toxicity, risk assessment, exposure limits.

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Manganese (Mn) is present in the soil and dust on Mars. It is also found embedded in rock and concentrated in coatings on outer surfaces of rock and in fractures.[8] According to Mars rover data,[77–79] Mn is present as a cation in inhalable, basaltic dust at levels ranging from 0.31–0.38 wt% total Mn (reported as total Mn, or MnO_T). In disturbed soil at Anchor Point, concentrations were slightly higher (0.75–1.01 wt%) than the average reported for dust.[8] In comparison, the average concentration in Earth soil and lunar dust is 0.1 wt%. Lanza et al. reported concentrations of 25–30 wt% MnO_T in the outer surface of Martian rocks and up to 76 ± 18 wt% MnO_T in a sulfate-rich rock vein at Gale crater.[61] In these cases, low-albedo regions implicate the presence of possible oxidized Mn-bearing (Mn^{3+} and Mn^{4+}) material, however, the exact speciation of Mn in global Martian dust is unknown. In addition to observations in the Gale and Endeavor Craters, high abundances of Mn have also been observed in Martian meteorites, suggesting that Mn deposits may be widespread on Mars.[60] Due to global dust storms, the composition of the dust is thought to be fairly homogenous.[73] Thus the high concentrations associated with rock are localized occurrences and are not representative of dust on the Martian surface. Mn (primarily as MnO_2) is visible as a dark coating on Martian rock surfaces but is not likely to transfer to suits upon contact, as it is

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hardened on the surface (Morris R. Personal communication; Mars Dust Workshop, Houston, TX; 2017). However, if drilling or grinding rock material occurs, higher localized concentrations may be a greater concern in terms of crew exposure or health.

On Earth, dusts and soil erosion represent the most important Mn source in the atmosphere (mean concentration in U.S. ambient air is 0.02 $\mu g \cdot m^{-3}$); however, ambient concentrations near industrial sources, the primary source of excess exposure, can reach 0.3 $\mu g \cdot m^{-3}$.[3] The principal inhalational sources are welding, Mn alloy and dry-cell battery production, mining operations, and steel casting, where emission occurs mainly in the form of Mn oxides[53] and vehicle exhaust in the form of Mn phosphate and Mn sulfate-containing particulate matter.[106]

Since the Mn speciation in Mars dust is unknown, the reported concentration of Mn in the dust is the upper limit concentration for Mn-oxides or Mn-salts and is the basis for calculation of maximum exposure limits if the dust were composed of entirely respirable (< 10 μm) particles. Insoluble forms of Mn (e.g., Mn oxides), however, are soluble in weak acids, which is of biological importance because pH is low in parts of the gastrointestinal tract and within cellular lysosomes. The mean dust particle diameter is reported as 3.0 ± 0.4 μm from Martian surface measurements,[66] with MnO_T concentration as a function of dust particle diameter yet to be fully characterized. Additional information regarding relevant Mars dust characteristics is located in **Appendix A** online: https://doi.org/10.3357/amhp.5264sd.2019.

Exposures to dust on Mars may be similar to those encountered with lunar dust. Crews exploring the surface of the Moon returned samples to the spacecraft, including uncontained dust, which was statically adhered to the surfaces of suits. On Mars, repetitive EVAs are planned, which may increase the likelihood for repetitive exposure or eventual accumulation of dust inside the spacecraft or habitat unless plans are implemented to doff suits before re-entering the habitable volume. With less gravity, particles would be expected to remain suspended longer following release or disturbance. Assuming crew will be exposed to airborne dust and regolith, limits must be set to inform design criteria. These limits should incorporate consideration of astronaut superior health status, but must also take into account any unique susceptibilities associated with long-duration exposure to space (reduced gravity, radiation, etc.).

Manganese adequate intake is considered to be 2.3 and 1.8 $mg \cdot d^{-1}$ for adult males and females, respectively.[44] Manganese is essential for the synthesis and activity of multiple enzymes (including Mn-SOD, the reactive oxygen species scavenger of the mitochondria) and is required for adequate central nervous system (CNS) function. Mn is also important in the formation of cartilage and bone. Interactions with other nutritional elements, including calcium and iron, are thought to affect Mn absorption from the gastrointestinal tract. Therefore the nutritional state of the astronaut exposed to Mars regolith and dust may impact Mn absorption and toxicological outcome.

METHODS

Aligned with methods previously defined through extensive interaction between NASA and the National Research Council,[27,80] a thorough literature search (details provided in Auxiliary Material) was performed, then disposition (absorption, distribution, metabolism, and excretion) and toxicity were summarized, followed by development of an AC for each potential toxic effect for a series of exposure durations. Appropriate uncertainty factors were applied to noncarcinogenic study points of departure established from results in the published literature. Spaceflight-associated effects that are expected to alter sensitivity to Mn exposure-related effects were considered in the calculations, when necessary. The most sensitive endpoint at each time point was used to derive the associated SMAC.

TOXICOKINETICS

Absorption

Manganese is absorbed following inhalation and ingestion, but does not readily penetrate the skin upon dermal exposure.[3] Oral exposure to Mn (inorganic salts) has been evaluated previously by the NASA Johnson Space Center's (JSC) Toxicology Group to determine an acceptable NASA Spacecraft Water Exposure Guideline.[86] Following inhalation, Mn may be absorbed by the nasal mucosa, in the lung, and within the gastrointestinal tract following mucociliary clearance, where the low pH of the stomach solubilizes water-insoluble particles (e.g., Mn oxides). Although it is known that ingestion following the pulmonary mucociliary clearance mechanism accounts for a significant portion of inhaled particles, the percentage absorbed by each route is not well defined. Uptake and elimination are under homeostatic control, which generally allows for a wide range of dietary intakes,[58] but significant interindividual differences in absorption and retention are known to occur. Absorption of Mn deposited in the lung is known to be higher for soluble forms of Mn compared with relatively insoluble forms.[10] As stated earlier, speciation of Mn in Mars dust is not known, which forces the conservative assumption that it exists in a soluble form(s).

Typically, particle size has a great effect on the deposition location following inhalation, with larger particles that may affect and remain in the upper airways and smaller particles capable of traveling deeper into the alveolar spaces. In the context of total airborne particles, the particle size able to penetrate 50% in the thoracic and respirable fractions is 10 and 4.0 μm, respectively.[4,23] Because clearance mechanisms and biological half-life are dependent on deposition site, this is important for determination of particle absorption and biological fate. Darquenne et al. showed that deposition of particles > 0.5 μm in 1 G occurs primarily in the alveolar region, whereas in microgravity the majority occurs in the large airways, but increased deposition of particles < 5 μm occurs in microgravity compared to 1 G.[29] Therefore it can be anticipated

that on Mars (with 38% Earth's gravity), particles (at least those > 0.5 μm) will be more likely to deposit in the larger airways compared to 1 G, but not to the extent as observed in microgravity. While this may lead to faster pulmonary clearance, toxicological impacts of exposure are expected to continue following mucociliary clearance via ingestion and solubilization of the particles in the acidic stomach. For those insoluble particles that do deposit in the lower airways, macrophage ingestion and subsequent cellular recycling events are expected. Reactive oxygen species-mediated cellular toxicity resulting from intracellular Mn (II) ion release may occur.[83]

Low ferritin concentrations are associated with increased Mn uptake[42] and individuals exposed to excess Mn who are iron deficient are at greater risk for susceptibility to Mn toxicity.[11] Mn and iron are absorbed through similar gastrointestinal (GI) uptake mechanisms, which is the likely cause of this inverse relationship. Iron supplementation has been shown to prevent Mn uptake at the cellular level.[99] However, Mn toxicity may still occur with iron coexposures, as evidenced by the incidence of manganism in ferromanganese fume and dust-exposed workers.[97]

Distribution Following Inhalational Exposure

Following exposure in mammals, Mn distributes to all tissues; however, the liver, pancreas, kidney, and adrenal glands generally contain the highest concentrations.[32] The brain, heart, lungs, testes, and ovaries contain intermediate concentrations.[81]

Following inhalation, Mn can be transported several ways: 1) into olfactory or trigeminal presynaptic nerve endings within the nasal mucosa and subsequently delivered to the brain; 2) across pulmonary epithelial linings into blood or lymph fluids; and/or 3) across GI epithelial linings into the blood following mucociliary elevator clearance from the lungs.[9,36,91] The portion of inhaled Mn that is absorbed in the lung is particle size-dependent, but has been reported to be 60% following nonhuman primate (NHP) exposure to a soluble form ($MnSO_4$).[6] For fine dusts deposited in the alveoli, the absorption rate has been reported to be near 100%.[13]

Because Mn is transported directly to the brain via the blood stream (bypassing the liver and the opportunity for first-pass hepatic clearance), the toxicity of inhaled Mn is greater than ingested Mn.[40] Increasing exposure to Mn, through either diet or inhalation, has been shown to decrease gastrointestinal absorption, increase biliary elimination, or both.[30,34,35,102] Additional information regarding Mn absorption and distribution is located in Appendix A.

Metabolism

In the body, Mn can exist in different oxidation states, or complex with biological molecules such as bicarbonate, albumin, transferrin, metalloproteinases, bile salts, and nucleotides.[81] Oxidation state transformation occurs and this is thought to alter the rate and extent of Mn retention.[48] However, it is not known whether the difference in valence state significantly affects toxicological outcome.

Excretion

Manganese is predominantly excreted in the feces. Less than 2% is excreted via the urine and smaller amounts through sweat.[3] Since elimination primarily occurs through the bile, individuals with impaired liver function are particularly susceptible to excessive Mn exposures. In humans, approximately 60% of Mn deposited in the lung in the form of inhaled Mn chloride or Mn tetroxide is fecally excreted within 4 d.[74] Some studies have shown that urinary excretion is higher in males chronically exposed to Mn-containing dust and fumes,[24,70,88,89] with differences in exposure duration and frequency likely influencing the amounts reported. Attempts to reduce Mn burden and neurological effects with chelation and other pharmaceutical treatments have shown mixed success.[3]

TOXICITY

Toxicity Summary

The primary toxicological outcomes following Mn exposure that are likely to result in a health-based recommendation and are relevant to astronaut crews are neurotoxicity and respiratory inflammation. Of these, neurotoxicity presents the most sensitive endpoint. However, Mn may exert other effects, such as cardiotoxicity, that are also relevant to astronauts. In assessing Mn, all potential endpoints were evaluated, but for the sake of brevity only respiratory, neurological, reproductive, and cardiovascular toxicological endpoints are discussed in the main document. Additional information regarding Mn toxicity is located in Appendix A.

Respiratory Toxicity

Inhalation of high Mn dust concentrations can cause a respiratory inflammatory response. In humans, inhalational exposure, especially to Mn dioxide and tetroxide, can cause cough, bronchitis, pneumonitis, and minor reduction in pulmonary function.[3] However, these symptoms are thought to be associated with the irritation of particulate matter exposure in general, rather than the Mn content.[39,93] Based on previous results from studies of exposed students near a ferromanganese plant[82] and Mn workers,[89,94] mild respiratory symptoms may occur at an average airborne concentration of 1 $mg \cdot m^{-3}$.[3] However, exposure to other respiratory irritants may exacerbate symptoms or cause them to occur at lower concentrations.[94] A report of chronic exposure to concentrations averaging 210 $mg \cdot m^{-3}$ were associated with pneumonia, but the lowest-observed-adverse-effect level (LOAEL) was determined to be much lower (3.6 $mg \cdot m^{-3}$).[68] Six deaths from pneumonia in a Norwegian ferromanganese/silicomanganese plant were attributed to occupational Mn exposures.[50] Another investigation involving welders revealed that Mn exposure was responsible for three fatalities due to metal fume fever leading to pneumonia.[103] These men reported symptoms of metal fume fever several times each year. Since there is a lack of appropriately controlled, relevant acute toxicity data for humans, the CDC Immediately Dangerous to Life or Health concentration has

been set at 500 mg · m^{-3} (as Mn) based on acute toxicity data in animals.[49]

In a multipart study, Dorman et al. reported that inhalation of 0.3 or 1.5 mg Mn · m^{-3} $MnSO_4$ (6 h/d, 5 d/wk) for 65 d or 1.5 mg Mn · m^{-3} for 15, 33, or 65 exposure days resulted in increased lung Mn concentrations in Rhesus monkeys (4–6 animals per group).[33,36] Histological analysis of subacutely exposed (15 d) animals revealed mild bronchiolitis (3/4 animals), alveolar duct inflammation (3/4), and proliferation of bronchus-associated lymphoid tissue (2/4). These effects were not evident in any of the control animals. This pattern of effects was also consistent at 33 d. The inflammatory changes were absent 45 d postexposure, indicating that Mn-induced lesions are reversible upon cessation of subchronic, high-dose exposure. Rhesus monkeys exposed to 0.7 mg · m^{-3} MnO_2 for 10 mo (22 h/d) also produced mild lung inflammation.[98] Rats exposed for 13 wk (6 h/d, 5 d/wk) to $MnSO_4$ and $Mn_3(PO_4)_2$ developed transient nasal epithelial inflammatory responses.[31] Sprague-Dawley rats exposed to MnO_2 at higher concentrations (43 mg · m^{-3}, 6 h/d for 10 d) developed pneumonitis and increased lung weight.[96] Following short-term exposure (1–4 d) to 69 mg · m^{-3} MnO_2, mice challenged with a bacterial pathogen showed increased susceptibility to pneumonia.[72] However, others reported a lack of change in susceptibility.[68] Respiratory and other relevant, nonneurological responses are presented in **Table I**.

Neurotoxicity

Although homeostatic mechanisms generally limit Mn toxicity following oral exposure, occupational exposure to inhaled Mn has produced symptoms that call into question the effectiveness of such protective mechanisms. The majority of human inhalation exposure studies reporting neurological effects have involved Mn dioxide, but compounds containing Mn(II) and Mn(III) can also cause manganism.[3] Neurotoxic responses by concentration are presented in **Table II**.

Exposure to high concentrations of Mn produces a condition known as manganism. Affected individuals display progressively debilitating muscular dystonia, hypokinesia, and motor disturbances, similar to Parkinson's disease (PD). Although neurological symptoms can improve when exposure ceases, symptoms most typically persist for many years beyond the return of tissue and blood levels within normal range.[52] Fine, symmetrical tremor may also be present. Manganism in its early stage can cause severe personality changes, including impulsivity, aggression, destructiveness, and depression, but these symptoms generally resolve with time,. Early clinical symptoms include weakness, fatigue, muscle pain, stiffness, anorexia, irritability, headache, apathy, slow speech, dull facial expression, uncoordinated movement of the arms and legs, insomnia, impotence, and loss of libido.[3] Progression of manganism leads to a characteristic stagger in gait and movements become increasingly unintentional.

In a study of 43 bridge welders exposed to confined-space welding fume containing Mn (mean time weighted avg 0.11–0.46 mg · m^{-3}, > 90% respirable particulate, avg. 1.5 yr exposure), workers reported sleep disturbance (79.1%), tremors (41.9%), numbness (60.5%), excessive fatigue (65.1%) sexual dysfunction (58.1%), hallucinations (18.6%), depression (53.5%), and anxiety (39.5%).[20] In studies of Mn miners, it was determined that accumulation of exposure over time increased the percentage of workers that developed symptoms.[87,95] Both studies reported that the majority of cases required years before onset of disease symptoms, but the larger study results indicated that 6 individuals (5.2%) developed symptoms with 1–3 mo of exposure and 68% by 1–2 yr. A thorough description of the miners without frank manganism was not provided in either case. In a more recent reanalysis of existing epidemiological data from the 1994 Mergler et al.[75] and 2007–2008 Bouchard et al. studies,[18,19] exposure duration was a strong predictor of neurobehavioral outcomes.[85] Although occupational cases of overt manganism have been reported to require > 5 mg Mn · m^{-3} exposures,[100] lower levels (0.07-8.61 mg · m^{-3}, 0.97 mg · m^{-3} median Mn concentration in total dust as a mixture of soluble and insoluble Mn forms) resulted in preclinical effects, including slowed visual reaction time, hand tremor, altered hand-eye coordination, and audioverbal short-term memory deficits in a 1987 study.[89] All subjects examined (141 exposed Mn oxide and Mn salt company workers and 104 controls from a chemical plant nearby) in this study were male and the group average exposure was 7.1 yr (range 1–19 yr). Similar findings were reported by Roels et al.,[88] in which MnO_2 in total dust ranging from 0.046 to 10.840 mg Mn · m^{-3} (mean 0.948 mg Mn · m^{-3}) and in respirable dust from 0.021 to 1.32 mg Mn · m^{-3} (mean 0.215 mg Mn · m^{-3}) (exposure ranged from 0.2–17.7 yr, average 5.5 yr) caused similar symptoms.[88] This study consisted of 92 exposed workers and 101 matched control workers in a dry alkaline battery plant. Air concentrations were measured using personal dosimeters in different areas within the factory where workers performed different tasks. Neurological outcomes were monitored with an audioverbal test for short-term memory, a visual reaction time test, and measurements of hand steadiness, coordination, and dexterity. Peripheral tremor occurred when the lifetime integrated exposure to Mn dust exceeded 3575 or 730 ug · m^{-3} × year for total and respirable dust, respectively. According to the authors' statistical model, exposure to 0.05, 0.02, and 0.007 mg Mn · m^{-3} respirable particles would be expected to cause impaired hand steadiness in 5%, 2.5%, and 1% of individuals.[3] These results are supported by a recent PBPK study suggesting that neurological effects of Mn exposure are unlikely when inhalation exposure is less than ~10 μg · m^{-3} since target tissue accumulation (beyond endogenous levels) did not occur below this concentration.[47]

In an 8-yr prospective study of 92 battery plant workers classified by low (0.4 mg Mn · m^{-3}), medium (0.6 mg Mn · m^{-3}), and high (2 mg Mn · m^{-3}) Mn average exposures, Roels et al. determined that reduction (0.4 to 0.13 mg Mn · m^{-3}) of exposure over time was associated with improved hand-forearm movement, but higher exposure level groups did not improve hand steadiness and visual reaction time with reduced concentration.[88,90] These findings were corroborated in a separate follow-up study of 24 ex-employees who were not exposed to

Table I. Inhalation Toxicity Summary – Respiratory and Other Effects.

CONCENTRATION AND FORM	EXPOSURE DURATION	SPECIES	EFFECTS	CITATION
0.5 mg · m^{-3} $MnSO_4$	13 wk (6 h/d, 5 d/wk)	Rat (CD)	Temporary inflammatory changes in nasal respiratory epithelium	31
0.7 mg · m^{-3} MnO_2	10 mo (22 h/d)	Monkey (Rhesus)	Mild lung inflammation	98
0.71 mg · m^{-3} MnO_2 (median conc)	6.2 yr (median)	Human	Number of children birthed by wives of workers was not affected	46
0.97 mg · m^{-3} Mn salts and oxides, total dust	1–19 yr	Human	Cough, decreased lung function	89
0.97 mg · m^{-3} Mn salts and oxides, total dust	1–19 yr	Human	Decreased fertility in males (number of children fathered)	63
1 mg · m^{-3} Mn alloy, Mn oxide, and Mn salt	Varied	Human	Average concentration at which mild respiratory effects are noticed in children and occupationally exposed workers	3
1.5 mg Mn · m^{-3} $MnSO_4$	15 d (6 h/d, 5 d/wk)	Monkey (Rhesus)	Reversible mild bronchiolitis, alveolar duct inflammation, and proliferation of bronchus-associated lymphoid tissue, decreased total bilirubin	33,36
1.5 mg Mn · m^{-3} $MnSO_4$	65 d (6 h/d, 5 d/wk)	Monkey (Rhesus)	17% decrease in relative heart weight 90-d postexposure	36
2 mg Mn · m^{-3} $MnCl_2$	5 d (6 h/d)	Mouse (FVB/N)	Failed to cause lung lesions, but elicited twofold pulmonary vascular endothelial growth factor (VEGF) mRNA induction	21
2.8 mg · m^{-3} Mn_3O_4	2 h	Mouse (CD-1)	Respiratory NOAEL	1
2.82 mg · m^{-3} MnO_2	1 yr	Human	Abnormal sperm	105
3.6 mg · m^{-3} MnO_2 (average 210 mg · m^{-3}), total dust	Occupational; duration not specified	Human	Pneumonia LOAEL	68
14 mg · m^{-3} MnO_2	1 h	Guinea Pig	Respiratory NOAEL	14
43 mg · m^{-3} MnO_2	10 d (6 h/d)	Rat (Sprague Dawley)	Pneumonitis and increased lung weight	96
69 mg · m^{-3} MnO_2, respirable	1-4 d (3 h/d)	Mouse (CD-1)	Increased susceptibility to pneumonia	72
90 mg · m^{-3}	7.5 yr (avg)	Human	Increased prevalence of impaired pulmonary function in miners	16

Mn for 3 yr following employment as MnO_2 workers. In this study, hand-eye coordination significantly improved, but hand steadiness and visual reaction time did not.[90] At approximately 0.07 to 0.97 mg Mn · m^{-3}, chronically exposed workers exhibited subclinical (but spaceflight-relevant) effects, including significantly reduced hand-eye coordination, hand steadiness, postural stability, reaction time, decreased performance on neurobehavioral tests, and lower levels of cognitive flexibility.[3] Laohaudomchok et al. also found that lower levels of Mn exposure (~0.0129 mg · m^{-3}) caused neuropsychological changes including altered mood and deficits in attention span and fine motor control.[62] Although lower concentration Mn exposures are not likely to produce manganism, less severe neurocognitive deficits may still occur. The association between Mn exposure and these subtle subclinical cognitive or neuromotor alterations is objectively identifiable via neurocognitive testing; however, the impact (clinical or operational) is unknown.

Species differences in Mn neurotoxicity are recognized, with NHP replicating the neurological effects observed in humans while rodents do not. As such, rodents are not an ideal animal model for Mn inhalation and rodent-to-human extrapolation of results is difficult. NHP model human Mn toxicity well, accumulating Mn in the same brain region as humans, and displaying effects similar to occupationally-exposed workers, including ataxia, slowed movements, unsteady gait, grimacing, and tremor.[3,36] Of note is the fact that the exposure route in NHP studies has involved routes other than inhalation, so it is unclear whether the dose-response would be similar between human and NHP. Data are lacking for short-duration exposures associated with neurobehavioral effects in NHP or humans. Although it was shown that subchronic exposure to $MnSO_4$ (6 h/d, 5 d/wk) for 65 exposure days at 0.06, 0.3, and 1.5 mg Mn · m^{-3} caused 1.5 to 6 times increases in pallidal Mn, no statistically significant increase in neurotransmitter levels were detected indicating that short-duration exposures at these concentrations and/or testing periods are not sufficient to produce detectable neurobehavioral changes. The neurofunctional impairment associated with chronic Mn over-exposure has been shown to occur through disruption of dopaminergic signaling and other neurotransmitter systems, in addition to brain tissue damage.[37,71]

Reproductive Toxicity

Reproductive effects of Mn include decreased or total loss of libido, impotence, and impaired fertility. Occupational exposure to Mn (2.82 mg · m^{-3} Mn dioxide) for at least 1 yr in males caused abnormal sperm.[105] Lower level occupational exposure to Mn salts and oxides (0.07 to 8.61 mg · m^{-3}, average 0.97 mg · m^{-3}) caused decreased fertility in men.[63] In 70 men exposed occupationally to MnO_2 dust (median conc. 0.71 mg · m^{-3}, median duration 6.2 yr) in a Belgian dry alkaline battery plant, the number of children birthed by their wives was not affected.[46] In animal studies, high concentrations caused decreased sperm quality, reduced testicular weights, and altered reproductive tract development in males, although studies indicate that

Table II. Inhalation Toxicity Summary – Neurological Effects.

CONCENTRATION AND FORM	EXPOSURE DURATION	SPECIES	EFFECTS	CITATION
0.007 mg Mn · m^{-3} Respirable	0.2-17.7 yr (avg 5.3 yr)	Human	Impairment of hand steadiness in 1% of individuals (derived from data)	5,88
0.009 mg Mn · m^{-3} (0.03 mg $MnSO_4$ · m^{-3})	13 wk (6 h/d, 5 d/wk)	Rat (Sprague-Dawley)	Increased locomotor activity	101
0.035 mg Mn · m^{-3} Respirable (Total Mn 0.23 mg Mn · m^{-3})	16.7 yr (avg)	Human	Reduced performance on neurobehavioral and neurophysical tests (e.g., motor function, cognitive flexibility, emotional state)	75
0.035 mg Mn · m^{-3} Respirable (Total Mn 0.23 mg Mn · m^{-3})	19.3 yr (avg)	Human	Decrease in neuromotor, cognitive, and sensory function with age	17
0.035 mg Mn · m^{-3} Respirable (Total Mn 0.23 mg Mn · m^{-3})	15.7 yr (avg)	Human	Higher scores for depression, anxiety	19
0.035 mg Mn · m^{-3} Respirable (Total Mn 0.23 mg Mn · m^{-3})	15.3 yr (avg)	Human	Decrease in neuromotor function, increase in confusion-bewilderment	18
0.036 mg Mn · m^{-3} (geometric mean, respirable)	2.1-41 yr (20.2 yr avg)	Human	Hand tremor	12
0.038 mg Mn · m^{-3}, MnO_x - Primarily MnO_2 (geometric mean, respirable)	11.5 yr (avg)	Human	Deficit in neurobehavioral exam performance	69
0.05 mg Mn · m^{-3} respirable	0.2-17.7 yr (avg 5.3 yr)	Human	Impairment of hand steadiness in 5% of individuals (derived from data)	5,88
0.07 mg Mn· m^{-3} Respirable	0.2-17.7 yr (avg 5.3 yr)	Human	$BMDL_{10}$ value for NOAEL	2
0.0967 mg · m^{-3} MnO_2, Mn_3O_4	11.5 y (avg)	Human	Lower performance on neurobehavioral testing	69
0.099 mg Mn · m^{-3}, respirable	0.2-17.7 yr (avg 5.3 yr)	Human	$BMCL_{10}$ value for decrements in eye-hand coordination	88
0.11 mg · m^{-3} $MnPO_4$	12 wk (6 h/d, 5 d/wk)	Rat (Sprague Dawley)	Astrocytic nodules, focal glial cell proliferation	38
0.14 mg · m^{-3} MnO_2	1-35 yr (2.6 yr median)	Human	Decreased reaction time, finger tapping	54
0.149 mg · m^{-3} MnO_2 and other Mn oxides	1-28 yr	Human	Reduced neurobehavioral performance in multiple tests	70
0.179 mg · m^{-3} MnO_2	5.3 yr	Human	Impaired eye-hand coordination, hand steadiness, and visual reaction time	88
0.202 mg Mn · m^{-3}, respirable	0.2-17.7 yr (avg 5.3 yr)	Human	$BMCL_{10}$ value for decrements in hand steadiness	88
0.257 mg Mn · m^{-3}, respirable	0.2-17.7 yr (avg 5.3 yr)	Human	$BMCL_{10}$ value for decrements in visual reaction time	88
0.97 mg · m^{-3} Mn salts and oxides, total dust	1-19 yr	Human	Altered reaction time, short-term memory loss, and decreased hand steadiness	89
1.1 mg · m^{-3} $MnPO_4$	12 wk (6 h/d, 5 d/wk)	Rat (Sprague Dawley)	Neuronal degeneration	38
1.59 mg · m^{-3} MnO_2	1.1-15.7 yr	Human	Impaired balance when eyes closed	25
2.6 mg · m^{-3} unspecified form	Not specified	Human	Tremor, decreased reflexes	94
3 mg · m^{-3} $MnPO_4$/$MnSO_4$ mixture	90 d (5 d/wk, 6 h/d)	Rat (Sprague-Dawley)	Substantial decrease in neuronal cells within globus pallidus and caudate putamen	92
3.5 mg · m^{-3}, unspecified form	1 yr	Human	Weakness, ataxia, anorexia	104
5 mg · m^{-3}	Occupational –Unspecified duration and form	Human	Weakness, ataxia, pain	100
6 mg · m^{-3} MnO_2	1-9 yr	Human	Multiple psychomotor disturbances, muscle weakness, and pain	95
20 mg · m^{-3}	Occupational – varied	Human	Average concentration at which signs of overt manganism are evident	97
22 mg · m^{-3}	Occupational-Duration not specified	Human	Bradykinesia, expressionless face	26
30 mg · m^{-3} MnO_2	2 yr (5d/wk, 6 h/d)	Monkey (Rhesus)	Decreased dopamine levels in caudate and globus pallidus brain tissue	15

reproduction in females (humans and laboratory animals) is generally not affected by excess exposure to Mn.[3]

Cardiovascular/Vasodilation

Although animal studies using high dose IV injections and perfused rat heart models indicate that overexposure to Mn can affect cardiac function, including changes in blood pressure, heart rate, and P-R and QRS intervals (ECG), determination of dose-related effects in humans is difficult because there is a lack of quantitative epidemiological evidence from which individual exposure concentrations were reported. Occupational Mn exposure can result in vasodilation and hypotension, which can also cause CNS effects. At a geometric mean of 0.13 mg · m^{-3} MnO_2, this effect was most common in younger workers, which may be due to better elasticity of blood vessels allowing for increased vasodilation; however, at the number of abnormal echocardiograms was not significantly different than the matched controls.[55] Mn cardiotoxicity has been reported to occur as a result of inhibited myocardial contractions caused by the direct action of Mn on mitochondrial function. High concentrations of

intravenous MnCl and MRI contrast agent mangafodipir trisodium antagonizes calcium and can induce negative inotropy (weakens strength of contraction), reflex tachycardia, and hypotension.[56] However, the authors of this study explain that these ex vivo results obtained in isolated perfused rat hearts and isolated bovine mesenteric arteries are not observed in vivo (canines) due to reduction of active Mn^{+2} ions in the plasma via extensive protein binding, and the release of catecholamines to maintain blood pressure and heart rate. For these reasons, an acceptable concentration (AC) was not derived for cardiotoxicity. A detailed summary of the available literature on Mn-induced cardiotoxicity is available in the Appendix.

CONSIDERATION OF SPACEFLIGHT-ASSOCIATED FACTORS

Central Nervous System (CNS) Effects

The etiology of CNS effects susceptibility during Mars missions is expected to be complex. Carbon dioxide (CO_2) levels in spacecraft (and presumably Mars habitats) are approximately 2.5–4 times the level of the typical indoor environment on Earth. Cephalad fluid shifting in microgravity or reduced gravity could potentiate CO_2-induced cerebral vasodilation, resulting in CNS symptoms at lower than expected levels of CO_2 exposure.[64] The neuromuscular, neurovestibular, and cerebrovascular systems each have an effect on the CNS and are thought to be affected by microgravity.[57] A 30-d, 6° head-down-tilt bed rest (HDTBR) study including 14 males revealed that gray matter associated with performance, locomotion, learning, memory, and coordination was significantly decreased following HDTBR compared to before HDTBR.[67] The authors speculated that these regional alterations may be related to brain function decline and adaptation frequently encountered during spaceflight. Miller et al. found that length of mission was directly related to the severity of functional performance deficits immediately following flight, suggesting that extended axial unloading in transit to Mars may elicit uncoordinated balance even in partial gravity that may contribute to Mn exposure-related effects.[76] Elevated levels of CO_2 and other factors have also been associated with decreased sleep on ISS, which may also contribute to CNS effects susceptibility in space.[22,51,65]

Due to longer missions and the lack of protection from Earth's magnetic field in low-Earth orbit (LEO), Mars exploration and long-duration lunar crews will encounter a greater amount of radiation than previous astronauts. During the course of a mission, the potential CNS risk associated with radiation exposure is altered cognitive function, which includes changes in behavior and decreases in motor function and short-term memory, whereas delayed effects include the possibility of premature aging and development of dementia including Alzheimer's disease.[28] It is known that areas of the brain associated with cognitive detriments in animal studies include the striatum, hippocampus, and the prefrontal cortex. Because Mn accumulates in the striatum and produces similar effects upon exposure, and because radiation-induced CNS effects are a greater risk for exploration mission crews, radiation also contributes to an adjustment factor for CNS effects susceptibility. Although animal and cellular data suggest that the amount of total radiation crewmembers encounter in space can cause neurotoxicity, human exposure data are lacking and studies explaining effects caused by a variety of particle types and dose rates are needed. Therefore an uncertainty factor, rather than a spaceflight safety factor, will be applied to the recommended maximum exposure limits. Additional information regarding CNS susceptibility as a Spaceflight Safety Factor is located online in Appendix A.

SMAC DEVELOPMENT

Derivation of 1-h AC and 24-h ACs

There are no acute ($\leq$ 24 h) inhalation toxicity data in species relevant for determination of cognitive effects. Several acute animal studies have been conducted that measured pulmonary endpoints. Insoluble forms of Mn were administered to mice (Mn_3O_4 inhalation for 2 h) and guinea pigs (MnO_2 inhalation for 1 h), which resulted in no significant treatment-related histopathic lung lesions.[1,14] No Observable Adverse Effects Level (NOAEL) values were determined to be 2.8 mg $\cdot$ m^{-3} and 14 mg $\cdot$ m^{-3} for mice and guinea pigs, respectively. However, without LOAEL values, these studies are not ideal for risk determination. In mice, inhalation of 2 mg Mn $\cdot$ m^{-3} as $MnCl_2$ aerosol (6 h/d for 5 d) failed to cause lung lesions, but caused a twofold induction of pulmonary vascular endothelial growth factor (VEGF) mRNA.[21] It is uncertain whether this response could be considered significant in terms of adverse response that could serve as a risk assessment point of departure (POD), especially without data indicating corresponding levels of protein upregulation or microscopic evidence of pathological change. Mice receiving a much higher exposure concentration (69 mg $\cdot$ m^{-3}) for 1–4 d (3 h/d) were more susceptible to lung infection upon exposure to bacterial pathogens following Mn dust inhalation.[72] However, these data are not ideal for a POD since a pathogen was required for the response. Therefore, due to a lack of appropriate short-term studies, existing NIOSH values were adopted. Because those values were derived from studies in which animals were dosed via oral or intraperitoneal routes, the earlier mentioned Dorman paper[33] describing minimal airway effects following 15 d exposure to 1.5 mg Mn $\cdot$ m^{-3} (as $MnSO_4$) is used as a supporting study. This study suggests that steady state Mn lung concentration is likely reached at some point prior to the earliest time point (15 d) since there is no change in concentrations from 15 to 65 d. This study also reported dose-dependent findings using a soluble form of Mn (expected to induce a greater effect compared to insoluble forms). The short-duration SMACs, which are based on non-inhalational exposure data, are within the same range as the concentration shown to cause limited respiratory effects in this NHP study. As per standard NASA procedure, the 1 and 24 h SMACs are set at levels that allow for minor, temporary effects in an off-nominal situation. Therefore, the AC for 1 h is

set at the NIOSH STEL of 3 mg · m^{-3}, and the AC for 24 h is set at the NIOSH REL of 1 mg · m^{-3}.

Considering a 0.38 wt% MnO_T presence in the dust, the maximum total dust exposure for 1-h and 24-h durations is 789.47 mg · m^{-3} and 263.16 mg · m^{-3}, respectively. If rocks were to be drilled and inhaled as a dust, higher concentrations in rock surfaces or veins would allow for less total dust exposure. At a concentration of 25%, the total maximum allowable dust concentration for 1 h and 24 h would be 12.0 mg · m^{-3} and 4.0 mg · m^{-3}, respectively, and at a MnO_T concentration of 75%, the total maximum allowable dust concentration would be 4.0 mg · m^{-3} and 1.3 mg · m^{-3}, respectively. These higher MnO_T levels were considered as possible exposure concentrations for the acute duration SMACs only since it is not expected that the duration of activities that would generate dust containing these levels would exceed those periods.

Derivation of 7-d and 30-d ACs (for Irritation)

Because the Dorman et al.[33] NOAEL is 0.3 mg · m^{-3} for up to 65 d and irritation is more a function of localized concentration rather than duration, a factor to adjust for continuous exposure is not applied. A value of 0.3 mg · m^{-3} is used as the AC for both 7 d and 30 d. As the data were collected in NHP, no species factor is applied. These results are supported by another study by the same authors in which rodents were exposed to 0.01, 0.1, or 0.5 mg Mn · m^{-3} for 90 d.[31] Only the 0.5 mg · m^{-3} concentration led to nasal irritation, which was reversible. These AC values are within a factor of 3 from the NIOSH REL (TLV) of 1 mg · m^{-3}. Considering a 0.38 wt% MnO_T presence in the dust, the maximum total dust exposure for 7 d and 30 d durations is 78.95 mg · m^{-3}.

Derivation of 180-d and 1000-d AC (for Neurotoxicity)

The Roels et al.[88] study was chosen as the key neurological study because adequately described humans subjects were evaluated, individual-level exposure concentrations were documented, and appropriate effects were monitored for and discussed. A benchmark concentration limit ($BMCL_{10}$), the 95% lower confidence limit on the maximum likelihood estimate of the concentration corresponding to 10% risk (142 μg · m^{-3} for respirable Mn), was derived by ATSDR[3] based on the earlier discussed Roels et al.[88] epidemiological study results, generated from 92 battery factory workers exposed to MnO_2. The $BMCL_{10}$ value can be used for 1000 d (2.7 yr) as such without adjusting for continuous exposure (hours per day and days per week); however, an adjustment is made from 10 m^3 inhaled air per day to 20 $m^3 \cdot d^{-1}$ to account for continuous exposure. Also, as the Mn literature indicates that soluble Mn could be more potent in causing neurotoxicity than insoluble Mn, a safety factor of 3 is applied. Based on earlier described CNS susceptibility factors encountered during spaceflight, an additional uncertainty factor of 3 is included in the 1000-d SMAC calculation. This value is also conservatively applied to 180-d exposure duration, which was included in the range of occupational exposures described by Roels et al.:[88]

180-d and 1000-d AC for Mn is:

$$142\ \mu g/m^3 \times \frac{10m^3}{20m^3} \times \frac{1}{3} \times \frac{1}{3} = 7.89 \mu g/m^3$$

Considering a 0.38 wt% MnO_T presence in the dust, the maximum total dust exposure for 180-d and 1000-d durations is 2.08 mg · m^{-3}. Based on the calculated limits and average percentage in globally distributed dust on Mars, the amount of allowable total dust inhalation for a given exposure duration period is shown in **Table III**.

DISCUSSION

There are several points of uncertainty associated with toxicological risk assessment for Mn compounds in Mars dust. Of particular importance is the concentration of Mn in the dust, which could be substantially different, depending on the crew activity. Specifically, any disturbance of rock (i.e., crushing, grinding, drilling) that generates inhalable particles would be expected to contain concentrations of Mn that are higher than in the globally distributed dust. As mentioned earlier, rock surfaces and veins have been found to contain 25% and 75% Mn, respectively, but the exact concentrations are expected to vary. Thus, higher localized Mn concentration exposures would require a different type of assessment with modified exposure assumptions. For the 1- and 24-h guidelines, we have included maximum allowable total dust concentrations (1–4 mg · m^{-3}) addressing these specific exposure scenarios. The assumption is that it will not be necessary to account for these higher Mn concentrations in the dust for longer durations, but this may need to be re-evaluated based on actual mission parameters.

Another point of uncertainty is the degree to which the iron, which is present in the dust at much greater concentrations (18.2 wt% as iron oxides) than the Mn, could influence the uptake of Mn. The presence of relatively much greater amounts

Table III. Maximum Allowable Total Dust.

EXPOSURE DURATION	EXPOSURE LIMIT (mg · m^{-3})	% MnO_T IN GLOBAL DUST	AMT ALLOWED TOTAL GLOBAL DUST (mg · m^{-3})
1 h	3	0.38	789.47
24 h	1	0.38	263.16
7 d	0.3	0.38	78.95
30 d	0.3	0.38	78.95
180 d	0.00789	0.38	2.08
1000 d	0.00789	0.38	2.08

of iron compared to Mn may prevent absorption of Mn to some degree following mucociliary clearance and ingestion or inhalation of dust.[59] Increased uptake of Mn is associated with anemia whereas excess iron stores have been found to suppress uptake of Mn in rodents, NHP, and humans.[41,84] However, more recent research indicates that dietary iron supplementation does not effectively protect and may even exacerbate brain Mn accumulation in mammals subchronically exposed to Mn.[43] The biochemical relationship between iron and Mn contributes to ongoing discussions in the field regarding the role of inhaled Mn in the causation of neurological effects in populations that have concurrent exposures to both metals.[45] Similar to the Mars dust, welding fumes also typically contain proportionately much higher concentrations of iron than Mn and other additive metals,[7] but individuals inhalationally exposed in this occupation still develop Mn toxicity.

There is an inherent relationship between risk assessment for total dust on Mars and the individual toxic components carried within that dust matrix. As described in Table II, the amount of total dust allowed based on the estimated Mn content ranges from 2–789 $mg \cdot m^{-3}$ depending on exposure duration. Even considering the possibility of acute (1–24 h) exposure to dust containing up to 75% Mn, the total dust allowed to ensure acceptable Mn exposure is 1–4 $mg \cdot m^{-3}$. To provide risk assessment context for these limits, the lowest end of these ranges are less stringent than the total dust limit set for lunar dust (0.3 $mg \cdot m^{-3}$), as an example. While a corresponding total dust limit for Mars has not yet been established, it would appear that a total dust limit for Mars would also be adequately protective of Mn (assuming a total dust limit for Mars is $\leq 0.3\ mg \cdot m^{-3}$). In conclusion, this assessment demonstrates that Mn in Martian dust has the potential to be a concern for crew health, but this risk is manageable within the context of likely overarching controls for total dust exposure on Mars.

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APPENDIX A. AUXILIARY MATERIAL

Literature Search Approach

A PECOT (Populations, Exposure, Comparator, Outcomes, and Time) statement was used to develop a data-specific search string (manganese OR 7439-96-5 OR EC 231-105-1 OR EINECS 231-105-1) based on relevant synonyms identified in the ChemID*plus* database from the National Library of Medicine for the literature search. The search was conducted between January 1, 2017 and February 9, 2017 and the following databases were used:

1. ProQuest (selected databases: Toxicology Abstracts, Health & Safety Science Abstracts, Risk Abstracts, and in some cases Dissertations & Theses A&I & Global)
2. ToxLine
3. PubMed
4. EBSCOhost (selected databases: Academic Search Complete, Academic Search Premier)
5. ISI Web of Science/Science Citation Index (selected databases: Web of Science Core Collection, Citation Indexes, Science Citation Index Expanded, Conference Proceedings Citation Index, Emerging Sources Citation Index, and Life Sciences Data Archive)
6. Scopus

A total of 377 studies encompassing those most relevant to developing a SMAC (human and animal toxicity studies with relevant exposure route) were considered, in addition to in vitro study data. An additional search for authoritative agency documentation yielded 28 files, several of which were not available in the published literature. Additional internet searches were performed for Mars dust toxicity and Mars dust manganese between March 6, 2017 and May 10, 2018.

Dust Characteristics

The manganese (Mn) concentration, as a function of dust particle diameter, is unknown and could be inversely proportional to particle diameter. As on Earth, differences in chemical composition by particle size are possible, if not likely. Although the full size distribution has yet to be characterized, the abundance of clay-sized (< 2 μm) particles has recently been estimated to be 3% based on CheMin X-ray amorphous and Mössbauer Fe mineralogy at Mars rover landing sites.[35] Both smaller[46] and larger[10] particles have been reported. A greater percentage of smaller particles, which would be expected to deposit deeper in the lung, are detected at higher altitudes on Mars because gravity-induced fall velocities are lower due to smaller mass following events that carry particles into the atmosphere,[30] but smaller particles also exist at the surface where they originate, in combination with a range of other particle sizes.

Absorption

Gastrointestinal absorption of Mn is rapid and has been reported to range from 3 to 8% of the total amount present.[41] Unless exposure by ingestion is excessive or liver function is not optimal, Mn is maintained at relatively stable levels in human tissues via regulated absorption by the gut and excretion by hepatobiliary transport.[2,22] As with the bioavailability relationship between Mn and iron, a similar relationship exists with Mn and other divalent minerals. It has been shown that the addition of calcium to human milk reduced Mn absorption from 4.9 to 3.0%.[14] Intestinal transfer of calcium and Mn ions in rodents was found to be competitive.[20] Magnesium supplementation has been shown to decrease Mn bioavailability in healthy adults, although it is not known whether this is due to decreased absorption or increased excretion.[33] As mentioned in the main text, absorption varies greatly between individuals. In humans administered a dose of radiolabeled Mn in an infant formula, the mean absorption was 5.9 $\pm$ 4.8%, but ranged from 0.8 to 16%, a 20-fold difference.[15] Retention at day 10 ranged from 0.6 to 9.2%, with the highest and lowest values differing by a factor of 15. Speciation influences absorption and distribution patterns. For example, peak blood concentrations occur earlier (0.5 h) after intratracheal Mn chloride administration compared with Mn dioxide (168 h) and are approximately fourfold higher in rats exposed to Mn chloride than in rats exposed to Mn dioxide.[47] Rats exposed to Mn sulfate (0.1 mg Mn $\cdot$ m^{-3}, 6 h/d, 5 d/wk for 13 wk) showed higher olfactory bulb and striatum Mn accumulation than rats exposed to 0.1 mg Mn $\cdot$ m^{-3} in the less soluble form of Mn phosphate.[17] Similarly, rats exposed to $MnSO_4$ had higher brain, but lower lung Mn concentrations compared with levels achieved following similar Mn_3O_4 exposures.[18]

Distribution

The olfactory translocation route has previously been documented for soluble Mn compounds,[17,52] a process for which the efficiency is thought to be determined by species solubility.[18] Addressing the fate of inhaled, poorly soluble Mn oxide particles, Elder et al. (2006) showed that Mn concentrations in the olfactory bulb of rats were increased 3.5-fold over controls following 12-d inhalational exposure to 30 nm Mn oxide particles (distribution: 1–110 nm, ~0.5 mg MnO_2/m^3), compared with twofold increased lung concentrations.[21] Although no indication of pulmonary inflammation was noted by lung lavage analysis, multiple markers of inflammation, including tumor necrosis factor-α mRNA and protein, were noted in the olfactory bulb, providing support for the direct particle transport pathway from the nasal mucosa via the olfactory neuronal tract to the olfactory bulb. Elder et al. also determined that when the right nares were occluded, Mn accumulated in the left olfactory bulb only. In rats, this mechanism of transport to the olfactory bulb was shown to be saturable.[25] The contribution of this pathway to total Mn accumulation in the brain in humans is unknown, but could potentially be less important compared to rodents since the human olfactory bulb and olfactory epithelium comprise a smaller proportion of the CNS and nasal epithelium, respectively. However, it has been shown that rodents exposed to larger particles (MMAD 1.6 um) accumulated less Mn than Elder et al. reported, with the key difference being particle size. Since the diameter of olfactory neurons narrows

to ~200 nm at the cribriform plate pores, particles must be < 200 nm in order to pass through from the olfactory mucosa.[16,45] Elder et al. also reported that, although a maximum of only 1.5% of the Mn in the oxide form was solubilized, similar Mn burdens (given as a percentage of the instilled Mn) were found in the left olfactory bulb tissue 24 h after intranasal instillation of Mn chloride (8.2 ± 3.6%) or Mn oxide (8.2 ± 0.7%).

It is known that larger inhaled dust particles are primarily coughed up from the lungs through what is known as the mucociliary escalator mechanism that assists in clearance of debris in the central and upper airways, then swallowed. Following ingestion via this route, Mn enters the portal circulatory system where it is probably absorbed as Mn (II), binds to plasma proteins, and is then shunted to the liver; what is not delivered to the bile for fecal excretion enters the systemic circulation, where it is conjugated to transferrin and can enter neurons.[2] It is important to note that not all Mn is bioavailable. Maintenance of normal tissue Mn levels following Mn ingestion is regulated by intestinal absorption and hepatic processing, allowing for a wide range of concentrations to be tolerated.[3,31] Pharmacokinetic modeling was used to better understand the Mn homeostatic control mechanisms in a series of papers by Teeguarden et al. who also showed increased exposure from the diet or by inhalation shifts uptake of ingested Mn to the liver for excretion in the bile, decreasing intestinal absorption.[49–51]

Dermal and Ocular Toxicity

Although potassium permanganate can be corrosive to skin and mucous membranes, dermal exposure to other Mn compounds, even water-soluble forms, does not result in significant damage to or absorption through intact skin.[2] Draize irritation testing with neat MMT did not cause ocular irritation.[26] Rabbits exposed to lethal levels (140–795 mg · kg^{-1}) of neat commercial grade MMT on shaved areas of their trunks for 24 h experienced polypnea, vocalization, excitation, ataxia, tremors, cyanosis, and convulsions.[26] A case report of a man burned with a hot acid solution containing 6% Mn indicated that the man had slightly elevated urinary Mn levels (11–14 vs. 1–8 mg · L^{-1}).[34]

Cardiotoxicity

Overexposure to Mn can cause vasodilation. Following acute exposures (16 mg · kg^{-1} · d^{-1}), dogs developed significant hypotension and reflex tachycardia.[32] In dogs, 10 mg · kg^{-1} by intravenous administration resulted in bradycardia, followed by death.[29] In dogs, 20 min of 15–25 μmol · L^{-1} IV perfusion caused a dose-dependent relaxation in coronary vessels.[32] Chronic exposure to Mn in rats and dogs has also been associated with a decline in myocardial contraction.[1,9] Dogs administered an intravenous injection of 0.5–5 mg Mn · kg^{-1} as $MnCl_2$ exhibited prolonged P-R and Q-T intervals and broadened QRS waves.[9] However, results of one study indicated that short-term inhalational exposure (3 h on each of 3 successive days) to 0.05 mg · m^{-3} aerosolized oxide and sulfate forms of Mn particles had little effect on the ECGs of older dogs with preexisting cardiac abnormalities.[40] In monkeys, $MnSO_4$ (1.5 mg · m^{-3}, 90 d, 6 h/d, 5 d/wk) caused a 17% decrease in relative heart weight 90 d postexposure.[19] The NOAEL was determined to be 0.3 mg · m^{-3}.

In workers, Saric and Hrustic reported that those with the highest level of Mn exposure exhibited the lowest systolic blood pressure.[48] The incidence of abnormal electrocardiogram (ECG) results in Mn-exposed workers have been reported to be significantly higher than control subjects. As reviewed by Jiang and Zheng, abnormal ECG results primarily involved sinus tachycardia, sinus bradycardia, sinus arrhythmia, sinister megacardia, and ST-T changes.[28] Women exhibited higher rates of accelerated heartbeat and shortened P-R interval. Young women, in particular, experienced significantly lower mean diastolic blood pressure than the control subjects and male exposed workers. Low concentrations may also exert an effect. Jiang et al. found that MnO_2 exposure (geometric mean: 0.13 mg · m^{-3}) in 656 Mn milling, smeltering, and sintering workers (547 males, 109 females) was associated with a greater incidence of low diastolic blood pressure.[27] The workers' duration of exposure ranged from 0 to 35 yr. The effect was most common in young workers with the lowest tenure in the plant, which may be due to better elasticity of blood vessels at younger ages, allowing for increased vasodilation. No difference in the number of abnormal ECGs was observed between workers and their matched controls. In Mn smelting workers (geometric mean concentration of airborne Mn as MnO_2 in the air was 0.07 mg · m^{-3}) heart rate was significantly faster and P-R intervals were significantly shorter in female smelting workers than those of female controls.[28] QRS and T waves were also wider and of greater magnitude, respectively, in both male and female smelting workers than in controls. When the geometric mean concentrations of airborne MnO_2 in the working air ranged from 0.05 and 2.15 mg · m^{-3}, abnormal ECG incidence in workers was markedly increased compared to control subjects.[54] In addition, Mn-exposed workers displayed altered autonomic nervous function,[4,36] which may be indirectly related to other forms of Mn cardiotoxicity as cardiovascular function is tightly regulated by the autonomic nervous system.

Immunotoxicity

Although the adaptive immune system is activated, leading to macrophage recruitment and increased numbers of leukocytes following inhalation of Mn-laden particles, Mn compounds are not known to be immunotoxic. A study of welders exposed to 0.29–0.64 mg · m^{-3} inorganic Mn for an unknown amount of time revealed T and B lymphocyte suppression,[5] but the study was confounded by the fact that the workers were also exposed to other compounds, vibration, and noise, making it impossible to parse out the effect of the Mn alone.

Developmental Toxicity

Developmental effects, particularly neurological symptoms, occur in children exposed to high levels of Mn, but this information will not be covered in any further detail due to lack of relevance for astronaut crews.

Genotoxicity and Mutagenicity

Manganese (II) did not induce mutations in standard *Salmonella typhimurium* mutagenicity testing, regardless of whether exogenous metabolic activation occurred.[39] Another study reported sister chromatid exchange induction[23]; however, this test is fairly nonspecific and the positive result is less concerning without a positive Ames test.

Carcinogenicity

There has been no evidence that Mn compounds cause cancer in humans (IRIS: D, not classifiable; A4 designation). The Environmental Protection Agency (EPA) has indicated that Mn is not classifiable as to human carcinogenicity, meaning that existing scientific information cannot determine whether excess Mn can cause cancer.

CNS Spaceflight-Associated Factor

The combination of fluid shift and neurovestibular alterations resulting from exposure to microgravity causes an autonomic condition called "space motion sickness" (SMS), resulting in nausea, vomiting, headache, anorexia, pallor, etc. The incidence of SMS is approximately 70%.[12]

During missions, some astronauts have reported seeing flashes of light at night, which are thought to result from high-energy particles interacting with the eyes and brain. But formal studies specific to spaceflight are lacking. Laboratory studies have been conducted, but the majority have exposed smaller numbers of animals (< 10) to higher doses of radiation (annual galactic cosmic ray (GCR) dose $\sim$0.1 Gy/yr at solar maximum and $\sim$0.2 Gy/yr at solar minimum with $< 50\%$ from HZE particles) than what would be encountered in space. It has been estimated that an astronaut on a Mars mission will be cumulatively exposed to no more than 0.2 Gy/yr, with less than 50% from HZE particles.[13] No studies have been performed in which the exposure was chronic or with a mixed radiation field that occurs in space. Therefore, translating the results of these studies to human risk assessment is difficult.

It is known that individuals treated with cranial radiotherapy for the mitigation of brain malignancies develop severe and progressive cognitive deficits that are irreversible.[8,37] In space, concerns of acute and chronic risks to the CNS from galactic cosmic rays (GCRs) and solar proton events (SPEs) have been documented for human exploration.[11] Astronauts will be chronically exposed to low-LET electromagnetic radiation, in addition to the periodic GCR exposures. Although radiation dose and type differ substantially between clinical treatment and exposure in space, more recent research investigating the effects of space-relevant doses of charged particles has provided evidence that cognitive deficits occur and persist at lower levels than once thought.[6,53] At mission relevant doses (15–20 cGy of 1 GeV/nucleon ^{56}Fe particles), measures of executive function, including discriminatory and attention-based tasks, were significantly compromised in juvenile and socially mature rats.[6,35] Spatial learning and novel object recognition in rodents also were significantly impaired with exposure to 10–50 cGy of 1 GeV/nucleon ^{56}Fe and other species.[7,24] Although the mechanisms involved in CNS radiation damage are complex, recent studies suggest that low dose exposure compromises the structural complexity and synaptic integrity of mature neurons in rodents throughout different regions of the brain, affecting neurotransmission and cognitive performance.[42–44] Similar types of alterations have been shown to be the basis for a variety of neurodegenerative conditions that result in dementia.

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