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DRAFT BIBLIOGRAPHY OF

PROPOSED KEY LITERATURE FOR THE TOXICOLOGICAL REVIEW OF MANGANESE

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In Support of Summary Information on the Integrated Risk Information System (IRIS)

for

National Center for Environmental Assessment
U.S. ENVIRONMENTAL PROTECTION AGENCY
Research Triangle Park, North Carolina 27711

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TABLE OF CONTENTS

OVERVIEW

This document contains a summary description of the literature search process employed to support a toxicological review of manganese (Mn). The relevant articles identified in the literature search are then described in relation to the Toxicological Review template contents and the associated topics of interest.

SEARCH STRATEGY

Battelle performed a literature search that included a comprehensive investigation of the database sources listed in the work assignment. This list of sources included links to appropriate EPA health assessment documents, guidelines, articles offered in response to the Federal Register Notice, and source of other federal documents (e.g., U.S. Agency for Toxic Substances Disease Registry [ATSDR] Toxicological Profiles) that were used to identify information to assess the potential adverse human health effects that may occur from exposure to manganese. All sources were searched for the period covering 1995 to date. Because manganese is a chemical with both nutritional benefits and potential toxic effects, there was a large body of published literature available. To aid in the performance of more targeted literature searches, the Table of Contents of the Toxicological Review template was consulted for guidance in selection of search terms covering the subject areas of interest. In doing so, Battelle also ensured that the literature search addressed all health effects in animals and humans resulting from inhalation, oral, dermal, and intravenous exposure studies related to the assessment of cancer and non-cancer endpoints. Also of interest was literature addressing absorption, distribution, metabolism, and elimination studies that are relevant to the toxicity of manganese. The literature search also included all physiologically-based toxicokinetic models available for manganese. In addition, information was sought that might be specifically useful to addressing risks to children and other susceptible subgroups, including women. Finally, an attempt was made to ensure that the literature search product was inclusive of toxicological-type studies across all durations, including chronic (i.e., lifetime), less-than-lifetime, acute (single exposure in a single day), short-term (e.g., from 1 to 30 days) and subchronic (> 30 days < lifetime).

Studies identified in the searches of the various resources were reviewed for relevance and incorporated into an ENDNOTE™ library. The final review and curation of the ENDNOTE™ library for categorization and determination of principle studies was made by Justin Teeguarden, the task leader and a board certified toxicologist. Determination of relevancy was based on study abstracts or other detailed information found within the literature. Whenever possible, the determination of relevancy was not based solely on the study title.

ORGANIZATION OF RESULTS

No relevant, in-progress health assessment activities within EPA or other federal agencies were identified. Therefore, no summary documentation was submitted to the EPA WAM for review or is included in the summary reference list.

The literature search process resulted in 539 references identified as potentially relevant. Of those, 201 are categorized as potential key references with the remaining 338 serving as supporting references. The literature search product detailing all the key and supporting studies identified is provided in the following sections. This detailed description of the bibliography contents and a report on the resulting articles is structured in a manner consistent with the layout of the Table of Contents of the Toxicological Review template. Full reference citations are provided separately in Appendices in various formats. Appendix A contains the complete alphabetical list of 539 references without abstracts. Appendix B contains the list of proposed key studies without abstract divided by subject. Appendix C contains a similar list of supporting studies without abstract divided by subject. Appendix D contains a subject bibliography, in which each subject section provides a list of the relevant key and supporting references and their abstracts.

The lists of key references are proposed based on an evaluation of the abstract. However, additional evaluation of report contents for each reference will need to be performed to accurately access whether a study should be classified as a key study or if it instead provides supporting evidence. Battelle has made an effort to acquire readily available PDF copies of the key articles in the given time frame and is providing an electronic copy to EPA on the project Sharepoint site as agreed by the EPA WAM. However, given the large number of potential key studies identified, it was not possible to acquire copies of all the references. A list of the key studies Battelle was not able to acquire within the given time constraint and resources is provided in Appendix E of this report.

The complete list of 539 citations in an ENDNOTE™ Library is also being provided to EPA on the project Sharepoint site. Where available, links to electronic versions of selected literature retrieved in the search are included in the ENDNOTE™ Library.

Because of the large number of references identified and categorized, a table of contents is provided to aid in the navigation of this report of the results. As described above, the organization of the resulting references closely follows the organizational structure of the Toxicological Review template, with subcategory breakdowns where necessary.

SUBJECT BIBLIOGRAPHY FOR MANGANESE

1. INTRODUCTION

No specific studies were identified for this section. The EPA boilerplate text provided in the template should be used and tailored for the manganese search where appropriate.

2. CHEMICAL AND PHYSICAL INFORMATION

Information from review articles should largely be used to populate this section. A listing and discussion of the review articles can be found in section 4.6 of this report.

3. TOXICOKINETICS

The incorporation of toxicokinetic data in the risk assessment of manganese is complicated by its status as an essential micronutrient. Establishing normal levels of tissue and blood Mn are important because deficiency leads to specific pathologies. The toxicokinetics data here includes some human and rodent studies whose focus was not toxicokinetics, but contain information on normal blood and tissues levels of Mn.

Manganese tissue and blood concentrations are under strict, coordinated control of the liver and GI tract. A series of publications reporting the consequences of liver/GI tract disease or the bypass of liver/GI tract regulation of Mn on blood and tissue Mn are included (topic area: Liver/GI function). In vitro and in vivo studies of the role of divalent metal transporters on the cellular uptake of Mn are listed because they provide important insights into regulation of Mn uptake and disposition.

Publications in these two groupings are not listed as key studies because they do not report relationships between exposure/dose and tissue blood Mn time course. Nonetheless, they deserve review in the IRIS assessment.

The literature of relevance to this section is organized below into three categories: toxicokinetics, physiologically based pharmacokinetic models (PBPK) and Liver/GI Function.

3.1 TOXICOKINETICS

This section contains articles on toxicokinetics, excluding physiologically based toxicokinetic (PBPK) models and liver/GI function studies. For this topic, 72 key articles and 45 supplementary articles were identified.

3.2 PHYSIOLOGICALLY BASED TOXICOKINETIC MODELS

This section contains references associated with PBPK modeling. Seven key articles were identified on this topic but no supporting references were found.

3.3 LIVER/GI FUNCTION

There were no key studies identified in this grouping, but 12 supporting references on liver/GI function were found.

4. HAZARD IDENTIFICATION

All references found for this topic are divided into the following subsections of relevance.

4.1. STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, AND CLINICAL CONTROLS

This section contains epidemiological studies, case reports, and clinical controls but does not contain any kinetic studies. There were 34 key studies and 57 supporting references identified on this topic.

4.2. LESS-THAN-LIFETIME AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

Studies found for this section are divided into the following subsections.

4.2.1 Less-than-lifetime and Chronic Studies

Both subchronic and chronic studies are contained in this section. On this subject, 32 key references and 3 supporting references were found.

4.2.2 Cancer bioassays

No key or supporting studies concenring cancer bioassays were identified.

4.3. REPRODUCTIVE/DEVELOPMENTAL STUDIES—ORAL AND INHALATION

Studies with reproductive and developmental endpoints are combined for this study from both oral and inhalation exposures. There were 12 key studies and 93 supporting references identified on this topic.

4.4. OTHER ENDPOINT-SPECIFIC STUDIES [*e.g., in vivo neurological, immunological studies*]

Chronic and subchronic studies reporting or focused on neurological endpoints are reported in Section 4.2. No other key or supporting references discussing other standard endpoint specific studies were identified.

4.5 MECHANISTIC DATA AND OTHER STUDIES IN SUPPORT OF THE MODE OF ACTION [*e.g., in vitro and ex vivo studies using isolated target tissues/organs or cells, metabolite studies, genotoxicity, SAR, etc.*]

A large body of literature exploring possible mechanisms of Mn induced neurotoxicity has accumulated in the last decade. Because there appears to be no consensus regarding the MOA, it is not possible to separate key studies from the larger pool of mechanistic studies. We list as key studies, several important review articles and selected in vivo studies we felt should be the starting point for the review of literature on this topic. For this section there were 25 key studies and 146 supporting studies.

4.6. REVIEW ARTICLES

Review articles of general interest regarding risk assessment of Mn are listed below. These articles comprise those believed to be valuable but either are not associated with specific topics in the IRIS document or were not key studies in those topic areas. They may also provide content for the Background/Introduction Section. Eighteen key and 71 supporting studies were found.

APPENDIX A:

COMPLETE ALPHABETIZED BIBLIOGRAPHY
WITHOUT ABSTRACTS

All References in Alphabetical Order (539)

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APPENDIX B:

KEY REFERENCES BY SUBJECT

3.1 TOXICOKINETICS (72)

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3.3 LIVER/GI FUNCTION (0)

There were no key studies identified for this group.

4.1 STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS (34)

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No cancer bioassays were found.

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4.4 OTHER ENDPOINT-SPECIFIC STUDIES [e.g., in vivo neurological, immunological studies] (0)

No other standard endpoint specific studies were identified.

4.5 MECHANISTIC DATA AND OTHER STUDIES IN SUPPORT OF THE MODE OF ACTION (25)

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APPENDIX C:

SUPPORTING REFERENCES BY SUBJECT

3.1 TOXICOKINETICS (45)

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4.2 LESS-THAN-LIFETIME AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

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No supporting studies of cancer bioassays were found.

4.3 REPRODUCTIVE AND DEVELOPMENTAL STUDIES—ORAL AND INHALATION (93)

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4.4 OTHER ENDPOINT-SPECIFIC STUDIES [e.g., in vivo neurological, immunological studies] (0)

No other standard endpoint specific studies were identified.

4.5 MECHANISTIC DATA AND OTHER STUDIES IN SUPPORT OF THE MODE OF ACTION (146)

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APPENDIX D:

KEY AND SUPPORTING REFERENCES WITH ABSTRACTS BY SUBJECT

Key and Supporting References by Subject with Abstracts

3.1 TOXICOKINETICS

Key References (72)

1. Arnich N, Cunat L, Lanhers MC, Burnel D. (2004) Comparative in situ study of the intestinal absorption of aluminum, manganese, nickel, and lead in rats. Biological Trace Element Research 99(1-3):157-171.
This comparative study of the intestinal absorption of four toxic metals (aluminum, manganese, nickel, and lead) carried out in rats using the in situ intestinal perfusion technique was able to measure the partition of each metal between the intestine (intestinal retention), the blood circulation, and target tissues after 1 h. The perfused metal solutions were at concentrations likely to occur during oral intoxication. It was found that aluminum (48 and 64 mM), even as a citrate complex, crossed the brush border with difficulty (0.4% of the perfused amount); about 60% of this was retained in the intestine and the remainder was found in target tissues (about 36%). Conversely, lead (4.8-48 muM) penetrated the intestine more easily (about 35% of the perfused amount), was slightly retained (about 12% of the input), and was soon found in the tissues (about 58% of the input) and to a lesser degree in circulation (about 29%). Within the same concentration range, nickel and manganese showed certain similarities, such as a reduced crossing of the brush border proportional to the increase in the concentration perfused (0.17-9.5 mM). There was similar intestinal retention and absorption (about 80% and 20% of the input, respectively). Manganese crossed the brush border more easily and was diffused more rapidly into tissues. Finally, the addition of equimolar amounts of iron (4.7 mM) produced opposite effects on the absorption of the two elements, inhibiting manganese and showing a trend to increase in nickel absorption. This could be the result of competition between Fe2+ and Mn2+ for the same transcellular transporters and the slight predominance of paracellular mechanism in the event of "Fe2+-Ni2+" association.

2. Aschner M. (2005) Manganese transport, toxicity and speciation in the CNS. Journal of Neurochemistry 94:8-8.

3. Aschner M. (2006) The transport of manganese across the blood-brain barrier. Neurotoxicology 27(3):311-314.
The mammalian central nervous system (CNS) possesses a unique and specialized capillary adaptation, referred to as the blood-brain barrier (BBB). The BBB maintains an optimal neuronal microenvironment, regulating blood-tissue exchange of macromolecules and nutrients. The BBB is characterized by individual endothelial cells that are continuously linked by tight junctions, inhibiting the diffusion of macromolecules and solutes between adjacent endothelial cells. This review will focus on pertinent issues to BBB maintenance. and survey recent dogmas on the transport mechanisms for the essential metal, manganese, across this barrier. Specifically, putative carriers for manganese into and out of the brain will be discussed.

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The use of methylcyclopentadienyl manganese tricarbonyl (MMT) in unleaded gasoline has given rise to numerous debates on the potential public health risk associated with manganese emissions. In fact, combustion products are mainly Mn phosphate, Mn sulfate, and Mn phosphate/sulfate mixture. Our research group did several inhalation studies in order to assess the toxicity of each Mn species. The objective of this study is to determine the physical and the chemical characteristics of a mixture of Mn phosphate/sulfate used in one of these inhalation toxicology studies. First, the mixture was analyzed by X-ray diffraction in order to obtain the specific peak of Mn phosphate and Mn sulfate. These peaks were used as reference. Second, samples of the mixture were collected on filters in the inhalation chamber at a concentration level of 3000 mug/m(3). They were analyzed by scanning electron microscopy (SEM), analytical transmission electron microscopy (ATEM), and x-ray energy-dispersive spectrometry (EDS) to show their size, morphology, and chemical composition. Results indicate that 33% of the particles were found to be agglomerated, while free particles accounted for 44% for Mn phosphate and 23% for Mn sulfate.

6. Brain JD, Heilig E, Donaghey TC, Knutson MD, Wessling-Resnick M, Molina RM. (2006) Effects of iron status on transpulmonary transport and tissue distribution of Mn and Fe. American Journal of Respiratory Cell and Molecular Biology 34(3):330-337.
Manganese transport into the blood can result from inhaling metal-containing particles. Intestinal manganese and iron absorption is mediated by divalent metal transporter 1 (DMT1) and is upregulated in iron deficiency. Since iron status alters absorption of Fe and Mn in the gut, we tested the hypothesis that iron status may alter pulmonary transport of these metals. DMT1 expression in the lungs was evaluated to explore its role in metal transport. The pharmacokinetics of intratracheally instilled Mn-54 or Fe-59 in repeatedly bled or iron oxide-exposed rats were compared with controls. Iron oxide exposure caused a reduction in pulmonary transport of Mn-54 and Fe-59, and decreased uptake in other major organs. Low iron status from repeated bleeding also reduced pulmonary transport of iron but not of manganese. However, uptake of manganese in the brain and of iron in the spleen increased in bled rats. DMT1 transcripts were detected in airway epithelium, alveolar macrophages, and bronchial-associated lymphoid tissue in all rats. Focal increases were seen in particle-containing macrophages and adjacent epithelial cells, but no change was observed in bled rats. Although lung DMT1 expression did not correlate with iron status, differences in pharmacokinetics of instilled metals suggest that their potential toxicity can be modified by iron status.

7. Brenneman KA, Cattley RC, Ali SF, Dorman DC. (1999) Manganese-induced developmental neurotoxicity in the CD rat: Is oxidative damage a mechanism of action? Neurotoxicology 20(2-3):477-487.
Inhalation of high concentrations of manganese (Mn) is associated with an extrapyramidal motor disorder in humans. Oxidative damage, mediated by increased levels of Mn in dopaminergic brain regions and mitochondria, is a hypothesized mechanism of action for Mn-induced neuronal degeneration and loss. To test this proposed mechanism, developing CD rats, which may be at an increased risk for Mn-induced neurotoxicity, were exposed orally to 0, 25, or 50 mg/kg/day of

MnCl2 from postnatal day (PND) I to 49 Brain regional and mitochondrial Mn levels, brain regional reactive oxygen species (ROS) levels, and whole-brain nuclear and mitochondrial 8-OHdG levels were used to evaluate Mn-mediated oxidative damage. High-dose Mn exposure was associated with increased spontaneous motor activity on PND 21 and decreased body weights on PND 49. On PND 21, Mn concentrations were increased in brain regions and mitochondrial fractions in both low- and high-dose groups. ROS levels were elevated in cerebellum but not striatum. On PND 49, Mn concentrations in brain regions and mitochondrial fractions were increased only in the high-dose group. Mn exposure did not significantly alter 8-OHdG levels in either mitochondrial or nuclear DNA. Selective uptake of Mn by the striatum or mitochondrial fraction was not demonstrated at either time point. These data allow us to conclude that oral exposure to high levels of Mn in developing CD rats resulted in increased brain regional and mitochondrial Mn levels, increased motor activity, and decreased body weights but not in selective accumulation of Mn in the striatum or mitochondr ial fraction of any brain region or elevations in striatal ROS or whole-brain 8-OHdG levels. These findings do not support the hypothesis that oxidative damage, as assessed by ROS and 8-OHdG levels, is a mechanism of action in Mn-induced developmental neurotoxicity in the CD rat. (C) 1999 Inter Press, Inc.

8. Brenneman KA, Wong BA, Buccellato MA, Costa ER, Gross EA, Dorman DC. (2000) Direct olfactory transport of inhaled manganese ((MnCl2)-Mn-54) to the rat brain: Toxicokinetic investigations in a unilateral nasal occlusion model. Toxicology and Applied Pharmacology 169(3):238-248.

Inhalation exposure of humans to high concentrations of manganese (Mn) is associated with elevated Mn levels in the basal ganglia and an extrapyramidal movement disorder. In the rat, direct olfactory transport of Mn from the nose to the brain has been demonstrated following intranasal instillation of (MnCl2)-Mn-54. However, the contribution this route makes to brain Mn delivery following inhalation is unknown and was the subject of our study. Male 8-week old CD rats underwent a single 90-min nose-only exposure to a (MnCl2)-Mn-54 aerosol (0.54 mg Mn/m(3); MMAD 2.51 mum). The left and right sides of the nose and brain, including the olfactory pathway and striatum, were sampled at 0, 1, 2, 4, and 8 days postexposure. Control rats were exposed to (MnCl2)-Mn-54 with both nostrils patent to evaluate the symmetry of Mn delivery. Another group of rats had the right nostril plugged to prevent nasal deposition of (MnCl2)-Mn-54 on the occluded side. Gamma spectrometry (n = 6 rats/group/time point) and autoradiography (n 1 rat/group/time point) were used to compare the levels of Mn-54 found on the left and right sides of the nose and brain to determine the contribution of olfactory uptake to brain Mn-54 levels. Brain and nose samples from the side with the occluded nostril had negligible levels of Mn-54 activity, validating the nasal occlusion procedure. High levels of Mn-54 were observed in the olfactory bulb and tract/tubercle on the side or sides with an open nostril within 1-2 days following inhalation exposure. These results demonstrated, for the first time, that the olfactory route contributes the majority (up to > 90%) of the Mn-54 found in the olfactory pathway, but not in the striatum, of the rat brain up to 8 days following a single inhalation exposure. These findings suggest that the olfactory route may make a significant contribution to brain Mn levels following inhalation exposure in the rat. (C) 2000 Academic Press.

9. Chen MK, Lee JS, McGlothan JL, Furukawa E, Adams RJ, Alexander M, Wong DF, Guilarte TR. (2006) Acute manganese administration alters dopamine transporter levels in the non-human primate striatum. Neurotoxicology 27(2):229-236.
We used positron emission tomography (PET) to measure non-invasively the effect of acute systemic administration to manganese sulfate (MnSO4) on dopamine transporter (DAT) levels in the living non-human primate brain. Baboons received [C-11]-WIN 35,428 PET scans to measure DAT levels before and after acute MnSO4 administration. In one animal, we observed a 46% increase in DAT binding potential (BP), a measure of DAT binding site availability, I week after Mn administration. DAT levels returned to baseline values at 4 months and remained constant at 10 months after treatment. A subsequent single MnSO4 injection to the same animal also resulted in a 57% increase in DAT-BP, 2 days after administration. In a second animal, a 76% increase in DAT-BP relative to baseline was observed at 3 days after Mn injection. In this animal, the DAT-BP returned to baseline levels after I month. Using in vitro receptor binding assays, we found that Mn inhibits [H-3]-WIN 35,428 binding to rat striatal DAT with an inhibitory constant (K-i) of 2.0 +/- 0.3 mM (n = 4). Saturation isotherms and Scatchard analysis of [H-3]-WIN 35,428 binding to rat striatal DAT showed a significant decrease (30%, $p < 0.001$) in the maximal number of binding sites (B-max) in the presence of 2 mM MnSO4. No significant effect of Mn was found on binding affinity (K-d). We also found that Mn inhibits [H-3]-dopamine uptake with an IC50 of 11.4 +/- 1.5 mM (n = 4). Kinetic studies and Lineweaver-Burk analysis showed a significant decrease (40%, $p < 0.001$) in the maximal velocity of uptake (V-max) with 5 mM MnSO4. No significant effect of Mn was found on Michael is-Menton constant (K-m). These in vitro findings Suggest that the increase in DAT levels in vivo following acute Mn administration may be a compensatory response to its inhibitory action on DAT. These findings provide helpful insights on potential mechanisms of Mn-induced neurotoxicity and indicate that the DAT in the striatum is a target for Mn in the brain.

10. Chen MT, Cheng GW, Lin CC, Chen BH, Huang YL. (2006) Effects of acute manganese chloride exposure on lipid peroxidation and alteration of trace metals in rat brain. Biological Trace Element Research 110(2):163-177.
Although manganese (Mn) is an essential element, exposure to excessive levels of Mn and its accumulation in the brain can cause neurotoxicity and extrapyramidal syndrome. We have investigated the differences in the accumulated levels of Mn, the degree of lipid peroxidation, and its effects on the levels of trace elements (Fe, Cu, and Zn) in various regions in the brain of rats having undergone acute Mn exposure. The rats in the dose-effect group were injected intraperitoneally (ip) with MnCl2 (25, 50, or 100 mg MnCl2/kg) once a day for 24 h. The Mn significantly accumulated ($p < 0.05$) in the frontal cortex, corpus callosum, hippocampus, striatum, hypothalamus, medulla, cerebellum, and spinal cord in each case. The rats in the time-course group were ip injected with MnCl2 (50 mg MnCl2/kg) and then monitored 12, 24, 48, and 72 h after exposure. The Mn accumulated in the frontal cortex, corpus callosum, hippocampus, striatum hypothalamus, medulla, cerebellum, and spinal cord after these periods of time, In both the dose-effect and time-course studies, we observed that the concentration of malondialdehyde, an end product of lipid peroxidation, increased significantly in the frontal cortex, hippocampus, striatum, hypothalamus, medulla, and cerebellum. However, no relationship between the concentrations of Mn in the brain and the extent of lipid peroxidation was observed. In addition, we found that there was a significant increase ($p < 0.05$) in the level of Fe in the hippocampus,

striatum, hypothalamus, medulla, and cerebellum, but the Cu and Zn levels had not changed significantly. These findings indicated that Mn induces an increase in the iron level, which provides direct evidence for Fe-mediated lipid peroxidation in the rats' brains; these phenomena might play important roles in the mechanisms of Mn-induced neurotoxicology.

11. Chen MT, Yiin SJ, Sheu JY, Huang YL. (2002) Brain lipid peroxidation and changes of trace metals in rats following chronic manganese chloride exposure. Journal of Toxicology and Environmental Health-Part A 65(3-4):305-316.
The aim of this study was to investigate the effects of chronic daily, 30-d administration of manganese chloride (MnCl2) to male Sprague-Dawley rats on lipid peroxidation and changes of trace elements (manganese, iron, copper, zinc) in various brain regions. Rats were intraperitoneally injected with MnC2 (20 mg/kg) once daily for 30 consecutive days. The Mn accumulated in frontal cortex, corpus callosum, hippocampus, striatum, hypothalamus, medulla, cerebellum, and spinal cord. Malondialdehyde, an end product of lipid peroxidation, was markedly decreased in frontal cortex and cerebellum. An increased level of Cu was observed in frontal cortex, medulla, and a cerebellum. A decreased Fe level was found only in cerebellum, and a decreased Zn level was observed in hippocampus and striatum. In a second group of animals, Mn (20 mg/kg/d) and glutathione (CSH, 75 mg/kg/d) were administered ip for 30 d. In CSH-Mn-treated rats, compared to Mn-treated rats, MDA concentrations were significantly reduced in frontal cortex, medulla and cerebellum. The changes of trace elements in rat brain were similar to the Mn-treated group. We suggest that Mn is an atypical antioxidant, as well as not involved in oxidative damage in rat brain. Fe and Cu may play roles in the protective effect of Mn against lipid peroxidation in rat brain.

12. Chua ACG, Morgan EH. (1996) Effects of iron deficiency and iron overload on manganese uptake and deposition in the brain and other organs of the rat. Biological Trace Element Research 55(1-2):39-54.
Manganese (Mn) is an essential trace element at low concentrations, but at higher concentrations is neurotoxic. It has several chemical and biochemical properties similar to iron (Fe), and there is evidence of metabolic interaction between the two metals, particularly at the level of absorption from the intestine. The aim of this investigation was to determine whether Mn and Fe interact during the processes involved in uptake from the plasma by the brain and other organs of the rat. Dams were fed control (70 mg Fe/kg), Fe-deficient (5-10 mg Fe/kg), or Fe-loaded (20 g carbonyl Fe/kg) diets, with or without Mn-loaded drinking water (2 g Mn/L), from day 18-19 of pregnancy, and, after weaning the young rats, were continued on the same dietary regimens. Measurements of brain, liver, and kidney Mn and nonheme Fe levels, and the uptake of Mn-54 and Fe-59 from the plasma by these organs and the femurs, were made when the rats were aged 15 and 63 d. Organ nonheme Fe levels were much higher than Mn levels, and in the liver and kidney increased much more with Fe loading than did Mn levels with Mn loading. However, in the brain the increases were greater for Mn. Both Fe depletion and loading led to increased brain Mn concentrations in the 15-d/rats, while Fe loading also had this effect at 63 d. Mn loading did not have significant effects on the nonheme Fe concentrations. Mn-54, injected as MnCl2 mixed with serum, was cleared more rapidly from the circulation than was Fe-59, injected in the form of diferric transferrin. In the 15-d-rats, the uptake of Mn-54 by brain, liver, kidneys, and femurs was increased by Fe loading, but this was not seen in the 63-d rats. Mn supplementation led to increased Fe-59 uptake by the brain, Liver, and kidneys of the rats fed the control and Fe-

deficient diets, but not in the Fe-loaded rats. It is concluded that Mn and Fe interact during transfer from the plasma to the brain and other organs and that this interaction is synergistic rather than competitive in nature. Hence, excessive intake of Fe plus Mn may accentuate the risk of tissue damage caused by one metal alone, particularly in the brain.

13. Crossgrove JS, Allen DD, Bukaveckas BL, Rhineheimer SS, Yokel RA. (2003) Manganese distribution across the blood-brain barrier I. Evidence for carrier-mediated influx of manganese citrate as well as manganese and manganese transferrin. Neurotoxicology 24(1):3-13.
Manganese (Mn) is an essential element and a neurotoxicant. Regulation of Mn movement across the blood-brain barrier (BBB) contributes to whether the brain Mn concentration is functional or toxic. In plasma, Mn associates with water small molecular weight ligands and proteins. Mn speciation may influence the kinetics of its movement through the BBB. In the present work, the brain influx rates of Mn-54(2+), Mn-54 citrate and Mn-54 transferrin (54) Mn Tf) were determined using the in situ brain perfusion technique. The influx rates were compared to their predicted diffusion rates, which were determined from their octanol/aqueous partitioning coefficients and molecular weights. The in situ brain perfusion fluid contained (54) Mn2+, (54) Mn citrate or (54) Mn Tf and a vascular volume/extracellular space marker C-14-sucrose, which did not appreciably cross the BBB during these short experiments (15-180 s). The influx transfer coefficient (K-in) was determined from four perfusion durations for each Mn species in nine brain regions and the lateral ventricular choroid plexus. The brain K-in was (5-13) X 10(-5), (3-51) x 10(-5) and (2-13) X 10(-5) Mn-54 citrate, and Mn-54 Tf respectively. Brain K-in values for any one of the three Mn species generally did not significantly differ among the nine brain regions and the choroid plexus. However the brain Kin for Mn citrate was greater than Mn2+ and Mn Tf K-in values in a number of brain regions. When compared to calculated diffusion rates, brain K-in values suggest carrier-mediated brain influx of Mn-54(2+), Mn-54 citrate and Mn-54 Tf. Mn-55 citrate inhibited Mn-54 citrate uptake, and Mn-55(2+) inhibited Mn-54(2+) Uptake, supporting the conclusion o carrier-mediated brain Mn influx. The greater Kin values for Mn citrate than Mn2+ and its presence as a major non-protein-bound Mn species in blood plasma suggest Mn citrate may be a major Mn species entering the brain.

14. Dorman DC. (2003) Metal speciation in human health risk assessment: Challenges posed by manganese, iron, and other essential nutrients. Toxicological Sciences 72:117-117.

15. Dorman DC, McElveen AM, Marshall MW, Parkinson CU, James RA, Struve MF, Wong BA. (2005) Tissue manganese concentrations in lactating rats and their offspring following combined in utero and lactation exposure to inhaled manganese sulfate. Toxicological Sciences 84(1):12-21.
There is little information regarding the tissue distribution of manganese in neonates following inhalation. This study determined tissue manganese concentrations in lactating CD rats and their offspring following manganese sulfate (MnSO4) aerosol inhalation. Except for the period of parturition, dams and their offspring were exposed to air or MnSO4 (0.05, 0.5, or 1 mg Mn/m(3)) for 6 h/day, 7 days/week starting 28 days prior to breeding through postnatal day (PND) 18. Despite increased manganese concentrations in several maternal tissues, MnSO4 inhalation exposure did not affect body weight gain, terminal (PND 18) body weight, or organ weights in the dams. Exposure to MnSO4 at 1 mg Mn/m(3) resulted in decreased pup body weights on PND

19 and decreased brain weights in some PND 14 to PND 45 pups. Exposure to MnSO4 at similar to 0.05 mg Mn/m(3) was associated with increased stomach content, blood, liver, and skull cap manganese concentrations in PND 1 pups, increased brain, lung, and femur manganese concentrations in PND 14 pups, and elevated olfactory bulb, cerebellum, and striatum manganese concentrations in PND 19 pups. When compared to controls, MnSO4 exposure to greater than or equal to 0.5 mg Mn/m(3) increased liver and blood manganese concentrations in PND 14 pups and increased liver, pancreas, and femur manganese concentrations in PND 19 pups. Manganese concentrations returned to control values in all offspring tissues by PND 45 +/- 1. Our data demonstrate that neonatal tissue manganese concentrations observed following MnSO4 inhalation are dependent on the MnSO4 exposure concentration and the age of the animal.

16. Dorman DC, McManus BE, Marshall MW, James RA, Struve MF. (2004) Old age and gender influence the pharmacokinetics of inhaled manganese sulfate and manganese phosphate in rats. Toxicology and Applied Pharmacology 197(2):113-124.
In this study, we examined whether gender or age influences the pharmacokinetics of manganese sulfate (MnSO4) or manganese phosphate (as the mineral form hureaulite). Young male and female rats and aged male rats (16 months old) were exposed 6 h day(-1) for 5 days week(-1) to air, MnSO4 (at 0.01, 0.1, or 0.5 mg Mn m(-3)), or hureaulite (0.1 mg Mn m(-3)). Tissue manganese concentrations were determined in all groups at the end of the 90-day exposure and 45 days later. Tissue manganese concentrations were also determined in young male rats following 32 exposure days and 91 days after the 90-day exposure. Intravenous 54 Mn tracer studies were also performed in all groups immediately after the 90-day inhalation to assess whole-body manganese clearance rates. Gender and age did not affect manganese delivery to the striatum, a known target site for neurotoxicity in humans, but did influence manganese concentrations in other tissues. End-of-exposure olfactory bulb, lung, and blood manganese concentrations were higher in young male rats than in female or aged male rats and may reflect a portal-of-entry effect. Old male rats had higher testis but lower pancreas manganese concentrations when compared with young males. Young male and female rats exposed to MnSO4 at 0.5 mg Mn m-3 had increased 54 Mn clearance rates when compared with air-exposed controls, while senescent males did not develop higher 54 Mn clearance rates. Data from this study should prove useful in developing dosimetry models for manganese that consider age or gender as potential sensitivity factors. (C) 2004 Elsevier Inc. All rights reserved.

17. Dorman DC, McManus BE, Parkinson CU, Manuel CA, McElveen AM, Everitt JI. (2004) Nasal toxicity of manganese sulfate and manganese phosphate in young male rats following subchronic (13-week) inhalation exposure. Inhalation Toxicology 16(6-7):481-488.
Growing evidence suggests that nasal deposition and transport along the olfactory nerve represents a route by which inhaled manganese and certain other metals are delivered to the rodent brain. The toxicological significance of olfactory transport of manganese remains poorly defined. In rats, repeated intranasal instillation of manganese chloride results in injury to the olfactory epithelium and neurotoxicity as evidenced by increased glial fibrillary acidic protein (GFAP) concentrations in olfactory bulb astrocytes. The purpose of the present study was to further characterize the nasal toxicity of manganese sulfate (MnSO4) and manganese phosphate (as hureaulite) in young adult male rats following subchronic (90-day) exposure to air, MnSO4 (0.01, 0.1, and 0.5 mg Mn/m(3)), or hureaulite (0.1 mg Mn/m(3)). Nasal pathology, brain GFAP

levels, and brain manganese concentrations were assessed immediately following the end of the 90-day exposure and 45 days thereafter. Elevated end-of-exposure olfactory bulb, striatum, and cerebellum manganese concentrations were observed following MnSO4 exposure to greater than or equal to0.01, greater than or equal to0.1, and 0.5 mg Mn/m(3), respectively. Exposure to MnSO4 or hureaulite did not affect olfactory bulb, cerebellar, or striatal GFAP concentrations. Exposure to MnSO4 (0.5 mg Mn/m(3)) was also associated with reversible inflammation within the nasal respiratory epithelium, while the olfactory epithelium was unaffected by manganese inhalation. These results confirm that high-dose manganese inhalation can result in nasal toxicity (irritation) and increased delivery of manganese to the brain; however, we could not confirm that manganese inhalation would result in altered brain GFAP concentrations.

18. Dorman DC, Struve MF, James RA, Marshall MW, Parkinson CU, Wong BA. (2001) Influence of particle solubility on the delivery of inhaled manganese to the rat brain: Manganese sulfate and manganese tetroxide pharmacokinetics following repeated (14-day) exposure. Toxicology and Applied Pharmacology 170(2):79-87.
Dissolution rate can influence the pulmonary clearance of a metal and thus affect its delivery to the brain and other organs. The goal of this study was to determine the exposure-response relationship for the relatively soluble sulfate (MnSO4) and insoluble tetroxide (Mn3O4) forms of inhaled manganese in adult male CD rats. Rats were exposed 6 h/day for 7 days/week (14 exposures) to either MnSO4 or Mn3O4 at 0, 0.03, 0.3, or 3 mg Mn/m(3). End-of-exposure olfactory bulb, striatum, cerebellum, bile, lung, liver, femur, serum, and testes (n = 6 rats/concentration/chemical) manganese concentrations and whole-body Mn-54 elimination were then determined. Increased whole-body Mn-54 clearance rates were observed in animals from the high-dose (3 mg Mn/m3) MnSO4 and Mn3O4 exposure groups. Elevated manganese concentrations in the lung were observed following MnSO4 and Mn3O4 exposure to greater than or equal to0.3 mg Mn/m(3). Increased olfactory bulb and femur manganese concentrations were also observed following MnSO4 exposure at greater than or equal to0.3 mg Mn/m(3). Elevated striatal, testes, liver, and bile manganese concentrations were observed following exposure to MnSO4 at 3 mg Mn/m(3). Elevated olfactory bulb, striatal, femur, and bile manganese concentrations were observed following exposure to Mn3O4 at 3 mg Mn/m(3). Animals exposed to MnSO4 (3 mg Mn/m(3)) had lower lung and higher olfactory bulb and striatal manganese concentrations compared with levels achieved following similar Mn3O4 exposures. Our results suggest that inhalation exposure to soluble forms of manganese results in higher brain manganese concentrations than those achieved following exposure to an insoluble form of manganese. (C) 2001 Academic Press.

19. Dorman DC, Struve MF, James RA, McManus BE, Marshall MW, Wong BA. (2001) Influence of dietary manganese on the pharmacokinetics of inhaled manganese sulfate in male CD rats. Toxicological Sciences 60(2):242-251.
Concerns exist as to whether individuals with relative manganese deficiency or excess may be at increased risk for manganese toxicity following inhalation exposure. The objective of this study was to determine whether manganese body burden influences the pharmacokinetics of inhaled manganese sulfate (MnSO4,). Postnatal day (PND) 10 rats were placed on either a low (2 ppm), sufficient (10 ppm), or high (100 ppm) manganese diet. The feeding of the 2 ppm manganese diet was associated with a number of effects, including reduced body weight gain, decreased liter manganese concentrations, and reduced whole-body manganese clearance rates. Beginning on

PND 77 +/- 2, male littermates were exposed 6 h/day for 14 consecutive days to 0, 0.092, or 0.92 mg MnSO4/m(3). End-of-exposure tissue manganese concentrations and whole-body Mn-54 elimination rates were determined. Male rats exposed to 0.092 mg MnSO4/m(3) had elevated lung manganese concentrations when compared to air-exposed male rats. Male rats exposed to 0.92 mg MnSO4/m(3) developed increased striatal, lung, and bile manganese concentrations when compared to air-exposed male rats. There were no significant interactions between the concentration of inhaled MnSO4 and dietary manganese level on tissue manganese concentrations. Rats exposed to 0.92 mg MnSO4/m(3) also had increased Mn-54 clearance rates and shorter initial phase elimination half-lives when compared with air-exposed control rats. These results suggest that, marginally manganese-deficient animals exposed to high levels of inhaled manganese compensate by increasing biliary manganese excretion. Therefore, they do not appear to be at increased risk for elevated brain manganese concentrations.

20. Dorman DC, Struve MF, Marshall MW, Parkinson CU, James RA, Wong BA. (2006) Tissue manganese concentrations in young male rhesus monkeys following subchronic manganese sulfate inhalation. Toxicological Sciences 92(1):201-210.
High-dose human exposure to manganese results in manganese accumulation in the basal ganglia and dopaminergic neuropathology. Occupational manganese neurotoxicity is most frequently linked with manganese oxide inhalation; however, exposure to other forms of manganese may lead to higher body burdens. The objective of this study was to determine tissue manganese concentrations in rhesus monkeys following subchronic (6 h/day, 5 days/week) manganese sulfate (MnSO4) inhalation. A group of monkeys were exposed to either air or MnSO4 (0.06, 0.3, or 1.5 mg Mn/m(3)) for 65 exposure days before tissue analysis. Additional monkeys were exposed to MnSO4 at 1.5 mg Mn/m(3) for 15 or 33 exposure days and evaluated immediately thereafter or for 65 exposure days followed by a 45- or 90-day delay before evaluation. Tissue manganese concentrations depended upon the aerosol concentration, exposure duration, and tissue. Monkeys exposed to MnSO4 at >= 0.06, mg Mn/m(3) for 65 exposure days or to MnSO4 at 1.5 mg Mn/m(3) for >= 15 exposure days developed increased manganese concentrations in the olfactory epithelium, olfactory bulb, olfactory cortex, globus pallidus, putamen, and cerebellum. The olfactory epithelium, olfactory bulb, globus pallidus, caudate, putamen, pituitary gland, and bile developed the greatest relative increase in manganese concentration following MnSO4 exposure. Tissue manganese concentrations returned to levels observed in the air-exposed animals by 90 days after the end of the subchronic MnSO4 exposure. These results provide an improved understanding of MnSO4 exposure conditions that lead to increased concentrations of manganese within the nonhuman primate brain and other tissues.

21. Dorman DC, Struve MF, Wong BA. (2002) Brain manganese concentrations in rats following manganese tetroxide inhalation are unaffected by dietary manganese intake. Neurotoxicology 23(2):185-195.
Manganese-deficient individuals hate decreased manganese elimination. This observation has prompted suggestions that relative manganese deficiency may increase the risk for manganese neurotoxicity following inhalation exposure. The objective of this study was to determine whether dietary manganese intake influences the pharmacokinetics of inhaled manganese tetroxide (Mn3O4). Postnatal day (PND) 10 rats were placed on either a low (2 ppm), sufficient (10 ppm), or high-normal (700 ppm) manganese diet for 2 months. Beginning on PND 77 +/- 2, male littermates were exposed 6 h per day for 14 consecutive days to 0, 0.042, or 0.42 mg

Mn3O4/m(3). End-of-exposure tissue manganese concentrations and whole-body Mn-54 elimination rates were determined. Tissue manganese concentrations were dependent on the dietary intake of manganese, thus confirming that altered hepatic manganese disposition or metabolism occurred. Male rats given 100 ppm manganese diet developed increased manganese concentrations in the femur; liver, and bile and had elevated whole-body Mn-54 clearance rates when compared to animals given 2 ppm manganese diet. Male rats exposed to 0.42 mg Mn3O4/m(3) had increased manganese concentrations in the olfactory bulb, lung, liver, and bile when compared to air-exposed male rats. A significant interaction between the concentration of inhaled Mn3O4 and dietary manganese level was observed only with the end-of-exposure liver manganese concentration. Our results indicate that animals maintained on either a manganese-deficient or high manganese diet do not appear to be at increased risk for elevated brain manganese concentrations following inhalation exposure to high levels of Mn3O4. (C) 2002 Elsevier Science Inc. All rights reserved.

22. Dorman DC, Struve MF, Wong BA, Dye JA, Robertson ID. (2006) Correlation of brain magnetic resonance imaging changes with pallidal manganese concentrations in rhesus monkeys following subchronic manganese inhalation. Toxicological Sciences 92(1):219-227.
High-dose manganese exposure is associated with parkinsonism. Because manganese is paramagnetic, its relative distribution within the brain can be examined using magnetic resonance imaging (MRI). Herein, we present the first comprehensive study to use MRI, pallidal index (PI), and T-1 relaxation rate (R1) in concert with chemical analysis to establish a direct association between MRI changes and pallidal manganese concentration in rhesus monkeys following subchronic inhalation of manganese sulfate (MnSO4). Monkeys exposed to MnSO4 at >= 0.06 mg Mn/m(3) developed increased manganese concentrations in the globus pallidus, putamen, olfactory epithelium, olfactory bulb, and cerebellum. Manganese concentrations within the olfactory system of the MnSO4-exposed monkeys demonstrated a decreasing rostralcaudal concentration gradient, a finding consistent with olfactory transport of inhaled manganese. Marked MRI signal hyperintensities were seen within the olfactory bulb and the globus pallidus; however, comparable changes could not be discerned in the intervening tissue. The R1 and PI were correlated with the pallidal manganese concentration. However, increases in white matter manganese concentrations in MnSO4-exposed monkeys confounded the PI measurement and may lead to underestimation of pallidal manganese accumulation. Our results indicate that the R1 can be used to estimate regional brain manganese concentrations and may be a reliable biomarker of occupational manganese exposure. To our knowledge, this study is the first to provide evidence of direct olfactory transport of an inhaled metal in a non-human primate. Pallidal delivery of manganese, however, likely arises primarily from systemic delivery and not directly from olfactory transport.

23. Elder A, Gelein R, Silva V, Feikert T, Opanashuk L, Carter J, Potter R, Maynard A, Finkelstein J, Oberdorster G. (2006) Translocation of inhaled ultrafine manganese oxide particles to the central nervous system. Environmental Health Perspectives 114(8):1172-1178.
BACKGROUND: Studies in monkeys with intranasally instilled gold ultrafine particles (UFPs; < 100 nm) and in rats with inhaled carbon UFPs suggested that solid UFPs deposited in the nose travel along the olfactory nerve to the olfactory bulb. METHODS: To determine if olfactory translocation occurs for other solid metal UFPs and assess potential health effects, we exposed groups of rats to manganese (Mn) oxide UFPs (30 nm; similar to 500 mu g/m(3)) with either

both nostrils patent or the right nostril occluded. We analyzed Mn in lung, liver, olfactory bulb, and other brain regions, and we performed gene and protein analyses. RESULTS: After 12 days of exposure with both nostrils patent, Mn concentrations in the olfactory bulb increased 3.5-fold, whereas lung Mn concentrations doubled; there were also increases in striaturn, frontal cortex, and cerebellum. Lung lavage analysis showed no indications of lung inflammation, whereas increases in olfactory bulb tumor necrosis factor-alpha mRNA (similar to 8-fold) and protein (similar to 30-fold) were found after 11 days of exposure and, to a lesser degree, in other brain regions with increased Mn levels. Macrophage inflammatory protein-2, glial fibrillary acidic protein, and neuronal cell adhesion molecule mRNA were also increased in olfactory bulb. With the right nostril occluded for a 2-day exposure, Mn accumulated only in the left olfactory bulb. Solubilization of the Mn oxide UFPs was < 1.5% per day. CONCLUSIONS: We conclude that the olfactory neuronal pathway is efficient for translocating inhaled Mn oxide as solid UFPs to the central nervous system and that this can result in inflammatory changes. We suggest that despite differences between human and rodent olfactory systems, this pathway is relevant in humans.

24. Erikson KA, Shihabi ZK, Aschner JL, Aschner M. (2002) Manganese accumulates in iron-deficient rat brain regions in a heterogeneous fashion and is associated with neurochemical alterations. Biological Trace Element Research 87(1-3):143-156.
Previous studies have shown that iron deficiency (ID) increases brain manganese (Mn), but specific regional changes have not been addressed. Weanling rats were fed one of three semipurified diets: control (CN), iron deficient (ID), or iron deficient/ manganese fortified (IDMn+). Seven brain regions were analyzed for Mn concentration and amino acid (glutamate, glutamine, taurine, gamma-aminobutyric acid) concentrations. Both ID and IDMn+ diets caused significant ($p<0.05$) increases in Mn concentration across brain regions compared to CN. The hippocampus was the only brain region in which the IDMn+ group accumulated significantly more Mn than both the CN and ID groups. ID significantly decreased GABA concentration in hippocampus, caudate putamen, and globus pallidus compared to CN rats. Taurine was significantly increased in the substantia nigra of the IDMn+ group compared to both ID and CN. ID also altered glutamate and glutamine concentrations in cortex, caudate putamen, and thalamus compared to CN. In the substantia nigra, Mn concentration positively correlated with increased taurine concentration, whereas in caudate putamen, Mn concentration negatively correlated with decreased GABA. These data show that ID is a significant risk factor for central nervous system Mn accumulation and that some of the neurochemical alterations associated with ID are specifically attributable to Mn accumulation.

25. Erikson KA, Syversen T, Steinnes E, Aschner M. (2004) Globus pallidus: a target brain region for divalent metal accumulation associated with dietary iron deficiency. Journal of Nutritional Biochemistry 15(6):335-341.
Recently, iron deficiency has been connected with a heterogeneous accumulation of manganese in the rat brain. The striatum is particularly vulnerable, for there is a significant negative correlation between accumulated manganese and gamma-aminobutyric acid levels. The effect of dietary iron deficiency on the distribution of zinc and copper, two other divalent metals with essential neurobiological roles, is relatively unexplored. Thus, the primary goal of this study was to examine the effect of manipulating dietary iron and manganese levels on the concentrations of copper, iron, manganese and zinc in five rat brain regions as determined with inductively

coupled plasma mass spectrometry analysis. Because divalent metal transporter has been implicated as a transporter of brain iron, manganese, and to a lesser extent zinc and copper, another goal of the study was to measure brain regional changes in transporter levels using Western blot analysis. As expected, there was a significant effect of iron deficiency ($P < 0.05$) on decreasing iron concentrations in the cerebellum and caudate putamen; and increasing manganese concentrations in caudate putamen, globus pallidus and substantia nigra. Furthermore, there was a significant effect of iron deficiency ($P < 0.05$) on increasing zinc concentration and a statistical trend ($P = 0.08$) toward iron deficiency-induced copper accumulation in the globus pallidus. Transporter protein in all five regions increased due to iron deficiency compared to control levels ($P < 0.05$); however, the globus pallidus and substantia nigra revealed the greatest increase. Therefore, the globus pallidus appears to be a target for divalent metal accumulation that is associated with dietary iron deficiency, potentially caused by increased transporter protein levels. (C) 2004 Elsevier Inc. All rights reserved.

26. Erikson KM, Jones SR, Aschner M. (2005) Brain manganese accumulation due to toxic exposure is mediated by the dopamine transporter. Faseb Journal 19(5):A1033-A1034.

27. Fechter LD. (1999) Distribution of manganese in development. Neurotoxicology 20(2-3):197-201.
Elimination of manganese is closely related to uptake in the normal adult and is believed to play a critical role in maintaining manganese homeostasis in the face of changing manganese intake. Data from immature rats, mice and cats have suggested that elimination of manganese undergoes a period of maturation with adult patterns of excretion developing at about the time of weaning. In addition, the uptake of manganese from the intestine appears to be more efficient in young animals than in adults. These two sets of findings raise the possibility that exposure to elevated manganese levels during the perinatal period might yield excessive concentrations of this metal in the developing organism. Such an outcome might lead to manganese accumulations in organ systems where subsequent mobilization might be difficult and might produce permanent toxic injury. This review evaluates the patterns of manganese uptake and distribution following prenatal and pre-weaning exposure using a variety of model systems. The data demonstrate that manganese does cross the placenta and enter fetal tissue although the extent of material crossing the placenta appears to be limited. The issue of neonatal manganese elimination following tracer and toxic exposure levels to manganese is addressed. The data show that that the neonatal rodent is significantly more effective in eliminating manganese than previously believed based upon tracer studies. Finally, data are presented on regional brain manganese distribution. These data highlight the lack of agreement on whether manganese is concentrated in specific brain areas. (C) 1999 Inter Press, Inc.

28. Fechter LD, Johnson DL, Lynch RA. (2002) The relationship of particle size to olfactory nerve uptake of a non-soluble form of manganese into brain. Neurotoxicology 23(2):177-183.
The essential element, manganese, can produce chronic neuromotor impairment related to basal ganglia (BG) damage when it is presented in excessive quantities. The uptake and elimination patterns of manganese following ingestion have been well studied and, under normal conditions, excretion appears to keep manganese levels under tight. control. Less is known about inhalation exposure, but it has been proposed that the lung might serve as a long-tern reservoir for manganese transport into blood. Recent data suggest that a third route of exposure, transport by

the olfactory nerve directly to the brain, might have importance in toxicology since such a route would bypass liver uptake and biliary excretion of manganese. In this study, we sought to determine how particle size and the use of a poorly soluble form of manganese might influence net systemic absorption of manganese dust and the potential role of the olfactory nerve in transport of manganese dioxide. Rats were exposed in nose-only exposure chambers to manganese dioxide (MnO2) aerosols of 1.3 and 18 mum mass median aerodynamic diameter (MMAD). The concentration of aerosols was kept constant at 3 mg/m(3); as Mn. Following 15 days of exposure (fire times per week for 3 weeks), rats were euthanized and tissues harvested for manganese determination carried out by graphite furnace atomic absorption spectroscopy. Small-particle MnO2 exposure resulted in an elevation in olfactory, bulb manganese concentration, presumably through uptake by the olfactory nerve, but the effect was highly variable. While small increases in cortical and neostriatal manganese levels were also observed in these rats, they did not reach statistical significance. By contrast, there was no evidence of olfactory nerve MnO2 uptake in rats receiving the large-particle exposure.

29. Fitsanakis VA, Erikson KM, Aschner M. (2006) Manganese transport in the CNS. Neurotoxicology 27(5):895-896.

30. Gallez B, Demeure R, Baudelet C, Abdelouahab N, Beghein N, Jordan B, Geurts M, Roels HA. (2001) Non invasive quantification of manganese deposits in the rat brain by local measurement of NMR proton T-1 relaxation times. Neurotoxicology 22(3):387-392.
Up to now, there is no reliable non invasive biomarker for the concentration of manganese (Mn) in the brain after intoxication to this metal. The aim of the present experimental study was to determine the predictive value of the localized measurement of the proton NMR relaxation time T-1 as a quantitative estimation of the concentration of Mn in brain. The relationship of the proton relaxation rates (1/T-1) was established in rat brain homogenates as a function of the Mn, iron, and copper concentration. Subsequently, an experimental model of Mn neurotoxicity was used: rats were stereotactically injected with increasing amounts of Mn2+ (as MnCl2) in the ventricles. After 3 weeks, local measurements of T-1 were carried out in live rats. They were then sacrificed in order to sample the striatum, the cortex and the cerebellum from the brain and to perform a quantitative determination of the concentration of Mn in these tissues by atomic absorption spectrometry (AAS). The results indicate excellent correlation coefficients between relaxation rates and tissue Mn concentrations (r = 0.84, 0.77 and 0.92 for the striatum, the cortex and the cerebellum. respectively). This methodology offers a unique tool for monitoring the degree of Mn concentration in different areas of the brain in animal models of Mn intoxication. In will be useful for evaluating the efficacy of treatments aimed at decreasing the metal in the brain. The method could be potentially useful for being transposed in the clinical situation for monitoring Mn-exposed workers.

31. Garcia SJ, Gellein K, Syversen T, Aschner M. (2006) A manganese-enhanced diet alters brain metals and transporters in the developing rat. Toxicological Sciences 92(2):516-525.
Manganese (Mn) neurotoxicity in adults can result in psychological and neurological disturbances similar to Parkinson's disease, including extrapyramidal motor system defects and altered behaviors. However, virtually nothing is known regarding excess Mn accumulation during central nervous system development. Developing rats were exposed to a diet high in Mn

via maternal milk during lactation (PN4-21). The high Mn diet resulted in changes in hematological parameters similar to those seen with iron (Fe) deficiency in dams (decreased plasma Fe; increased plasma transferrin [Tf]) and pups (decreased hemoglobin [Hb] and plasma Fe; increased plasma Tf and total iron binding capacity). Mn-exposed pups showed an increase in brain Mn, chromium, and zinc concurrent with a decrease in brain Fe. In conjunction with the altered transport and distribution of essential metals within the brain, there was enhanced protein expression of the divalent metal transporter-1 (DMT-1) and transferrin receptor (TfR) overall in the brain; there was a general increase in each region analyzed (cerebellum, cortex, hippocampus, midbrain, and striatum). Neurochemical changes were observed as an increase in gamma-aminobutyric acid (GABA) and the ratio of GABA to glutamate, indicating enhanced inhibitory transmission in the brain. The results of this study demonstrate that developing rats undergo alterations in the transport and distribution of essential metals translating to neurochemical perturbations after maternal exposure to a diet supplemented with excess levels of Mn.

32. Garcia SJ, Gellein K, Syversen T, Aschner M. (2007) Iron deficient and manganese supplemented diets alter metals and transporters in the developing rat brain. Toxicological Sciences 95(1):205-214.
Manganese (Mn) neurotoxicity in adults can result in psychological and neurological disturbances similar to Parkinson's disease, including extrapyramidal motor system defects and altered behaviors. Iron (Fe) deficiency is one of the most prevalent nutritional disorders in the world, affecting approximately 2 billion people, especially pregnant and lactating women, infants, toddlers, and adolescents. Fe deficiency can enhance brain Mn accumulation even in the absence of excess Mn in the environment or the diet. To assess the neurochemical interactions of dietary Fe deficiency and excess Mn during development, neonatal rats were exposed to either a control diet, a low-Fe diet (ID), or a low-Fe diet supplemented with Mn (IDMn) via maternal milk during the lactation period (postnatal days [PN] 4-21). In PN21 pups, both the ID and IDMn diets produced changes in blood parameters characteristic of Fe deficiency: decreased hemoglobin (Hb) and plasma Fe, increased plasma transferrin (Tf), and total iron binding capacity (TIBC). Treated ID and IDMn dams also had decreased Hb throughout lactation and ID dams had decreased plasma Fe and increased Tf and TIBC on PN21. Both ID and IDMn pups had decreased Fe and increased copper brain levels; in addition, IDMn pups also had increased brain levels of several other essential metals including Mn, chromium, zinc, cobalt, aluminum, molybdenum, and vanadium. Concurrent with altered concentrations of metals in the brain, transport proteins divalent metal transporter-1 and transferrin receptor were increased. No significant changes were determined for the neurotransmitters gamma aminobutyric acid and glutamate. The results of this study confirm that there is homeostatic relationship among several essential metals in the brain and not simply between Fe and Mn.

33. Garcia SJ, Syversen T, Gellein K, Aschner M. (2005) Iron Deficient And Manganese Enhanced Diets Alter Metals And Transporters In The Developing Rat Brain. Toxicol Sci 84(1-S):122.
Fe-deficiency is a prevalent nutritional disorder, affecting ~2 billion people, mostly pregnant and lactating women and children. Fe and Mn share similar transport mechanisms, competing for transport. In adults Mn toxicity leads to neurological disturbances, but little is known about developmental Mn toxicity. To study the interactions of Fe and Mn during brain development,

pregnant Sprague-Dawley rats were fed one of four semi-purified diets from gestational day 7 until postnatal day (PN)21: control (35 Fe:10 Mn mg/kg diet), low Fe (ID; 3 Fe:10 Mn), high Mn (Mn; 35 Fe:100 Mn), or low Fe with high Mn (IDMn; 3 Fe:100 Mn). Control neonates were cross-fostered to experimental or control dams on PN4 and exposed to the diets via lactation until PN21. Hematological measurements confirmed Fedeficiency (decreased Fe, hemoglobin; increased transferrin (Tf), total Fe binding capacity) in dams and pups fed "ID" or "IDMn" diets, while those fed "Mn" had some trends toward similar hematological changes. Western blot analysis revealed that both "ID" and "IDMn" increased expression of the metal transporters, Tf receptor and divalent metal transporter 1 (DMT1). Inductively coupled plasma mass spectrometry (ICP-MS) showed that all three experimental diets decreased brain Fe levels, while both Mn enhanced diets increased brain Mn levels. In addition, "ID" increased copper (Cu); "Mn" increased chromium (Cr); and "IDMn" increased Cr, Cu, cobalt (Co), zinc (Zn), and vanadium (V). Upregulated DMT1, a non-specific transporter, may be a route for increased metals in the brain following dietary manipulations. Because each of the metals affected by low Fe and/or high Mn are esessential metals for normal development and function, homeostatic disturbances may contribute to later consequences.

34. Gianutsos G, Morrow GR, Morris JB. (1997) Accumulation of manganese in rat brain following intranasal administration. Fundamental and Applied Toxicology 37(2):102-105. Manganese chloride (50-500 mu g) was injected unilaterally into the right nostril of rats and its accumulation in the central nervous system (CNS) was monitored. Brain manganese levels were elevated in a dose-dependent, time-dependent, and tissue-dependent manner. Elevated levels of manganese were detected in the right olfactory bulb and olfactory tubercle within 12 hr after instillation and remained elevated for at least 3 days. As little as 100 mu g of manganese chloride was sufficient to increase brain manganese levels, No changes were detected on the left side of the brain. The manganese content of the striatum, the target site for manganese neurotoxicity, was unchanged following acute administration, but was elevated when two injections were made 1 week apart, These results suggest that air-borne manganese can be retrogradely transported along olfactory neurons to the CNS and can reach deeper brain structures under appropriate exposure conditions. (C) 1997 Society of Toxicology.

35. Guidotti TL, Audette RJ, Martin CJ. (1997) Interpretation of the trace metal analysis profile for patients occupationally exposed to metals. Occupational Medicine-Oxford 47(8):497-503. Trace element profile analysis detects and quantifies the presence of several metals simultaneously at low concentrations in the body. In occupational medicine, it may be used to monitor exposure or to evaluate suspected toxicity. Clinical interpretation is often difficult because, with the exception of lead and possibly cadmium, there is little firm information on toxicity thresholds. For these tests, the reference ranges typically reflect low levels of exposure in the general population and it is expected that workers handling metals in occupations such as welding and industries such as steelmaking will have higher levels. Interpretation requires some knowledge of the toxicokinetics of the metal of interest and the preferred medium for analysis for each: serum, whole blood or urine (preferably 24-hour collection). Trends are often more informative than concentrations at one time. Trace element values are reported together with a reference range which must be distinguished from the normal range of other clinical tests. As a practical matter, the greatest interpretation problems tend to be found with manganese because serum levels have a poor correlation with both recent exposure and neurological symptoms.

Molybdenum and vanadium are often found to be elevated among workers exposed to metals who show no evidence of clinical illness. Interpretation of the trace element profile analysis overall when an elevation occurs generally requires close attention to the pattern of elevation, clinical context, absolute and relative magnitude of the elevation and knowledge of the exposure history.

36. Gwiazda R, Kern C, Smith D. (2005) Progression Of Neurochemical Effects In Different Brain Regions As A Function Of The Magnitude And Duration Of Manganese Exposure. Toxicol Sci 84(1-S):122-123.
Manganese (Mn) is known to elicit symptoms resembling those of Parkinson's disease (PD) at high exposure levels, but its effects at low levels of exposure are uncertain. Because of the similarity of behavioral deficits at elevated Mn exposure to PD symptoms, earlier Mn toxicity studies have proposed that striatal dopamine (DA) depletion, a hallmark of PD, is also produced by Mn, despite the observation in humans that Mn accumulates in the globus pallidus. To reconcile this, we have proposed the hypothesis that there is a progression of effects from the globus pallidus to striatum as a function of increasing magnitude of Mn dose and treatment duration (Gwiazda et al., NeuroToxicology, 95:1-8, 2002). To test this, we administered Mn ip 3 times/wk to Sprague-Dawley rats at nominal doses of 0, 1.2, 4.8 and 9.6 mg/Kg over 5 wks, and 0, 1.2, 4.8 mg/Kg over 15 wks. We conducted a battery of motor tests, spontaneous motor activity (SMA) and rotorod measurements, evaluated brain, blood, and plasma Mn levels, and neurochemical levels in the striatum, globus pallidus, substantia nigra and motor regions of the thalamus. Mn treatment increased DA levels in the globus pallidus in animals receiving the highest Mn doses over both 5 and 15 wks, but had no effect on striatal or substantia nigra DA levels. Motor deficits measured as impairment in the balance beam and in hind limb hopping, and shorter latency to fall from the rotorod were observed at the highest dose at 5 weeks. No Mn effects were detected on SMA. Blood and brain Mn showed similar relative increases as a function of nominal dose at 5 and 15 wks, even though the cumulative Mn doses of 15 wks animals were three times higher than in animals exposed for 5 wks. These results suggest that 1) Across a wide range of Mn doses the globus pallidus is a more sensitive locus of Mn toxicity compared to the striatum, and 2) The magnitude of the Mn nominal dose is more important than exposure duration in bringing about an increase in Mn body burden and eliciting Mn toxicity.

37. Henriksson J, Tallkvist J, Tjalve H. (1999) Transport of manganese via the olfactory pathway in rats: Dosage dependency of the uptake and subcellular distribution of the metal in the olfactory epithelium and the brain. Toxicology and Applied Pharmacology 156(2):119-128.
The dosage dependency of the uptake of Mn from the olfactory epithelium via olfactory neurons into the brain was studied after intranasal administration of the metal in rats. The results indicate that the Mn transport is saturable both regarding the uptake into the olfactory epithelium and the transfer to the olfactory bulb. Further, our data indicate that Mn moves relatively freely from the olfactory bulb to the olfactory cortex at an amount dependent on the level of influx into the bulb. The transport to the rest of the brain was related to the amounts in the olfactory bulb and the olfactory cortex, but the relative proportion reaching this area increased with increasing doses. Cell fractionations showed that the Mn was present both in the cytosol and in association with various cell constituents, Gel filtrations of the cytosol on a Superdex 30 column showed that about 20% of the Mn in the brain and about 3% in the olfactory epithelium was eluted together with high-molecular-weight materials (MW > 10,000), whereas the rest was eluted in the total

volume and may represent unbound metal. It is likely that the metal has been loosely associated with protein(s) or other constituents at the application to the column, but that this association is too loose to be retained during the passage through the column, Our results show that the olfactory neurons provide a pathway with a considerable capacity to transport Mn into the brain. We propose that the neurotoxicity of inhaled Mn is related to an uptake via this route. (C) 1999 Academic Press.

38. Henriksson J, Tjalve H. (2000) Manganese taken up into the CNS via the olfactory pathway in rats affects astrocytes. Toxicological Sciences 55(2):392-398.
Manganese (Mn), administered intranasally in rats, is effectively taken up in the CNS via the olfactory system. In the present study, Mn (as MnCl2) dissolved in physiological saline, was instilled intranasally in rats at doses of 0 (control), 10, 250, or 1000 mu g. At the start of the experiment each rat received an intranasal instillation. Some rats were killed after one week without further treatment (the l-w group), whereas the remaining rats received further instillations after one and two weeks and were killed after an additional week (the 3-w group). The brains were removed and either used for ELISA-determination of the astrocytic proteins glial fibrillary acidic protein (GFAP) and S-100b or histochemical staining of GFAP and S-100b, microglia (using an antibody against the iba1-protein) and the neuronal marker Fluoro-Jade. There were no indications that the Mn induced neuronal damage. On the other hand, the ELISA showed that both GFAP and S-100b decreased in the olfactory cortex, the hypothalamus, the thalamus, and the hippocampus of the 3-w group. The only effect observed in the l-w group was a decrease of S-100b in the olfactory cortex at the highest dose. The immunohistochemistry showed no noticeable reduction in the number of astrocytes. We assume that the decreased levels of GFAP and S-100b are due to an adverse effect of Mn on the astrocytes, although this effect does not result in astrocytic demise. In the 3-w group, exposed to the highest dose of Mn, increased levels of GFAP and S-100b were observed in the olfactory bulbs, but these effects are probably secondary to a Mn-induced damage of the olfactory epithelium. Our results indicate that the astrocytes are the initial targets of Mn toxicity in the CNS.

39. Ingersoll RT, Montgomery EB, Aposhian HV. (1995) Central-Nervous-System Toxicity of Manganese .1. Inhibition of Spontaneous Motor-Activity in Rats after Intrathecal Administration of Manganese Chloride. Fundamental and Applied Toxicology 27(1):106-113.
The intrathecal administration of MnCl2 to young male rats caused dopamine depletion in the caudate-putamen and a decrease in spontaneous motor activity. Our experiments demonstrate that in the young rat: (a) the lateral choroid plexus protects the cerebrospinal fluid (CSF) from high concentrations of Mn in the blood by sequestering and thus preventing large amounts of this metal ion from entering the CSF. As blood Mn levels rise, the lateral choroid plexus may become overwhelmed and leak an increasing amount of Mn into the CSF. (b) The lateral choroid plexus does not remove Mn2+ from the CSF. (c) The injection of MnCl2 into the CSF of rats caused a rapid decrease in spontaneous motor activity which is dose-dependent and reversible under the present experimental conditions. Intrathecal Mn results in a substantial decrease in striatal dopamine but not homovanillic acid or 3,4-dihydroxyphenylacetic acid (DOPAC) concentrations and is associated with an increase in the Mn concentration of the substantia nigra and caudate-putamen. (C) 1995 Society of Toxicology.

40. Kanayama Y, Tsuji T, Enomoto S, Amano R. (2005) Multitracer screening: Brain delivery of trace elements by eight different administration methods. Biometals 18(6):553-565.
Trace elements are closely associated with the normal functioning of the brain. Therefore, it is important to determine how trace elements enter, accumulate, and are retained in the brain. Using the multitracer technique, which allows simultaneous tracing of many elements and comparison of their behavior under identical experimental conditions, we examined the influence of different administration methods, i.e., intravenous (IV), intraperitoneal (IP), intramuscular (IM), subcutaneous (SC), intracutaneous (IC), intranasal (IN), peroral (PO), and percutaneous (PC) administration, on the uptake of trace elements. A multitracer solution containing 16 radionuclides (i.e.,Be-7, Sc-46, V-48, Cr-51, Mn-54, Fe-59, Co-56, Zn-65, As-74, Se-75, Rb-83, Sr-85, Y-88, Zr-88, Tc-95m, and Ru-103) was used. The results indicated that the Rb-83 brain uptake rate with intranasal administration was approximately twice those obtained with the other administration methods. This result indicated that a portion of Rb was delivered into the brain circumventing the blood circulation and that delivery could be accomplished mainly by olfactory transport. Multitracer screening of trace element delivery revealed differences in brain uptake pathways among administration methods.

41. Kimura M, Ujihara M, Yokoi K. (1996) Tissue manganese levels and liver pyruvate carboxylase activity in magnesium-deficient rats. Biological Trace Element Research 52(2):171-179.
To investigate the manganese status in mag,nesium deficiency, 40 male Wistar rats, 3 wk old, were divided into two groups and fed a magnesium deficient diet or a normal synthetic diet for 2 wk. Dietary magnesium depletion decreased magnesium levels in brain, spinal cord, lung, spleen, kidney, testis, bone, blood, and plasma, while it elevated the magnesium level in liver. In magnesium-depleted rats, calcium concentration was increased in lung, liver, spleen, kidney, and testis, while it was decreased in tibia. In magnesium-depleted rats, manganese concentration was decreased in plasma and all tissues except adrenal glands and blood. Dietary magnesium depletion diminished pyruvate carboxylase (EC 6.4.1.1) activity in the crude mitochondrial fraction of liver. Positive correlation was found between the liver manganese concentration and the pyruvate carboxylase activity. In the magnesium-depleted rats, glucose was decreased while plasma lipids (triglycerides, phospholipids, and total cholesterol) were increased. These results suggest that dietary magnesium deficiency changes manganese metabolism in rats.

42. Kobayashi H, Uchida M, Sato I, Suzuki T, Hossain MM, Suzuki K. (2004) Neurotoxicity and brain regional distribution of manganese in mice. (vol 22, pg 679, 2003). Journal of Toxicology-Toxin Reviews 23(4):556-557.

43. Kostial K, Blanusa M, Piasek M. (2005) Regulation of manganese accumulation in perinatally exposed rat pups. Journal of Applied Toxicology 25(2):89-93.
The risk of manganese (Mn)-related ill effects in the neonate has been the topic of several investigations because in formula-fed infants Mn intake is much higher than in breast-fed infants. In the young, when Mn homeostasis is not yet developed, increased Mn intake might pose a neurotoxic risk. Our work aimed at collecting new data on Mn accumulation during the perinatal period by using an experimental rat model in pups whose mothers were exposed orally to Mn in drink (as manganese chloride; dose of 2000 ppm, Mn) throughout pregnancy and 11 days of lactation. Pups were cross-fostered at birth and placental and mammary transfer of Mn at

birth and at the age of 11 days was evaluated. The total pup body burden of Mn was analysed by atomic absorption spectrometry. Concentrations of iron (Fe), zinc (Zn) and calcium (Ca) also were analysed at the end of the experiment. The concentration of Mn in perinatally exposed pups was 6-8 times higher than in controls, irrespective of the period and duration of exposure. After cessation of exposure, the Mn concentration decreased almost to control levels. Concentrations of other essential elements (Fe, Zn, Ca) were not affected by Mn exposure. Our results indicate the existence of an accurate regulation of Mn accumulation in pups exposed to Mn during the perinatal period. Copyright (c) 2005 John Wiley T Sons, Ltd.

44. Lewis J, Bench G, Myers O, Tinner B, Staines W, Barr E, Divine KK, Barrington W, Karlsson J. (2005) Trigeminal uptake and clearance of inhaled manganese chloride in rats and mice. Neurotoxicology 26(1):113-123.
Inhaled manganese (Mn) can enter the olfactory bulbs via the olfactory epithelium, and can then be further transported trans-synaptically to deeper brain structures. In addition to olfactory neurons, the nasal cavity is innervated by the maxillary division of the trigeminal nerve that projects to the spinal trigerninal nucleus. Direct uptake and transport of inhaled metal particles in the trigeminal system has not been investigated previously. We studied the uptake, deposition, and clearance of soluble Mn in the trigeminal system following nose-only inhalation of environmentally relevant concentrations. Rats and mice were exposed for 10-days (6 h/day, 5 days/week) to air or MnCl2 aerosols 3 ;containing 2.3 +/- 1.3 mg/m(3) Mn with mass median aerodynamic diameter (MMAD) of 3.1 +/- 1.4 mum for rats and 2. 0 +/- 0.09 mg/n(3) Mn MnCl2 with MMAD of 1.98 +/- 0.12 mum for mice. Mn concentrations in the trigeminal ganglia and spinal trigeminal nucleus were measured 2 h (0-day), T, 14-, or 30-days post-exposure using proton induced X-ray emission (PIXE). Manganese-exposed rats and mice showed statistically elevated levels of Mn in trigeminal ganglia 0-, 7- and 14days after the 10-days exposure period when compared to control animals. The Mn concentration gradually decreased over time with a clearance rate (t(1/2)) of 7-8-days. Rats and mice were similar in both average accumulated Mn levels in trigeminal ganglia and in rates of clearance. We also found a small but significant elevation of Mn in the spinal trigeminal nucleus of mice 7-days post-exposure and in rats 0- and 7-days post-exposure. Our data demonstrate that the trigeminal nerve can serve as a pathway for entry of inhaled Mn to the brain in rodents following nose-only exposure and raise the question of whether entry of toxicants via this pathway may contribute to development of neurodegenerative diseases. (C) 2004 Elsevier Inc. All rights reserved.

45. Li G, Liu J, Waalkes MP, Zheng W. (2005) Manganese Exposure Alters Iron Regulatory Mechanisms At Blood-Cerebrospinal Fluid Barrier (BCB) And Selected Regions Of Bloodbrain Barrier (BBB) In Rats. Toxicol Sci 84(1-S):121-122.
Previous in vitro data suggest that manganese (Mn) exposure increases the expression of mRNAs encoding transferrin receptor (TfR), which possess an iron (Fe) response element (IRE), by altering binding of iron regulatory protein-1 (IRP1) to TfR mRNA. The current study tested the hypothesis that in vivo exposure to Mn alters TfR expression at both BBB and BCB, leading to altered Fe transport at brain barriers. Male SD rats received daily oral gavages at doses of 5 or 15 mg Mn/kg as MnCl2 for 30 days. Blood, cerebrospinal fluid (CSF) and choroids plexus were collected. Brain capillaries from striatum, hippocampus, frontal cortex, and cerebellum, were separated from parenchyma. Atomic absorption spectrophotometry revealed that the Fe concentration in controls was about 17-22 fold higher in choroid plexus than in other brain

regions. Mn exposure resulted in a 67% decrease of serum Fe and an increased Fe in CSF (25%) and choroid plexus (67%) compared to control, while the concentrations of Mn and Fe in most brain regions tested did not change significantly. Capillary depletion followed by gel shift assay using S100 cytosolic extracts showed that binding of IRP1 to [32P] IRE-RNA probes was significantly enhanced in choroid plexus and capillaries of striatum, hippocampus, and frontal cortex ($p < 0.01$). Quantitative real-time RT-PCR demonstrated increased levels of TfR mRNA in choroid plexus and capillaries of striatum and hippocampus ($p < 0.05$), but not in frontal cortex and cerebellum capillaries, suggesting an up-regulation of TfR in BCB and selected regional BBB. The mRNA levels of ferritin, an Fe storage protein, were reduced by 87% in the choroid plexus and 34% in striatum capillary. Taken together, these data indicate that Mn, on the way to brain, alters Fe regulatory mechanisms at BCB and selected regions of BBB. This may underlie the distorted Fe homeostasis in the CSF.

46. Malecki EA, Devenyi AG, Beard JL, Connor JR. (1999) Existing and emerging mechanisms for transport of iron and manganese to the brain. Journal of Neuroscience Research 56(2):113-122.
The metals iron (Fe) and manganese (Mn) are essential for normal functioning of the brain. This review focuses on recent developments in the literature pertaining to Fe and Mn transport, These metals are treated together because they appear to share several transport mechanisms. In addition, several neurological diseases such as Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease are all associated with Fe mismanagement in the brain, particularly in the striatum and basal ganglia. Similarly, Mn accumulation in brain also appears to target the same brain regions. Therefore, stringent regulation of the concentration of these metals in the brain is essential, The homeostatic mechanisms for these metals must be understood in order to design neurotoxicity prevention strategies. J, Neurosci, Res. 56:113-122, 1999, (C) 1999 Wiley-Liss, Inc.

47. Normandin L, Beaupre LA, Salehi F, St-Pierre A, Kennedy G, Mergler D, Butterworth RE, Philippe S, Zayed J. (2004) Manganese distribution in the brain and neurobehavioral changes following inhalation exposure of rats to three chemical forms of manganese. Neurotoxicology 25(3):433-441.
The central nervous system is an important target for manganese (Mn) intoxication in humans; it may cause neurological symptoms similar to Parkinson's disease. Manganese compounds emitted from the tailpipe of vehicles using methylcyclopentadienyl manganese tricarbonyl (MMT) are primarily Mn phosphate, Mn sulfate, and Mn phosphate/ sulfate mixture. The purpose of this study is to compare the patterns of Mn distribution in various brain regions (olfactory bulb, frontal parietal cortex, globus pallidus, striatum and cerebellum) and other tissues (lung, liver kidney, testis) and the neurobehavioral damage following inhalation exposure of rats to three Mn species. Rats (n = 15 rats per Mn species) were exposed 6 h per day, 5 days per week for 13 consecutive weeks to metallic Mn, Mn phosphate or Mn phosphate/ sulfate mixture at about 3000 mug m(-3) and compared to controls. At the end of the exposure period, spontaneous motor activity was measured for 36 h using a computerized autotrack system. Mn in tissues was determined by instrumental neutron activation analysis (INAA). The Mn concentrations in the brain were significantly higher in rats exposed to Mn phosphate and Mn phosphate/sulfate mixture than in control rats or rats exposed to metallic Mn. Exposure to Mn phosphate/sulfate mixture caused a decrease in the total ambulatory count related to locomotor activity. Our results

confirm that Mn species and solubility have an influence on the brain distribution of Mn in rats. (C) 2003 Elsevier Inc. All rights reserved.

48. Ponzoni S, Gaziri LCJ, Britto LRG, Barreto WJ, Blum D. (2002) Clearance of manganese from the rat substantia nigra following intra-nigral microinjections. Neuroscience Letters 328(2):170-174.
Chronic exposure to manganese (Mn) positively correlates with the occurrence of Parkinsonism but little is known about mechanisms of its neurotoxicity. In the present study, we determined the clearance of Mn from rat substantia nigra after its nigral injection and correlated it with the establishment of apomorphine-induced rotational behaviour and loss of striatal tyrosine hydroxylase (TH) immunoreactivity. Our results suggest that Mn is slowly cleared from the substantia nigra, following a first-order kinetics with a t(1/2) of 3 days. Appearance of apomorphine-induced rotational behaviour and loss of TH immunoreactivity within the striatum follows metal clearance were both detected 24 hours after intra-nigral Mn microinjection and maximal 72 hours after injection. The present data suggest that the cellular mechanisms induced by Mn and leading to dopaminergic cell death, occurred shortly after its injection and that the metal concentration needs to reach a threshold value to induce neurotoxic effects. This would indicate that nigral damages are a direct consequence of Mn accumulation. (C) 2002 Elsevier Science Ireland Ltd. All rights reserved.

49. Roels H, Meiers G, Delos M, Ortega I, Lauwerys R, Buchet JP, Lison D. (1997) Influence of the route of administration and the chemical form [MnCl2, MnO2) on the absorption and cerebral distribution of manganese in rats. Archives of Toxicology 71(4):223-230.
The absorption and cerebral distribution of manganese (Mn) have been studied with respect to the route of administration and the chemical form of the Mn compound. Different groups of adult male rats received either MnCl2 . 4H(2)O or MnO2 once a week for 4 weeks at a dose of 24.3 mg Mn/kg body wt. (b.w.) by oral gavage (g.) or 1.22 mg Mn/kg b.w. by intraperitoneal injection (i.p.) or intratracheal instillation (i.t.). Control rats were treated with 0.9% saline. Four days after the last administration the rats were killed and the concentration of Mn measured in blood, hepatic and cerebral tissues (cortex, cerebellum, and striatum). The liver Mn concentration was not affected by the treatments whatever the chemical form or the route of administration of the Mn compound. Administration of MnCl2 by g., i.p., and i.t. routes produced equivalent steady-state blood Mn concentrations (about 1000 ng Mn/100 mi), representing increases of 68, 59, and 68% compared with controls, respectively. Mn concentrations were significantly increased in the cortex but to a lesser extent (g., 22%; i.p., 36%; i.t., 48%) and were higher in the cerebellum after i.p. and i.t. administrations than after oral gavage. Rats treated i.t. with MnCl2 showed an elective increase of the striatal Mn concentration (205%). In contrast, MnO2 given orally did not significantly increase blood and cerebral tissue Mn concentrations; the low bioavailability is most likely due to the lack of intestinal resorption. Administration of MnO2 i.p. and i.t., however, led to significant increases of Mn concentrations in blood and cerebral tissues. These increments were not significantly different from those measured after MnCl2 administration, except for striatal Mn after i.t. which was markedly less (48%) after MnO2 administration. A comparison of the blood Mn kinetics immediately after g. and i.t. treatment with MnCl2 or MnO2 indicated that the higher elevation of blood Mn concentration (> 2000 ng Mn/100 mi) after i.t. administration of MnCl2 could account for the elective uptake of Mn in the striatum observed in repeated dosing experiments. It is concluded that the modulation of Mn distribution

in brain regions according to the route of administration and the chemical form of the Mn compound may be explained on the basis of different blood Mn kinetics and regional anatomic specificities of the striatal region.

50. Roth JA. (2006) Homeostatic and toxic mechanisms regulating manganese uptake, retention, and elimination. Biological Research 39(1):45-57.
This review attempts to summarize and clarify our basic knowledge as to the various factors that potentially influence the risks imposed from chronic exposure to high atmospheric levels of manganese (Mn). The studies describe the interrelationship of the different systems in the body that regulate Mn homeostasis by characterizing specific, biological components involved in its systemic and cellular uptake and its elimination from the body, A syndrome known as manganism occurs when individuals are exposed chronically to high levels of Mn, consisted of reduced speed, intellectual deficits, mood changes, and compulsive behaviors in the initial stages of the disorder to more prominent and irreversible extrapyramidal dysfunction resembling Parkinson's disease upon protracted exposure. Mn intoxication is most often associated with occupations in which abnormally high atmospheric concentrations prevail, such as in welding and mining. There are three potentially important, routes by which Mn in inspired air can gain access the body to: 1) direct uptake into the CNS via uptake into the olfactory or trigeminal presynaptic nerve endings located in the nasal mucosa and the subsequent retrograde axonal transport directly into the CNS: 2) transport across the pulmonary epithelial lining and its subsequent deposition into lymph or blood: and/or 3) mucocilliary elevator clearance from the lung and the subsequent ingestion of the metal in the gastrointestinal tract. Each of these processes and their overall contribution to the uptake of Mn in the body is discussed in this review as well as a description of the various mechanisms that have been proposed for the transport of Mn across the blood-brain barrier which include both a transferrin-dependent and a transferrin-independent process that may involve store-operated Ca channels.

51. Roughead ZK, Finley JW. (2001) Mucosal uptake and whole-body retention of dietary manganese are not altered in beta(2)-microglobulin knockout mice. Biological Trace Element Research 80(3):231-244.
To further examine the interrelationships between manganese and iron absorption, the mucosal uptake, initial rate of loss, whole-body retention, and tissue distribution of an orally administered Mn-54 radiotracer were compared between normal and beta (2)-microglobulin knockout [beta (2)m(-/-)] mice. These mutant mice are commonly used as a model for the study of human hemochromatosis, a hereditary iron-overload disease. Initial uptake of Mn-54 by the intestinal mucosa, the liver, and the brain was not different between the two strains. The mutant mice had much higher concentrations of nonheme and total iron in the liver, but hepatic manganese, copper, magnesium, and zinc concentrations were similar between the two strains. In summary, the mucosal uptake and whole-body retention of manganese and tissue manganese concentrations were not altered in beta (2)m(-/-) mice; this suggests that normal homeostasis of manganese is not affected by the altered HFE protein-beta (2)m complex in these mice.

52. Sato I, Matsusaka N, Kobayashi H, Nishimura Y. (1996) Effects of dietary manganese contents on 54Mn metabolism in mice. Journal of Radiation Research 37(2):125-132.
BIOSIS COPYRIGHT: BIOL ABS. Several parameters of 54Mn metabolism were noted in mice maintained on diets with manganese contents of 80 to 8000 mg/kg. Excretion of 54Mn was

promoted as the dietary manganese contents increased. Clearance of 54Mn from the liver, kidneys, pancreas, and spleen was markedly accelerated by feeding mice a high-manganese diet, but clearance from the muscles, femurs, and brain was relatively insensitive to the dietary manganese. Manganese concentrations in the tissues were regulated homeostatically upto the dietary manganese content of 2400 mg/kg, but marked accumulations of manganese occurred when mice were given 8000 mg/kg diet. No toxic symptoms were found up to the 2400 mg/kg diet, but consumption of the 8000 mg/kg diet was less than for other diets. These results suggest that an oral intake of excess manganese is effective for promoting the excretion of 54Mn from a body contaminated with this isotope.

53. Schafer U, Anke M, Seifert M, Fischer AB. (2004) Influences on the manganese intake, excretion and balance of adults, and on the manganese concentration of the consumed food determined by means of the duplicate portion technique. Trace Elements and Electrolytes 21(2):68-77.
Manganese intake, excretion and balance were investigated in German adults with mixed and vegetarian diets as well as in breast-feeding and not breast-feeding women. The daily manganese consumption and excretion were related to time, location, gender and a manganese supplementation. In addition, in 1996, the manganese intake of the persons consuming a mixed diet in Germany (2.4 mg/day for women and 2.7 mg/day for men) was compared with that in Mexico (2.0 and 2.1 mg/day, respectively). Breast-feeding women ingested 2.3 mg Mn/day. The supplementation with 300 mug Mn/day increased the manganese intake by 10% in young non-nursing and by 15% in breast-feeding women. These values analyzed by means of the duplicate portion technique were well within the assessment of the German Society of Nutrition (DGE) and the estimated safe and adequate daily dietary intake (ESADDI) of the Food and Nutrition Board of the National Research Council (NRC) of the USA, both of which provisionally recommend 2-5 mg Mn/day for adults. However, in our studies, German vegetarians consumed with 5.5 mg Mn/day (women) and 5.9 mg Mn/day (men) more than twice as much as individuals with a mixed diet. The manganese balances were found to be mostly negative. From the results of our intake, balance and placebo-controlled, double-blind studies, we assessed the normative requirement for manganese at 15 mug/kg body weight/day or 1 mg/day, as weekly average. Therefore, we recommend a mean intake of 30 mug Mn/kg body weight/day or 2 mg Mn/day, which we consider to be sufficient intake values for adult humans. The type of diet, year, gender, country, location and partly the Mn supplementation were found to have a statistically significant influence on daily manganese intake, whereas, interestingly, the concentration of consumed food was not influenced by gender. Though manganese is an essential trace element, manganese deficiency symptoms were not recognized in humans under healthy conditions and balanced nutrition.

54. St-Pierre A, Normandin L, Carrier G, Kennedy G, Butterworth R, Zayed J. (2001) Bioaccumulation and locomotor effect of manganese dust in rats. Inhalation Toxicology 13(7):623-632.
The primary goal of this study is to determine the effects of Mn exposure via inhalation. The bioaccumulation of Mn in different organs and tissues, the alteration of biochemical parameters, and the locomotor activity were assessed. A group of 26 male Sprague-Dawley rats (E) were exposed to 3750 mug/m(3) of Mn dust for 6 h/day, 5 days/wk for 13 consecutive weeks and compared to a control group of 12 rats (C) exposed to 4 mug/m(3). After exposure, neurological

evaluation was carried out for 36 h (a night-day-night cycle) using a computerized autotrack system. Rats were then sacrificed by exsanguination, and Mn content in organs and tissues was determined by neutron activation analysis. Mn concentrations in lung, putamen, and cerebellum were significantly higher in E than in C (0.30 vs. 0.17, 0.89 vs. 0.44, 0.63 vs. 0.48 ppm; $p < .01$), as well as in the kidney, frontal cortex, and globus pallidus (1.15 vs. 0.96, 0.84 vs. 0.47, 1.28 vs. 0.55 ppm; $p < .05$). Potassium concentration was significantly lower in E than in C (5.11 vs. 5.79 mmol/L; $p < .05$), as was alkaline phosphatase (106.9 vs. 129.6 U/L; $p < .01$). Locomotor activity indicated higher distance covered in the first 12-h period for E (45 383 vs. 36 098 cm; $p < .05$) and lower resting time in the last 12-h period for E (36 326 vs. 37 393 s; $p < .05$). This study is the first of several ongoing studies in our laboratory that address health concerns associated with inhalation exposure to different Mn species and to different levels of exposure.

55. Takeda A, Ishiwatari S, Okada S. (1999) Manganese uptake into rat brain during development and aging. Journal of Neuroscience Research 56(1):93-98.
Manganese (Mn) is an essential metal and plays an important role in the brain. To evaluate Mn uptake into the brain during development and aging, Mn-54 concentrations in the brain of rats aged from 5 days to 95 weeks were measured after injection of (MnCl2)-Mn-54. Mn-54 concentration in the brain of 5-day-old rats was the highest of all age groups tested. The liver and blood of 5-day-old rats also showed the highest Mn-54 concentrations among the age groups. These results suggest that Mn is required in a high amount during infancy and that a sufficient Mn supply is critical for normal brain development, The high uptake of Mn into the brain of neonatal rats may be due to high levels of Mn in the blood, which may be supplied from the liver. In the 5-day-old brain, Mn-54 was relatively concentrated in the hippocampal CA3 and dentate gyrus and the pens. In the aging brain, Mn-54 was relatively concentrated in the inferior colliculi, olivary nuclei and red nuclei. J, Neurosci, Res. 56:93-98, 1999, (C) 1999 Wiley-Liss, Inc.

56. Takeda A, Kodama Y, Ishiwatari S, Okada S. (1998) Manganese transport in the neural circuit of rat CNS. Brain Research Bulletin 45(2):149-152.
To study manganese (Mn) transport in the neural circuit of rat CNS, brain isotope distribution after Mn-54 injection into the brain was analyzed by autoradiography, One day after (MnCl2)-Mn-54 injection into the striatum, Mn-54 was highly distributed in the ipsilateral thalamus, hypothalamus, and substantia nigra, When (MnCl2)-Mn-54 was bilaterally injected into the striata after unilateral treatment with colchicine or vehicle into the medial forebrain bundle, Mn-54 was distributed in both sides of the substantia nigra of vehicle-treated rats, On the other hand, unilateral colchicine treatment caused a decrease of Mn-54 distribution in the ipsilateral substantia nigra, suggesting that Mn is subjected to axonal transport in the striatonigra and/or nigrostriatal pathways, In the case of unilateral injection of (MnCl2)-Mn-54 into the olfactory bulb, Mn-54 was distributed in the ipsilateral piriform, amygdaloid areas (the primary olfactory cortex), and entorhinal area (the secondary olfactory cortex), These results suggest that Mn is subject to widespread axonal transport in the neural circuits, Moreover, Mn may be taken up by the piriform neurons (the third olfactory neuron) after release from the secondary olfactory neuron terminals and transported to the entorhinal area. (C) 1998 Elsevier Science Inc.

57. Takeda A, Sawashita J, Okada S. (1995) Biological Half-Lives of Zinc and Manganese in Rat-Brain. Brain Research 695(1):53-58.

The brains of rats injected intravenously with (ZnCl2)-Zn-65 or (MnCl2)-Mn-54 were subjected to high-resolution autoradiography. The distribution of Zn-65 and Mn-54 in each brain region gradually decreased from 6 days to 42 days for Zn-65 and from 15 days to 60 days for Mn-54 after the injection. The biological half-lives of Zn in each region studied were in the range of 16-43 days; the longest was observed in the amygdaloid nuclei. The regions where the long biological half-life was observed were consistent with the ones with the high density of Zn-containing neuron terminals reported previously. The biological half-lives of Mn in each region determined were 51-74 days; the longest were those in the hypothalamic nuclei and thalamus.

58. Takeda A, Sawashita J, Okada S. (1998) Manganese concentration in rat brain: manganese transport from the peripheral tissues. Neuroscience Letters 242(1):45-48.
Mn-54 distribution in the brain and peripheral tissues was studied with the course of time after intravenous injection of (MnCl2)-Mn-54 to see manganese (Mn) transport from the peripheral tissues, i.e. the liver, to the brain. One hour after injection, Mn-54 concentrations in the brain were 0.15-0.25% dose/g, and Mn-54 was largely concentrated in the choroid plexus. One day after injection, Mn-54 in the choroid plexus decreased remarkably. Mn-54 in other brain regions increased gradually after then, and reached 0.30-0.40% dose/g 6 days after injection. This increase of Mn-54 was due to the redistribution from the peripheral tissues such as liver and pancreas, in which Mn-54 was maintained at high levels (2.0-4.0% dose/g). The increment of Mn-54 1 h to 6 days after injection was the largest in the hippocampus, but not in the striatum. These results suggest that the delivery of Mn from the liver to the brain is not involved in preferential Mn accumulation in the basal nuclei under physiological condition. This delivery may be important for brain function. (C) 1998 Elsevier Science Ireland Ltd.

59. Thompson K, Molina R, Donaghey T, Brain JD, Wessling-Resnick M. (2005) Olfactory uptake of manganese is upregulated by iron deficiency and involves DMT1. Faseb Journal 19(5):A1483-A1484.

60. Thompson K, Molina R, Donaghey T, Brain JD, Wessling-Resnick M. (2006) The influence of high iron diet on rat lung manganese absorption. Toxicology and Applied Pharmacology 210(1-2):17-23.
Individuals chronically exposed to manganese are at high risk for neurotoxic effects of this metal. A primary route of exposure is through respiration, although little is known about pulmonary uptake of metals or factors that modify this process. High dietary iron levels inversely affect intestinal uptake of manganese, and a major goal of this study was to determine if dietary iron loading could increase lung non-heme iron levels and alter manganese absorption. Rats were fed a high iron (1% carbonyl iron) or control diet for 4 weeks. Lung non-heme iron levels increased similar to 2-fold in rats fed the high iron diet. To determine if iron-loading affected manganese uptake, Mn-54 was administered by intratracheal (it) instillation or intravenous (iv) injection for pliarmacokinetic studies. Mn-54 absorption from the lungs to the blood was lower in it-instilled rats fed the 1% carbonyl iron diet. Pharmacokinetics of iv-injected Mn-54 revealed that the isotope was cleared more rapidly from the blood of iron-loaded rats. In situ analysis of divalent metal transporter-1 (DMTI) expression in lung detected mRNA in airway epithelium and bronchus-associated lymphatic tissue (BALT). Staining of the latter was significantly reduced in rats fed the high iron diet. in situ analysis of transferrin receptor (TfR) mRNA showed staining in BALT alone. These data demonstrate that manganese absorption from

the lungs to the blood can be modified by iron status and the route of administration. (c) 2005 Elsevier Inc. All rights reserved.

61. Thompson K, Molina RM, Donaghey T, Schwob JE, Brain JD, Wessling-Resnick M. (2007) Olfactory uptake of manganese requires DMT1 and is enhanced by anemia. Faseb Journal 21(1):223-230.
Manganese, an essential nutrient, can also elicit toxicity in the central nervous system (CNS). The route of exposure strongly influences the potential neurotoxicity of manganese-containing compounds. Recent studies suggest that inhaled manganese can enter the rat brain through the olfactory system, but little is known about the molecular factors involved. Divalent metal transporter-1 (DMT1) is the major transporter responsible for intestinal iron absorption and its expression is regulated by body iron status. To examine the potential role of this transporter in uptake of inhaled manganese, we studied the Belgrade rat, since these animals display significant defects in both iron and manganese metabolism due to a glycine-to-arginine substitution (G185R) in their DMT1 gene product. Absorption of intranasally instilled Mn-54 was significantly reduced in Belgrade rats and was enhanced in iron-deficient rats compared to iron-sufficient controls. Immunohistochemical experiments revealed that DMT1 was localized to both the lumen microvilli and end feet of the sustentacular cells of the olfactory epithelium. Importantly, we found that DMT1 protein levels were increased in anemic rats. The apparent function of DMT1 in olfactory manganese absorption suggests that the neurotoxicity of the metal can be modified by iron status due to the iron-responsive regulation of the transporter.

62. Tjalve H, Henriksson J, Tallkvist J, Larsson BS, Lindquist NG. (1996) Uptake of manganese and cadmium from the nasal mucosa into the central nervous system via olfactory pathways in rats. Pharmacology & Toxicology 79(6):347-356.
In the olfactory epithelium the primary olfactory neurones are in contact with the environment and via the axonal projections they are also connected to the olfactory bulbs of the brain. Therefore, the primary olfactory neurones provide a pathway by which foreign materials may gain access to the brain. In the present study we used autoradiography and gamma spectrometry to show that intranasal instillation of manganese (Mn-54(2+)) in rats results in initial uptake of the metal in the olfactory bulbs. The metal was then seen to migrate via secondary and tertiary olfactory pathways and via further connections into most parts of the brain and also to the spinal cord. Intranasal instillation of cadmium (Cd-109(2+)) resulted in uptake of the metal in the anterior parts of the olfactory bulbs but not in other areas of the brain. This indicates that this metal is unable to pass the synapses between the primary and secondary olfactory neurones in the bulbs. Intraperitoneal administration of Mn-54(2+) or Cd-109(2+) showed low uptake of the metals in the olfactory bulbs, an uptake not different from the rest of the brain. Manganese is a neurotoxic metal which in man can induce an extrapyramidal motor system dysfunction associated with occupational inhalation of manganese-containing dusts or fumes. We propose that the neurotoxicity of inhaled manganese is related to an uptake of the metal into the brain via the olfactory pathways. In this way manganese can circumvent the blood-brain barrier and gain direct access to the central nervous system.

63. Tran TT, Chowanadisai W, Crinella FM, Chicz-DeMet A, Lonnerdal B. (2002) Effect of high dietary manganese intake of neonatal rats on tissue mineral accumulation, striatal dopamine levels, and neurodevelopmental status. Neurotoxicology 23(4-5):635-643.

Mn is an essential element, but may become neurotoxic at high levels. Recent reports of high Mn levels in hair of children with neurodevelopmental deficits suggest that these deficits could be due to Mn-induced neurotoxic effects on brain dopamine (DA) systems, although the mechanism is not well understood. Infant formulas contain considerably higher concentrations of Mn than human milk. Thus, formula-fed infants are exposed to high levels of Mn at a time when Mn homeostasis is incompletely developed. We studied the effects of dietary Mn supplementation of rat pups on tissue Mn accumulation, brain dopamine levels, infant neurodevelopmental status, and behavior at maturity. Newborn rats were supplemented daily with 0, 50, 250, or 500 mug Mn given orally from day I to day 20. Mineral analysis of small intestine and brain at day 14 showed a significant increase of tissue Mn in supplemented rats. Neurodevelopmental tests conducted at various ages showed significant delays as a function of Mn supplementation. At day 32, there was a significant positive relationship between passive avoidance errors and Mn supplementation levels. Brains of animals killed on day 40 showed a significant inverse relationship between Mn supplementation level and striatal dopamine concentration. These observations suggest that dietary exposure to high levels of Mn during infancy can be neurotoxic to rat pups and result in developmental deficits. (C) 2002 Elsevier Science Inc. All rights reserved.

64. Tran TT, Kelleher SL, Lonnerdal B. (2002) Effect of high manganese intake and iron deficiency in infant rats on DMT-1 expression and tissue mineral accumulation. Faseb Journal 16(4):A617-A617.

65. Vezer T, Papp A, Hoyk Z, Varga C, Naray M, Nagymajtenyi L. (2005) Behavioral and neurotoxicological effects of subchronic manganese exposure in rats. Environmental Toxicology and Pharmacology 19(3):797-810.
In male Wistar rats, behavioral and electrophysiological investigations, and blood and brain manganese level determinations, were performed; during 10 weeks treatment with low-dose manganese chloride and a 12 weeks post-treatment period. Three groups of 16 animals each received daily doses of 14.84 and 59.36 mg/kg b.w. MnCl2 (control: distilled water) via gavage. During treatment period, Mn accumulation was seen first in the blood, then in the brain samples of the high-dose animals. Short- and long-term spatial memory performance of the treated animals decreased, spontaneous open field activity (OF) was reduced. The number of acoustic startle responses (ASR), and the pre-pulse inhibition (PPI) of these, diminished. In the cortical and hippocampal spontaneous activity, power spectrum was shifted to higher frequencies. The latency of the sensory evoked potentials increased, and their duration, decreased. By the end of the post-treatment period, Mn levels returned to the control in all samples. The impairment of long-term spatial memory remained, as did the number of acoustic startle responses. Pre-pulse inhibition, however, returned to the pre-treatment levels. The changes of the open field activity disappeared but a residual effect could be revealed by administration Of D-amphetamine. The electrophysiological effects were partially reversed. By applying a complex set of methods, it was possible to obtain new data for a better-based relationship between the known effects of Mn at neuronal level and the behavioral and electrophysiological outcomes of Mn exposure. © 2005 Elsevier B.V. All rights reserved.

66. Vitarella D, Moss O, Dorman DC. (2000) Pulmonary clearance of manganese phosphate, manganese sulfate, and manganese tetraoxide by CD rats following intratracheal instillation. Inhalation Toxicology 12(10):941-957.
Manganese (Mn) is ubiquitous in ambient air due to both industrial and crustal sources. It is also a component of the octane-enhancing fuel additive methylcyclopentadienyl manganese tricarbonyl (MMT). The combustion of MMT by the automobile engine results in the formation of Mn particulates including phosphate, sulfate, and oxide forms. The objectives of this study were to determine the contribution of particle dissolution on pulmonary clearance rates of Mn sulfate (MnSO4), Mn phosphate, and Mn tetraoxide (Mn3O4) in CD rats following an intratracheal instillation exposure. In addition, brain (striatal) Mn concentrations were evaluated following exposure. Adult CD rats were intratracheally instilled with 0, 0.04, 0.08, or 0.16 mu g Mn/g of either MnSO4, Mn phosphate, or Mn3O4. Rats were euthanized at 0, 1, 3, or 14 days after instillation. Lung and striatal Mn concentrations were measured by neutron activation analysis. Pulmonary clearance following single intratracheal instillation of MnSO4, Mn phosphate, or Mn3O4 was similar for each of the three compounds at each of the three doses used. All pulmonary clearance half-times were less than 0.5 day. At the concentrations used, striatal Mn levels were unaffected, and lung pathology was unremarkable. The dissolution rate constant of the Mn particles was determined in vitro using lung simulant fluids. The solubility of the Mn compounds was in general 20 to 40 times greater in Hatch artificial lung lining fluid than in Gamble lung simulant fluid. The dissolution rate constant of the water-soluble MnSO4 particles in Hatch artificial lung fluid containing protein was 7.5 x 10(-4) g (Mn)/cm(2)/day, which was 54 times that of relatively water-insoluble Mn phosphate and 3600 times that of Mn3O4. The dissolution rate constants for these compounds were sevenfold slower in Gamble lung fluid simulant. For both solutions, the time for half the material to go into solution differed only by factors of 1/83 to 1/17 to 1 for MnSO4, Mn phosphate, and Mn3O4, respectively, consistent with measured differences in size distribution, specific surface, and dissolution rate constant. These data suggest that dissolution mechanisms only played a role in the pulmonary clearance of MnSO4, while nonabsorptive (e.g., mechanical transport) mechanisms predominate for the less soluble phosphate and oxide forms of Mn.

67. Yasui M, Ota K, Garruto RM. (1995) Effects of calcium-deficient diets on manganese deposition in the Central Nervous system and bones of rats. Neurotoxicology (Little Rock) 16(3):511-517.
BIOSIS COPYRIGHT: BIOL ABS. The presence of both aluminum (AI) and manganese (Mn) in central nervous system tissues (CNS) has been reported in Parkinson's disease and in parkinsonism-dementia (PD) on Guam. Epidemiological surveys on Guam have suggested that low calcium (Ca), magnesium (Mg) and high Al and Mn in river, soil and drinking water may be implicated in the pathogenesis of PD. Experimentally, low Ca-Mg diets with or without added Al have been found to accelerate All deposition in the CNS of rats and monkeys. Although excessive deposition of Mn produces similar neurotoxic action to Al in CNS tissues, the mechanism of Mn deposition coupled with All loading in the presence of low Ca-Mg intake is not yet known. In this study, the deposition and metal-metal interaction of both Al and Mn in the CNS, visceral organs and bones of rats fed unbalanced mineral diets were analyzed. Male Wistar rats, weighing 200 g, were maintained for 90 days on the following diets: (A) standard diet, (B) low Ca diet

68. Yokel RA, Crossgrove JS, Bukaveckas BL. (2003) Manganese distribution across the blood-brain barrier II. Manganese efflux from the brain does not appear to be carrier mediated. Neurotoxicology 24(1):15-22.
There is concern about manganese (Mn) neurotoxicity. Mn can enter the brain by carrier-mediated influx. There have been no previous reports of investigation of Mn efflux from the brain. We used an established method that determines the rate of efflux out of the brain across the blood-brain barrier (BBB) from the product of the brain distribution volume (V-brain) and the apparent elimination rate constant (K-el). V-brain is determined as Mn-54 uptake into rat parietal brain slices versus time. Ke, is determined from the percentage of Mn-54 remaining in the brain at various times after its discrete injection into the parietal cortex, compared to a reference compound which is expected to very slowly diffuse out of the brain. The Mn ion, Mn citrate and Mn transferrin (Mn Tf) were studied. C-14-sucrose and C-14-dextran were used as reference compounds. The volume of distribution of the Mn species in brain slices was similar to3-5 ml/g, indicating concentrative uptake. Mn, as the Mn ion or Mn citrate, was injected into the brain with sucrose or dextran to determine K-el. Based on the rapid exchange rate of Mn with ligands and on thermodynamic calculations, injection of Mn ion or Mn citrate into the brain would be expected to result in rapid formation of the same Mn species, predominantly the Mn ion, Mn citrates and Mn phosphate, in brain extracellular fluid. After injection into the brain Mn did not efflux from the brain more rapidly than sucrose or dextran, which diffuse across the BBB. Brain capillary diffusion of the Mn ion and Mn citrate would be expected to be slower than sucrose or dextran. The rate of Mn efflux from the brain is consistent with diffusion.

69. Yu IJ, Park JD, Park ES, Song KS, Han KT, Han JH, Chung YH, Choi BS, Chung KH, Cho MH. (2003) Manganese distribution in brains of Sprague-Dawley rats after 60 days of stainless steel welding-fume exposure. Neurotoxicology 24(6):777-785.
Welders working in a confined space, as in the shipbuilding industry, are at risk of being exposed to high concentrations of welding fumes and developing pneumoconiosis or other welding-fume exposure related diseases. Among such diseases, manganism resulting from welding-fume exposure remains a controversial issue, as the movement of manganese into specific brain regions has not yet been clearly established. Accordingly, to investigate the distribution of manganese in the brain after welding-fume exposure, male Sprague-Dawley rats were exposed to welding fumes generated from manual metal arc-stainless steel (MMA-SS) at concentrations of 63.6 +/- 4.1 mg/m(3) (low dose, containing 1.6 mg/m(3) Mn) and 107.1 +/- 63 mg/m(3) (high dose, containing 3.5 mg/m(3) Mn) total suspended particulate (TSP) for 2 h per day in an inhalation chamber over a 60-day period. Blood, brain, lung, and liver samples were collected after 2 h, 15, 30, and 60 days of exposure and the tissues analyzed for their manganese concentrations using an atomic absorption spectrophotometer Although dose- and time-dependent increases in the manganese concentrations were found in the lungs and livers of the rats exposed for 60 days, only slight manganese increases were observed in the blood during this period. Major statistically significant increases in the brain manganese concentrations were detected in the cerebellum after 15 days of exposure and up until 60 days. Slight increases in the manganese concentrations were also found in the substantia nigra, basal ganglia (caudate nucleus, putamen, and globus pallidus), temporal cortex, and frontal cortex, thereby indicating that the pharmacokinetics and distribution of the manganese inhaled from the welding fumes

were different from those resulting from manganese-only exposure. (C) 2003 Elsevier Science Inc. All rights reserved.

70. Zaloglu N, Yildirim G, Bastug M, Koc E, Ficicilar H, Sayal A. (2002) High dosage of manganese chloride application and iron zinc copper status in rats. Trace Elements and Electrolytes 19(3):138-142.
We examined the distribution of manganese in rat liver, ileum and brain tissues after chronic administration (50 days) of high-dose MnCl2 and investigated spectrophotometrically the interactions between manganese and some other trace metals (iron, copper, zinc) levels. In the experimental group (n = 10), MnCl2 (30 mg/kg/day) was injected for 50 days intraperitoneally. Plasma, erythrocyte, brain, liver and ileum manganese levels were found elevated compared to control group (n = 10). Brain iron levels did not change whereas liver and ileum iron levels increased significantly. Moreover, brain copper and zinc levels did not change, but liver copper and zinc levels were found elevated. Ileum copper levels also increased, but ileum zinc levels did not change compared to control group. The significant increase in erythrocyte manganese content may be due to mitochondrial MnSOD in red blood cells. This situation might have helped to potantiate the antioxidant defense system of organism against free oxygen radicals produced by Mn-induced oxidation reaction.

71. Zheng W, Kim H, Zhao QQ. (2000) Comparative toxicokinetics of manganese chloride and methylcyclopentadienyl manganese tricarbonyl (MMT) in Sprague-Dawley rats. Toxicological Sciences 54(2):295-301.
The toxicokinetics of manganese (Mn) was investigated in male and female rats either following a single intravenous (iv) or oral dose of MnCl2 (6.0 mg Mn/kg), or following a single oral dose of methylcyclopentadienyl manganese tricarbonyl (MMT) (20 mg MMT/kg or 5.6 mg Mn/kg). The plasma concentrations of manganese were quantified by atomic absorption spectrophotometry (AAS). Upon iv administration of MnCl2, manganese rapidly disappeared from blood with a terminal elimination t(1/2) of 1.83 h and CLs of 0.43 L/h/kg. The plasma concentration-time profiles of manganese could be described by C = 41.9e(-4.24t) + 2.1e(-0.44t). Following oral administration of MnCl2, manganese rapidly entered the systemic circulation (T-max = 0.25 h). The absolute oral bioavailability was about 13%. Oral dose of MMT resulted in a delayed T-max (7.6 h), elevated C-max (0.93 mu g/ml), and prolonged terminal t(1/2) (55.1 h). The rats receiving MMT had an apparent clearance (CL/F = 0.09 L/h.kg) about 37-fold less than did those who were dosed with MnCl2. Accordingly, the area under the plasma concentration-time curves (AUC) of manganese in MMT-treated rats was about 37-fold greater than that in MnCl2-treated rats. A gender-dependent difference in toxicokinetic profiles of plasma manganese was also observed. Female rats displayed a greater AUC than that of male rats. Although the apparent volume of distribution of manganese was similar in both sexes, the apparent clearance in males was about twice that observed in females. The results indicated that after oral administration, the MMT-derived manganese displayed higher and more prolonged plasma concentration-time profiles than MnCl2-derived manganese. Thus, MMT-derived manganese appeared likely to accumulate in the body following repeated exposure.

72. Zheng W, Zhao QQ, Slavkovich V, Aschner M, Graziano JH. (1999) Alteration of iron homeostasis following chronic exposure to manganese in rats. Brain Research 833(1):125-132.

Recent studies suggest that manganese-induced neurodegenerative toxicity may be partly due to its action on aconitase, which participates in cellular iron regulation and mitochondrial energy production. This study was performed to investigate whether chronic manganese exposure in rats influenced the homeostasis of iron in blood and cerebrospinal fluid (CSF). Groups of 8-10 rats received intraperitoneal injections of MnCl2 at the dose of 6 mg Mn/kg/day or equal volume of saline for 30 days. Concentrations of manganese and iron in plasma and CSF were determined by atomic absorption spectrophotometry. Rats exposed to manganese showed a greatly elevated manganese concentration in both plasma and CSF. The magnitude of increase in CSF manganese (11-fold) was equivalent to that of plasma (10-fold). Chronic manganese exposure resulted in a 32% decrease in plasma iron ($p < 0.01$) and no changes in plasma total iron binding capacity (TIBC). However, it increased CSF iron by 3-fold as compared to the controls($p < 0.01$). Northern blot analyses of whole brain homogenates revealed a 34% increase in the expression of glutamine synthetase ($p < 0.05$) with unchanged metallothionein-I in manganese-intoxicated rats. When the cultured choroidal epithelial cells derived from rat choroid plexus were incubated with MnCl2 (100 mu M) for four days, the expression of transferrin receptor mRNA appeared to exceed by 50% that of control($p < 0.002$). The results indicate that chronic manganese exposure alters iron homeostasis possibly by expediting unidirectional influx of iron from the systemic circulation to cerebral compartment. The action appears likely to be mediated by manganese-facilitated iron transport at brain barrier systems.

Supporting References (45)

1. Alarcon OM, ReinosaFuller JA, Silva T, DeFernandez MR, Gamboa J. (1996) Manganese levels in serum of healthy Venezuelan infants living in Merida. Journal of Trace Elements in Medicine and Biology 10(4):210-213.
Taking up where a previous paper had left off (10) the purpose of this study was to examine in further detail the serum concentration of manganese of 180 apparently healthy Venezuelan infants (96 boys and 84 girls) ranging from 5 days to 12 months old, all residents of Merida. The flow injection analysis-atomic absorption spectrophotometric technique was used for the determination of manganese. The mean values of serum manganese were 0.42+/-0.12, 0.41+/-0.11, 0.39+/-0.13, 0.39+/-.1, 0.38+/-0.09. 0.37+/-0.11, 0.36+/-0.12 and 0.29+/-0.10 mu g/L in infants 5 days and 1,3,5,7,10,11 and 12 months old, respectively. These values indicate that the average concentration of manganese in serum decreases with age, but the mechanism involved is not yet known, nor are the consequences of the decrease. The statistical analysis did not show any significant influence of sex on the serum value of the metal in the age range of 5 days to 12 months.

2. Anderson JG, Cooney PT, Erikson KM. (2007) Brain manganese accumulation is inversely related to gamma-amino butyric acid uptake in male and female rats. Toxicological Sciences 95(1):188-195.
Iron (Fe) is an essential trace metal involved in numerous cellular processes. Iron deficiency (ID) is reported as the most prevalent nutritional problem worldwide. Increasing evidence suggests that ID is associated with altered neurotransmitter metabolism and a risk factor for manganese (Mn) neurotoxicity. Though recent studies have established differences in which the female brain responds to ID-related neurochemical alterations versus the male brain, little is known

about the interactions of dietary ID, Mn exposure, and sex on gamma-amino butyric acid (GABA). Male and female Sprague-Dawley rats were randomly divided into four dietary treatment groups: control (CN), control/ Mn supplemented, ID, and ID/Mn supplemented. After 6 weeks of treatment, both ID diets caused a highly significant decrease in Fe concentrations across all brain regions compared to CN in both sexes. Both ID and Mn supplementation led to significant accumulation of Mn across all brain regions in both sexes. There was no main effect of sex on Fe or Mn accumulation. Striatal synaptosomes were utilized to examine the effect of dietary intervention on H-3-GABA uptake. At 4 weeks, there was a significant correlation between Fe concentration and H-3-GABA uptake in male rats ($p < 0.05$). At 6 weeks, there was a significant inverse correlation between Mn concentration and 3H-GABA uptake in male and female rats and a postitive correlation between Fe concentration and H-3-GABA uptake in female rats ($p < 0.05$). In conclusion, ID-associated Mn accumulation is similar in both sexes, with Mn levels affecting GABA uptake in both sexes in a comparable fashion.

3. Anderson JG, Cooney PT, Erikson KM. (2007) Inhibition of DAT function attenuates manganese accumulation in the globus pallidus. Environmental Toxicology and Pharmacology 23(2):179-184.
Manganese (Mn) is an essential nutrient, though exposure to high concentrations may result in neurotoxicity characterized by alterations in dopamine neurobiology. To date, it remains elusive how and why Mn targets dopaminergic neurons although recently the role of the dopamine transporter has been suggested. Our primary goal of this study was to examine the potential roles of the monoamine transporters, dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET), in neuronal Mn transport. Using striatal synaptosomes, we found that only inhibition of DAT significantly decreased Mn accumulation. Furthermore, weanling rats chronically exposed to Mn significantly accumulated Mn in several brain regions. However, rats receiving the specific DAT inhibitor GBR 12909 (1 mg/kg bw, three times/week; 4 weeks) had significantly lower Mn levels only in the globus pallidus compared to saline-treated rats ($p < 0.05$). Our data show that inhibition of DAT exclusively inhibits Mn accumulation in the globus pallidus during chronic exposure.

4. Anderson JG, Fordahl SC, Cooney PT, Erikson KM. (2007) Iron deficiency and manganese exposure are associated with decreases in neurotransmitter uptake. Faseb Journal 21(6):A1065-A1065.

5. Arnaud J, Bourlard P, Denis B, Favier AE. (1996) Plasma and erythrocyte manganese concentrations - Influence of age and acute myocardial infarction. Biological Trace Element Research 53(1-3):129-136.
This study was carried out to assess manganese (Mn) status after an acute episode of myocardial infarction. Plasma and erythrocyte Mn concentrations were measured from admission to hospital to day 15 postadmission in 21 patients suffering from acute myocardial infarction and in three control groups. The determination of Mn in these biological fluids was performed by electrothermal atomic absorption spectrometry. Plasma Mn was higher ($p <0.01$) and erythrocyte Mn was similar in the acute myocardial infarction group compared to healthy age-matched control group. Plasma and erythrocyte Mn remained unchanged during the 2 wk after acute myocardial infarction and were not correlated to enzyme activities. A decrease of erythrocyte

Mn with age, expressed in nmol/L, was noted ($p < 0.02$). These results suggest that plasma and erythrocyte Mn do not provide an indication of myocardial damage. Nonetheless, Mn status in elderly merits further attention.

6. Arnold ML, McNeill FE, Chettle DR. (1999) The feasibility of measuring manganese concentrations in human liver using neutron activation analysis. Neurotoxicology 20(2-3):407-412.
Manganese is an element which is required by the human body. However, as with most metals, in large amounts manganese can be toxic. People who suffer from severe manganese intoxication have symptoms similar to those of Parkinson's disease. Preclinical symptoms of manganese intoxication have recently been detected in individuals working in industries which have manganese dioxide dust in the air. The concentration of many toxic elements can be measured in vivo using neutron activation. A small dose of neutrons is delivered to the organ of interest, the neutrons are readily captured by the target nuclei, and the gamma rays given off can be detected outside of the body. A neutron activation analysis system is being developed to measure manganese concentrations in humans. The McMaster KN-accelerator supplies the neutron beam and the thermal neutron capture reaction Mn-55(n,gamma)Mn-56 is used. The half-life of Mn-56 is 2.58 hr and thus counting can occur after irradiation. The 847 keV gamma ray given off when 56Mn decays is detected using a Nal detector. Calibration curves are made using phantoms with known concentrations of Mn. This system will be used to monitor manganese levels in individuals who have occupational exposure to the element. Preliminary measurements, using liver phantoms, give a minimum detectable limit for Mn in the liver of less than one part per million, which is well below normal levels. (C) 1999 Inter Press, Inc.

7. Aschner M. (2000) Manganese: Brain transport and emerging research needs. Environmental Health Perspectives 108:429-432.
Idiopathic Parkinson's disease (IPD) represents a common neurodegenerative disorder. An estimated 2% of the U.S. population, age 65 and older, develops IPD. The number of IPD patients will certainly increase over the next several decades as the baby-boomers gradually step into this high-risk age group, concomitant with the increase in the average life expectancy. While many studies have suggested that industrial chemicals and pesticides may underlie [PD, its etiology remains elusive. Among the toxic metals, the relationship between manganese intoxication and IPD has long been recognized. The neurological signs of manganism have received close attention because they resemble several clinical disorders collectively described as extrapyramidal motor system dysfunction, and in particular, IPD and dystonia. However, distinct dissimilarities between IPD and manganism are well established, and it remains to be determined whether Mn plays an etiologic role in IPD. It is particularly noteworthy that as a result of a recent court decision, methylcyclopentadienyl Mn tricarbonyl (MMT) is presently available in the United States and Canada for use in fuel, replacing lead as an antiknock additive. The impact of potential long-term exposure to low levels of MMT combustion products that may be present in emissions from automobiles has yet to be fully evaluated. Nevertheless, it should be pointed out that recent studies with Various environmental modeling approaches in the Montreal metropolitan (where MMT has been used for more than 10 years) suggest that airborne Mn revels were quite similar to those in areas where MMT was not used. These studies also show that Mn is emitted from the tail pipe of motor vehicles primarily as a mixture of manganese phosphate and manganese sulfate. This brief review characterizes the Mn speciation in the blood

and the transport kinetics of Mn into the central nervous system, a critical step in the accumulation of Mn within the brain, outlines the potential susceptibility of selected populations (e.g., iron-deficient) to Mn exposure, and addresses future research needs for Mn.

8. Aschner M, Vrana KE, Zheng W. (1999) Manganese uptake and distribution in the central nervous system (CNS). Neurotoxicology 20(2-3):173-180.
Information about the nature of manganese (Mn)-binding ligands in plasma and serum, and its transport mechanism across the blood-brain barrier (BBB) is sparse. Most studies to date have focused on distribution, excretion, and accumulation of intravenous and intraperitoneal solutions of soluble divalent salts of Mn. Mn is transported in the blood primarily in the divalent oxidation state (Mn2+) and crosses the BBB via specific carriers ata rate far slower than in other tissues. Mn transport across the BBB occurs both in the 2+ and 3+ oxidation state. Within the CNS, Mn accumulates primarily within astrocytes, presumably because the astrocyte-specific enzyme, glutamine synthetase (GS) represents an important regulatory target of Mn. Compared to Mn2+, Mn3+ has a slower elimination rate and therefore, may have a greater tendency to accumulate in tissues. Furthermore, in view of the dependence of Mn accumulation within the CNS on iron (Fe) homeostasis, the oxidation state of Mn may represent a key determinant in the differential distribution, accumulation and secretion profiles of Mn, a fact that has received little attention in experimental biology toxicology. Accordingly, the distribution and membrane transport of Mn emphasizes the importance of: 1) the oxidation state of Mn, as it governs the affinity of Mn to endogenous ligands, and 2) the reaction of Mn3+ with transferrin, the plasma iron-carrying protein. This review will focus on transport kinetics of Mn across the BBB (both in the 2+ and 3+ oxidation state), the putative role of transferrin in the transport of Mn across the BBB, the transport of Mn by astrocytes, as well as the physiological significance of Mn to the function GS. (C) 1999 Inter Press, Inc.

9. Boojar MMA, Goodarzi F, Basedaghat MA. (2002) Long-term follow-up of workplace and well water manganese effects on iron status indexes in manganese miners. Archives of Environmental Health 57(6):519-528.
The authors assessed the effect of water reconstitution in the workplace by evaluating the iron status of manganese mine workers during a long-term study. Subsequent analyses and biological monitoring were performed in a group of 150 manganese miners before, and 2.8 yr after, reconstitution of drinking water in the miners' workplace. The authors found significantly high concentrations of manganese in the workplace well water, as well as in the miners' blood, urine, and hair. There was a considerable prevalence of epithelial lesions, which resulted from iron deficiency, in the miners, compared with controls. The authors assessed the prevalence of iron deficiency grades (i.e., I > II > III > IV) before and after water reconstitution. Reconstitution of drinking water for the ultimate attainment of healthy levels of manganese and other minerals resulted in a significant improvement in the miners' iron status and a decreased prevalence of epithelial lesions. The authors concluded that alterations in iron status may result from the cumulative effect of high levels of manganese in consumed water, as well as in airborne dust, in the workplace. Such elevated levels should be considered as an occupational hazard because they have an ability to interfere with iron absorption.

10. Bouchard M, Mergler D, Baldwin M, Sassine MP, Bowler R, MacGibbon B. (2003) Blood manganese and alcohol consumption interact on mood states among manganese alloy production workers. Neurotoxicology 24(4-5):641-647.
Long-term exposure to manganese (Mn) can induce neurotoxic effects including neuromotor, neurocognitive and neuropsychiatric effects, but there is a great interpersonal variability in the occurrence of these effects. It has recently been suggested that blood Mn (MnB) may interact with alcohol use disorders, accentuating neuropsychiatric symptoms. The objective of the present study was to explore a possible interaction between alcohol consumption and MnB on mood states, using an existing data set on Mn exposed workers. Respirable Mn exposure in the plant averaged 0.23 mg/m(3) and was correlated with MnB. All participants for whom all data on MnB concentration and mood (assessed with the Profile of Mood States (POMS)) were available and who reported currently drinking alcohol were included in the analyses (n = 74). Workers were grouped according to their MnB concentration (<10 and greater than or equal to10 mug/l) and alcohol consumption (<400 and greater than or equal to400 g per week). Two-way ANOVAs were performed on each POMS scale and Mann-Whitney tests were used to assess group differences. Workers in the higher alcohol consumption group had higher scores on three POMS scales: tension, anger and fatigue. There was no difference for POMS scale scores between MnB subgroups. Dividing the group with respect to alcohol consumption and MnB showed that the group with high alcohol consumption and high MnB displayed the highest scores. In the lower MnB category, those in the higher alcohol consumption group did not have higher scores than the others. The interaction term for alcohol consumption and MnB concentration was statistically significant ($P < 0.05$) for the depression, anger fatigue and confusion POMS scales. There was a tendency for tension ($P < 0.06$), and it was not significant for vigor. This study shows the first evidence of an interaction between MnB and alcohol consumption on mood states among Mn exposed workers and supports the results from a previous population-based study.

11. Bressler JP, Olivi L, Cheong JH, Kim Y, Maerten A, Bannon D. (2007) Metal transporters in intestine and brain: their involvement in metal-associated neurotoxicities. Human & Experimental Toxicology 26(3):221-229.
The transport of essential metals and other nutrients across tight membrane barriers such as the gastrointestinal tract and blood-brain barrier is mediated by specific transport mechanisms. Specific transporters take up metals at the apical surface and export them at the basolateral surface, and are involved in their intracellular distribution. Transporters for each of the major essential metals, calcium, iron and zinc, have been identified. These transporters also mediate the transport of non-essential metals across tight membrane barriers. For example, the intestinal iron transporter divalent metal transporter 1 mediates the uptake of lead and cadmium. The levels of essential metals are strictly regulated by transporters. When dietary levels of essential metals are low, levels of the corresponding transporters increase in the intestine, after which there is a greater potential for increased transport of toxic metals. In the brain, the strict regulation of metals prevents injury that potentially would result from oxidative damage induced by the essential metals iron, copper and zinc. Indeed, the oxidative damage found in neurodegenerative diseases is likely to be due to higher levels of these metals. Involvement of intracellular transporters for copper and zinc has been shown in animal models of Alzheimer's disease, raising the possibility that higher levels of iron, zinc and copper might be due to a disruption in the

activity of transporters. Accordingly, exposure to toxicants that affect the activity of transporters potentially could contribute to the aetiology/progression of neurodegenerative diseases.

12. Bukalis K, Kyriakopoulos A, Alber D, Richarz AN, Behne D. (2006) Study on the distribution of trace elements and trace element-containing proteins in the lung of the rat. Trace Elements and Electrolytes 23(2):108-112.
The concentrations of arsenic, chromium, cobalt, iron, manganese, rubidium, selenium and zinc were determined by instrumental neutron activation analysis (INAA) in the homogenate and the subcellular fractions of lungs from rats fed either a selenium-adequate or a selenium-deficient diet. Feeding of the selenium-deficient diet led to a considerable decrease in the selenium levels in all samples investigated but had no significant effect on the concentrations of the other elements. All elements were distributed inhomogeneously among the subcellular fractions. Selenium, iron and zinc had their highest concentrations in the microsomal fraction, chromium and cobalt in the nuclear fraction and arsenic and rubidium in the cytosol. Information about the trace element-containing proteins in the lung cytosol was obtained by size exclusion chromatography and online multi-element analysis of the separated protein fractions by mass spectrometry in conjunction with an inductively coupled plasma (ICP-MS). The results suggested that arsenic, cadmium, cobalt, copper, iron, manganese, rnolybdenum, nickel, selenium and zinc are present in the rat lung cytosol in several protein-bound forms.

13. Chaki H, Furuta S, Matsuda A, Yamauchi K, Yamamoto K, Kokuba Y, Fujibayashi Y. (2000) Magnetic resonance image and blood manganese concentration as indices for manganese content in the brain of rats. Biological Trace Element Research 74(3):245-257.
Neurological disorders similar to parkinsonian syndrome and signal hyperintensity in brain on TI-weighted magnetic resonance (MR) images have been reported in patients receiving long-term total parenteral nutrition (TPN). These symptoms have been associated with manganese (Mn) depositions in brain. Although alterations of signal intensity on T-1-weighted MR images in brain and of Mn concentration in blood are theoretically considered good indices for estimating Mn deposition in brain, precise correlations between these parameters have not been demonstrated as yet. Male Sprague-Dawley rats received TPN with 10-fold the clinical dose of the trace element preparation (TE-5) for 7 d. At 0, 2, 4, 6, and 8 wk post-TPN, the cortex, striatum, midbrain, and cerebellum were evaluated by MR images, and Mn concentration in blood and Mn content in these brain sites were measured by atomic absorption spectrometry. Immediately after TPN termination, signal hyperintensity in brain sites and elevated Mn content in blood and brain sites were observed. These values recovered at 4 wk post-TPN. A positive correlation was observed between either the signal intensity in certain brain sites or Mn content in blood and the relevant brain sites.

14. Chen GT, Zhao L, Bao SF, Cong T. (2006) Effects of different proteins on the metabolism of Zn, Cu, Fe, and Mn in rats. Biological Trace Element Research 113(2):165-175.
Many factors are known to influence trace element metabolism and one of them is dietary protein. The present study examines the effects of casein, soybean protein, and peanut protein on the metabolism of the Zn, Cu, Fe, and Mn in growing rats. The results showed that Zn, Fe, and Mn excretions in the feces of peanut protein-fed rats (PPERs) were similar to that of casein-fed rats (CPFRs) ($p > 0.05$), whereas all of the Zn, Cu, Fe, and Mn excretions in the urine of PPFRs were significantly higher than that of CPFRs ($p < 0.05$), but its apparent absorption rate (AAR)

of Cu, Fe and its apparent retention rate (ARR) of Cu were all higher than that of CPFRs ($p < 0.05$). Hepatic Zn content of soybean protein-fed rats (SPFRs) was higher than that of CPFRs and PPFRs ($p < 0.05$ respectively) and serum, renal, and femoral Cu contents of SPFRs were significantly lower; however, hepatic Cu, and renal Mn contents were significantly higher than that of CPFRs ($p < 0.05$, respectively); The hepatic Fe content of SPFRs was significantly higher than that of CPFRs and PPFRs ($p < 0.01$, respectively). To sum up, compared to casein, soybean protein might be a good dietary source to make up for Zn and Fe deficiency, and also peanut protein to make up for Cu and Fe deficiency.

15. Chen MT, Sheu JY, Lin TH. (2000) Protective effects of manganese against lipid peroxidation. Journal of Toxicology and Environmental Health-Part A 61(7):569-577.
The aim of this study was to investigate the effects of chronic, daily, 30-d administration of manganese chloride (MnCl2) to male Sprague-Dawley rats on lipid peroxidation in various tissues. Rats were intraperitoneally injected with MnCl2 (20 mg/kg) once daily for 30 consecutive days. The Mn accumulated in liver, spleen, adrenal glands, heart, kidneys, lung, and testes. This was associated with decreased lipid peroxidation in liver, spleen, and adrenal glands and a decrease in the levels of Fe in these tissues. In a second group of animals, Mn (20 mg/kg/d) and glutathione (GSH, 15 mg/kg/d) were administered ip for 30 d. GSH counteracted the Mn-induced protective fall in lipid peroxidation, but Fe levels remained lower in liver and spleen. Mn decreases lipid peroxidation in certain tissues, which may involve lowering Fe content, but interaction with Fe is not the sole mechanism.

16. Chua ACG, Stonell LM, Savigni DL, Morgan EH. (1996) Mechanisms of manganese transport in rabbit erythroid cells. Journal of Physiology-London 493(1):99-112.
1. The mechanisms of manganese transport into erythroid cells were investigated using rabbit reticulocytes and mature erythrocytes and Mn-54-labelled MnCl2 and Mn-2-transferrin. In some experiments iron uptake was also studied. 2. Three saturable manganese transport mechanisms were identified, two for Mn2+ (high and low affinity processes) and one for transferrin-bound manganese (Mn-Tf). 3. High affinity Mn2+ transport occurred in reticulocytes but not erythrocytes, was active only in low ionic strength media such as isotonic sucrose and had a K-m of 0.4 mu M. It was inhibited by metabolic inhibitors and several metal ions. 4. Low affinity Mn2+ transport occurred in erythrocytes as well as in reticulocytes and had K-m values of approximately 20 and 50 mu M for the two types of cells, respectively. The rate of Mn2+ transport was maximal in isotonic KCl, RbCl or CsCl, and was inhibited by NaCl and by amiloride, valinomycin, diethylstilboestrol and other ion transport inhibitors. The direction of Mn2+ transport was reversible, resulting in Mn2+ efflux from the cells. 5. The uptake of transferrin-bound manganese occurred only with reticulocytes and depended on receptor-mediated endocytosis of Mn-Tf. 6. The characteristics of the three saturable manganese transport mechanisms were similar to corresponding mechanisms of iron uptake by erythroid cells, suggesting that the two metals are transported by the same mechanisms. 7. It is proposed that high affinity manganese transport is a surface representation of the process responsible for the transport of manganese across the endosomal membrane after its release from transferrin. Low affinity transport probably occurs by the previously described Na+ - Mg2+ antiport, and may function in the regulation of intracellular manganese concentration by exporting manganese from the cells.

17. Crossgrove JS, Yokel RA. (2004) Manganese distribution across the blood-brain barrier III - The divalent metal transporter-1 is not the major mechanism mediating brain manganese uptake. Neurotoxicology 25(3):451-460.
Manganese (Mn) is essential for and toxic to the brain. Brain Mn uptake utilizes both diffusion and transporter-mediated pathways. The divalent metal transporter-1 (DMT-1) has been suggested to mediate brain Mn uptake. The b/b Belgrade rat does not express significant amounts of functional DMT-1. In the present work, brain influx transfer coefficients of Mn-54 ion and Mn-54 transferrin (Mn Tf) were determined in b/b and +/b Belgrade and Wistar rats using the in situ brain perfusion technique. Brain Mn uptake was not significantly different among the three rat strains for either Mn species. We hypothesized that Mn may enter brain endothelial cells by a DMT-1-independent process but not be able to distribute across those cells into brain tissue due to the absence of DMT-1 activity. To test this hypothesis the brain capillary endothelial cells were isolated from b/b and +/b Belgrade rats and Wistar rats after in situ brain perfusion. Some animals received cerebrovascular washout after in situ brain perfusion to ascertain any affect of genotype on Mn-54 adsorption to the endothelial cell luminal surface. Less than 30% of the brain Mn-54 after Mn-54 ion or Mn-54 Tf perfusion remained associated with endothelial cells, suggesting the majority had distributed into brain extracellur fluid (ECF) and/or brain cells. Mn appears to distribute across the rat blood-brain barrier (BBB) into the brain by one or more carrier-mediated processes other than the DMT-1.

18. Erikson KM, Aschner M. (2006) Increased manganese uptake by primary astrocyte cultures with altered iron status is mediated primarily by divalent metal transporter. Neurotoxicology 27(1):125-130.
Neurotoxicity due to excessive brain manganese (Mn) accumulation can occur via occupational exposure to aerosols or dusts that contain extremely high levels (>1-5 mg Mn/m(3)) of Mn, or metabolic aberrations (decreased biliary excretion). Given the putative role of astrocytes in regulating the movement of metals across the blood-brain barrier, we sought to examine the relationship between iron (Fe) status and Mn transport in astrocytes. Furthermore, our study examined the effect of Fe status on astrocytic transferrin receptor (TfR) and divalent metal transporter (DMT1) levels and their relationship to Mn uptake, as both have been implicated as putative Mn transporters. All experiments were carried out in primary astrocyte cultures derived from neonatal rats when the cells reached full confluency (about three weeks in culture). Astrocytes were incubated for 24 h in astrocyte growth medium (AGM) containing 200 mu M desferroxamine (11)), 500 mu M ferrous sulfate (+Fe), or no compound (CN). After 24 h, 5 min Mn-54 uptake was measured and protein was harvested from parallel culture plates for DMT-1 and TfR immunoblot analysis. Both iron deprivation (ID) and iron overload (+Fe) caused significant increases ($p < 0.05$) in 54 Mn uptake in astrocytes. TfR levels were significantly increased ($p < 0.05$) due to ID and decreased in astrocytes exposed to +Fe treatments. As expected, DMT-1 was increased due to Fe deprivation, but surprisingly, DMT-1 levels were also increased due to +Fe treatment, albeit not to the extent noted in ID. The decreased TfR associated with +Fe treatment and the increased DMT-1 levels suggest that DMT-1 is a likely putative transporter of Mn in astrocytes.

19. Erikson KM, John CE, Jones SR, Aschner M. (2005) Manganese accumulation in striatum of mice exposed to toxic doses is dependent upon a functional dopamine transporter. Environmental Toxicology and Pharmacology 20(3):390-394.
The objective of this study was to determine the importance of the dopamine transporter (DAT) in manganese transport. Excessive manganese exposure is associated with a neurotoxicological disease known as manganism characterized by a specific accumulation of manganese in dopamine-rich brain regions. It has been hypothesized that the DAT mediates this specific transport, but its role in manganese neurotoxicity has not been directly examined. We examined brain tissues from manganese-ex posed dopamine transporter knockout (DAT-KO) and wildtype (WT) mice. There was significantly less ($p < 0.05$) manganese in the striatum of exposed DAT-KO mice compared to WT. However, the absence of a functioning DAT did not affect manganese accumulation in other brain regions examined. Furthermore, both iron and divalent metal transporter levels (two known modulators of brain manganese) were similar between DAT-KO and WT mice in all brain regions. These studies demonstrate that the DAT is involved in the facilitation of striatal manganese accumulation and that it may play a critical role in mediating manganese neurotoxicity.

20. Finley JW. (1998) Manganese uptake and release by cultured human hepato-carcinoma (Hep-G2) cells. Biological Trace Element Research 64(1-3):101-118.
The liver is the primary organ involved in manganese (Mn) homeostasis. The human hepato-carcinoma cell line, Hep-G2, shows many liver specific functions. Consequently, Hep-G2 cells were investigated as a possible model of hepatic metabolism of Mn. Initial experiments showed that the concentration of Mn in the diet, or culture medium, similarly affected the retention of Mn by isolated rat hepatocytes and Hep-G2 cells. Manganese uptake by Hep-G2 cells suggested that uptake was followed by release from the cell. Uptake was saturable and half-maximal at 2.0 mu mol Mn/L, and was inhibited by iodoacetate, vanadate, cold, and bepridil. The cations Fe2+, Cu2+ Ni2+, Cd2+, and Zn2+ decreased Mn uptake. Uptake was dependent on Calcium (Ca) concentration in a manner that resembled saturation kinetics. Cells that were pulsed with Mn-54 and then placed into nonradioactive medium quickly released a large portion of their internalized Mn. Release of internalized Mn could be inhibited by low temperature, nocodozole, quinacrine and sodium azide. These data show that Hep-G2 cells are a potentially good model of hepatic Mn metabolism. Mn is taken up by a facilitated process that may be related to Ca uptake. Release apparently is an active, controlled process, that may involve microtubules and lysosomes.

21. Finley JW, BriskeAnderson M, Gregoire B. (1996) Metabolism of manganese by isolated rat hepatocytes and by the Hep-G2 cell line. Faseb Journal 10(3):4736-4736.

22. Fitsanakis VA, Piccola G, Aschner JL, Aschner M. (2005) Manganese transport by rat brain endothelial (RBE4) cell-based transwell model in the presence of astrocyte conditioned media. Journal of Neuroscience Research 81(2):235-243.
Manganese (Mn), an essential nutrient, is neurotoxic at high levels and has been associated with the development of a parkinsonian syndrome termed manganism. Currently, the mechanisms responsible for transporting Mn across the blood-brain barrier (BBB) are unknown. By using rat brain endothelial 4 (RBE4) cell monolayers cultured in astrocyte-conditioned media (ACM), we examine the effects of temperature, energy, proton (pH), iron (Fe), and sodium (Na+)

dependence on Mn transport. Our results suggest that Mn transport is temperature, energy, and pH dependent, but not Fe or Na+-dependent. These data suggest that Mn transport across the BBB is an active process, but they also demonstrate that the presence of ACM in endothelial cell cultures decreases the permeability of these cells to Mn, reinforcing the use of ACM or astrocyte cocultures in studies examining metal transport across the BBB. (c) 2005 Wiley-Liss, Inc.

23. Fitsanakis VA, Piccola G, Aschner JL, Aschner M. (2006) Characteristics of manganese (Mn) transport in rat brain endothelial (RBE4) cells, an in vitro model of the blood-brain barrier. Neurotoxicology 27(1):60-70.
Manganese (Mn), an essential elemental nutrient, is known to be neurotoxic at high occupational levels. We examined the transport of Mn across a monolayer of rat brain endothelial cell (RBE4) to evaluate whether an electromotive permeability mechanism is responsible for Mn transport across the blood-brain barrier (BBB). The Mn-54(2+) apparent permeability and flux showed significant temperature-, energy- and pH-dependence, as well as partial sodium-dependence. Additionally, iron (Fe)-rich and Fe-deficient media significantly increased the apparent permeability of Mn-54(2+). Finally, Mn flux and permeability decreased when RBE4 cells were grown in astrocyte-conditioned media (ACM), compared to standard alpha-media. These data reinforce observations that transport of Mn across the BBB occurs in part through active transport process. (C) 2005 Elsevier Inc. All rights reserved.

24. Fitsanakis VA, Piccola G, dos Santos AP, Aschner JL, Aschner M. (2007) Putative proteins involved in manganese transport across the blood-brain barrier. Human & Experimental Toxicology 26(4):295-302.
Manganese (Mn) is an essential nutrient required for proper growth and maintenance of numerous biological systems. At high levels it is known to be neurotoxic. While focused research concerning the transport of Mn across the blood-brain barrier (BBB) is on-going, the exact identity of the transporter(s) responsible is still debated. The transferrin receptor (TfR) and the divalent metal transporter-1 (DMT-1) have long been thought to play a role in brain Mn deposition. However, evidence suggests that Mn may also be transported by other proteins. One model system of the BBB, rat brain endothelial (RBE4) cells, are known to express many proteins suspected to be involved in metal transport. This review will discuss the biological importance of Mn, and then briefly describe several proteins that may be involved in transport of this metal across the BBB. The latter section will examine the potential usefulness of RBE4 cells in characterizing various aspects of Mn transport, and basic culture techniques involved in working with these cells. It is hoped that ideas put forth in this article will stimulate further investigations into the complex nature of Mn transport, and address the importance as well as the limitation of in vitro models in answering these questions.

25. Gallez B, Baudelet C, Adline J, Geurts M, Delzenne N. (1997) Accumulation of manganese in the brain of mice after intravenous injection of manganese-based contrast agents. Chemical Research in Toxicology 10(4):360-363.
Because the manganese-based contrast agents used in magnetic resonance imaging are unstable in vivo, some concern exists about the potential toxicity coming from the Mn2+ released by the complexes. This potential problem arises because the manganese is known to accumulate in the brain of people intoxicated by this metal (manganism): this central accumulation leads to neurological disorders (i.e., parkinsonism-like syndrome). The aim of this study was to assess

the amount of Mn found in the brain after administration of MnCl2 or different chelates of Mn in normal mice as well as in mice with impaired biliary elimination. Male NMRI mice received an intravenous injection in a caudal vein of 5 mu mol/kg of Mn-54 compounds as MnCl2, manganese-diethylenetriaminepentaacetate (Mn-DTPA), or manganese-dipyridoxal diphosphate (Mn-DPDP). The radiolabeled complexes (1:1) were prepared by direct chelation (Mn-DTPA) or transchelation of preformed complex (Mn-DPDP), and the radiochemical purity was assessed by paper chromatography. The mice were killed at various times post-exposure (0-3 months), and the radioactivity present in the organs was determined by gamma counting. For each compound analyzed in the present study, we observed an accumulation of Mn (0.25-0.3% of the amount injected/g of tissue) in the mouse brain, reaching a plateau after 24 h, while the Mn content in the liver was decreasing with time. The amount of Mn accumulated in the brain remained unchanged 1 month later, but decreased to 40% of the maximum amount 3 months after the exposure. In mice whose bile ducts had been ligated 24 h before the administration of the manganese compound, we observed, 1 week after the injection, an amount of manganese accumulated in the brain 2 times higher than in normal mice.

26. Garrick MD, Dolan KG, Horbinski C, Ghio AJ, Higgins D, Porubcin M, Moore EG, Hainsworth LN, Umbreit JN, Conrad ME and others. (2003) DMT1: A mammalian transporter for multiple metals. Biometals 16(1):41-54.
DMT1 has four names, transports as many as eight metals, may have four or more isoforms and carries out its transport for multiple purposes. This review is a start at sorting out these multiplicities. A G185R mutation results in diminished gastrointestinal iron uptake and decreased endosomal iron exit in microcytic mice and Belgrade rats. Comparison of mutant to normal rodents is one analytical tool. Ectopic expression is another. Antibodies that distinguish the isoforms are also useful. Two mRNA isoforms differ in the 3' UTR: + IRE DMT1 has an IRE (Iron Responsive Element) but -IRE DMT1 lacks this feature. The +/- IRE proteins differ in the distal 18 or 25 amino acid residues after shared identity for the proximal 543 residues. A major function is serving as the apical iron transporter in the lumen of the gut. The + IRE isoform appears to have that role. Another role is endosomal exit of iron. Some evidence indicts the -IRE isoform for this function. In our ectopic expression assay for metal uptake, four metals - Fe2+,Mn2+,Ni2+ and Co2+ - respond to the normal DMT1 cDNA but not the G185 R mutant. Two metals did not - Cd2+ and Zn2+ -andtwo -Cu2+ and Pb2+ -remain to be tested. In competition experiments in the same assay, Cd2+,Cu2+ and Pb2+ inhibit Mn2+ uptake but Zn2+ did not. In rodent mutants, Fe and Mn appear more dependent on DMT1 than Cu and Zn. Experiments based on ectopic expression, specific antibodies that inhibit metal uptake and labeling data indicate that Fe3+ uptake depends on a different pathway in multiple cells. Two isoforms localize differently in a number of cell types. Unexpectedly, the -IRE isoform is in the nuclei of cells with neuronal properties. While the function of -IRE DMT1 in the nucleus is speculative, one may safely infer that this localization identifies new role(s) for this multifunctional transporter. Management of toxic challenges is another function related to metal homeostasis. Airways represent a gateway tissue for metal entry. Preliminary evidence using specific PCR primers and antibodies specific to the two isoforms indicates that -IRE mRNA and protein increase in response to exposure to metal in lungs and in a cell culture model; the + IRE form is unresponsive. Thus the -IRE form could be part of a detoxification system in which + IRE DMT1 does not participate. How does iron status affect other metals' toxicity? In the case of Mn, iron deficiency may enhance cellular responses.

27. Gavin CE, Gunter KK, Gunter TE. (1999) Manganese and calcium transport in mitochondria: Implications for manganese toxicity. Neurotoxicology 20(2-3):445-453.
Mn2+ is sequestered by liver and brain mitochondria via the mitochondrial Ca2+ uniporter. The mitochondrial Ca2+ uniporter is a cooperative transport mechanism possessing an external activation site and a transport site. Ca2+ binding to the activation site greatly increases the velocity of uptake of both Ca2+ and Mn2+. Electron paramagnetic resonance (EPR) shows that over 97% of the Mn2+ in the mitochondrial matrix is normally bound to the membrane or to matrix proteins. EPR measurements of manganese within living isolated mitochondria can be repeat-ed for hours, and during this time most of the manganese remains in the Mn2+ state. Mn2+ is transported out of mitochondria via the very slow Na+-independent efflux mechanism, which is an active (energy-requiring) mechanism. Mn2+ is not significantly transported over the Na+-dependent efflux mechanism, which is the dominant efflux mechanism in heart and brain mitochondria. Mn2+ inhibits the efflux of Ca2+ through both of these efflux mechanisms, having an apparent K-i of 7.9 nmol/mg protein on the Na+-independent efflux mechanism and an apparent K-i of 5.1 nmol/mg on the Na+-dependent efflux mechanism. Mn2+ inhibition of Ca2+ efflux may increase the probability of the mitochondria undergoing the mitochondrial permeability transition (MPT). Intramitochondrial Mn2+ also inhibits State 3 mitochondrial respiration using either succinate or malate plus glutamate as substrate. The data suggest that Mn2+ depletes cellular energy supplies by interfering with oxidative phosphorylation at the level of the F(1)ATPase and at much higher concentrations, at Complex I. Effects such as these could lead to apoptosis in active neurons. (C) 1999 Inter Press, Inc.

28. Harris WR. (2003) Modeling methods to determine Al and Mn speciation for toxicity assessment. Toxicological Sciences 72:117-117.

29. Heilig EA, Thompson KJ, Molina RM, Ivanov AR, Brain JD, Wessling-Resnick M. (2006) Manganese and iron transport across pulmonary epithelium. American Journal of Physiology-Lung Cellular and Molecular Physiology 290(6):L1247-L1259.
Pathways mediating pulmonary metal uptake remain unknown. Because absorption of iron and manganese could involve similar mechanisms, transferrin (Tf) and transferrin receptor (TfR) expression in rat lungs was examined. Tf mRNA was detected in bronchial epithelium, type II alveolar cells, macrophages, and bronchus-associated lymphoid tissue (BALT). Tf protein levels in lung and bronchoalveolar lavage fluid did not change in iron deficiency despite increased plasma levels, suggesting that lung Tf concentrations are regulated by local synthesis in a manner independent of body iron status. Iron oxide exposure upregulated Tf mRNA in bronchial and alveolar epithelium, macrophages, and BALT, but protein was not significantly increased. In contrast, TfR mRNA and protein were both upregulated by iron deficiency. To examine potential interactions with lung Tf, rats were intratracheally instilled with Mn-54 or Fe-59. Unlike Fe-59, interactions between Mn-54 and Tf in lung fluid were not detected. Absorption of intratracheally instilled Mn-54 from the lungs to the blood was unimpaired in Belgrade rats homozygous for the functionally defective G185R allele of divalent metal transporter-1, indicating that this transporter is also not involved in pulmonary manganese absorption. Pharmacological studies of Mn-54 uptake by A549 cells suggest that metal uptake by type II alveolar epithelial cells is associated with activities of both L-type Ca2+ channels and TRPM7, a member of the transient receptor potential melastatin subfamily. These results demonstrate that iron and manganese are

absorbed by the pulmonary epithelium through different pathways and reveal the potential role for nonselective calcium channels in lung metal clearance.

30. Kim Y, Park JK, Choi Y, Yoo CI, Lee CR, Lee H, Lee JH, Kim SR, Jeong TH, Yoon CS and others. (2005) Blood manganese concentration is elevated in iron deficiency anemia patients, whereas globus pallidus signal intensity is minimally affected. Neurotoxicology 26(1):107-111. Objectives: To determine whether blood manganese (Mn) concentration is elevated in patients with iron deficiency anemia (IDA), and whether this affects signal intensities in the globus pallidus. Methods: Twenty-seven patients with IDA and 10 control subjects were tested for blood Mn, and brain magnetic resonance images (MRI) were also examined. Seventeen of the 27 patients were followed-up after iron therapy. Results: IDA patients had a mean blood Mn concentration of 2.05 +/- 0.44 mug/dl, which was higher than controls. The mean pallidal index (PI) of anemic patients was not different from that of controls. There was a correlation between log blood Mn and PI ($p = 0.384$, $P = 0.048$; $n = 27$) in IDA patients. None of the patients showed increased signals in the globus pallidus in TI-weighted MRI Blood Mn levels decreased and hemoglobin levels increased after iron therapy ($P < 0.05$). Conclusion: Although blood Mn is elevated in IDA patients, there is no increase in globus pallidus MRI signal intensity. These findings stand in contrast to those of our other studies showing patients with chronic liver disease or occupational Mn exposure have elevated signal intensities remarkably.

31. Kucera J, Bencko V, Sabbioni E, Vandervenne MT. (1995) Review of Trace-Elements in Blood, Serum and Urine for the Czech and Slovak Populations and Critical-Evaluation of Their Possible Use as Reference Values. Science of the Total Environment 166(1-3):211-234.
The availability of accurate trace element reference values in human tissues represents an important indicator to the health status of the general population and occupational groups exposed to trace elements. The EURO TERVIHT project (Trace Element Reference Values in Human Tissues) aims to establish and compare trace element reference values in tissues from inhabitants of the European countries as baseline values for clinical/toxicological assessment studies [3]. In this context, one of the first steps considered is the critical evaluation (state of the art) of existing literature on trace element reference values in blood, serum and urine in the general population of each European country. This paper reviews the Czech and Slovak situation by assessing studies carried out in these countries for Al, As, Cd, Co, Cr, Cu, F, Mn, Hg, Ni, Pb, Rb, Sc, Se, V and Zn in blood, serum and urine. These studies show that most of the data available do not meet criteria designed recently for deriving reference intervals, especially regarding the number of subjects, the age of population sample studies as well as the use of appropriate sampling techniques and quality assurance procedures. Elements which present the highest potential risk for health in Czech and Slovak populations and for which reference values should be urgently established are: Cd, Hg, Pb (major pollutants); As, Cr, Ni (carcinogenic metals); Al, F, Mn, Tl, V (released into the environment by coal combustion and other industrial activities); Pt (increasing use of Pt catalyst in petrol-driven automobiles); essential trace elements such as I, Se and Zn for which a deficiency in Czech and Slovak populations was detected or is suspected.

32. Lai JCK, Minski MJ, Chan AWK, Leung TKC, Lim L. (1999) Manganese mineral interactions in brain. Neurotoxicology 20(2-3):433-444.

Manganese (Mn) is an essential mineral but is toxic when taken in excess. However, whether its interactions with other minerals in organs and cells are involved in mechanisms underlying Mn toxicity is poorly understood. We designed a developmental rat model of chronic Mn treatment (Group A: 1 mg MnCl2. 4H(2)O per mi of drinking water; Group B: 10 mg MnCl2. 4H(2)O per mi of drinking water; Group C: 20 mg MnCl2. 4H(2)O per mi of drinking water; Control Group given water without manganese addition). Employing the model and instrumental neutron activation analysis, we investigated two hypotheses: (i) chronic manganese treatment alters the brain regional distribution of manganese and this altered manganese distribution also leads to region-specific changes of other meta Is; (ii) chronic manganese treatment induces differential changes in subcellular distributions of metals and electrolytes. In the treated rats, brain Mn level showed dose-related increases, the most pronounced being noted in striatum, hypothalamus, and hippocampus: these increases also led to alterations in regional distribution pattern of Mn. In the treated rats, Fe level was increased in hypothalamus, cerebellum, hippocampus, pens and medulla, and striatum. CLI level was increased in pens and medulla, hippocampus, midbrain, and striatum. Se level was increased in cerebellum, striatum, midbrain, hypothalamus, and pens and medulla. Zn level was increased in hypothalamus and striatum. Ca level was increased in midbrain but decreased in cerebellum; however, Mg and Al levels were not markedly affected, in brains of fn-treated rats, Mn levels in subcellular fractions were all increased, being especially marked in nuclei, mitochondria, and synaptosomes; the subcellular distributions of Fe, Cu, Zn, and Mg were differentially altered although those of Al and Ca were minimally affected. These results are consistent with our hypotheses and may have implications in manganese neurotoxicity. The cellular and molecular mechanisms underlying manganese-mineral interactions in brain are still poorly defined and merit further investigation. (C) 1999 Inter Press, Inc.

33. Li GJJ, Zhang LL, Lu L, Wu P, Zheng W. (2004) Occupational exposure to welding fume among welders: Alterations of manganese, iron, zinc, copper, and lead in body fluids and the oxidative stress status. Journal of Occupational and Environmental Medicine 46(3):241-248. Welders in this study were selected from a vehicle manufacturer; control subjects were from a nearby food factory. Airborne manganese levels in the breathing zones of welders and controls were 1.45 +/- SD1.08 mg/m(3) and 0.11 +/- 0.07 mug/m(3), respectively. Serum levels of manganese and iron in welders were 4.3-fold and 1.9-fold, respectively, higher than those of controls. Blood lead concentrations in welders increased 2.5-fold, whereas serum zinc levels decreased 1.2-fold, in comparison with controls. Linear regression revealed the lack of associations between blood levels of five metals and welder's age. Furthermore, welders had erythrocytic superoxide dismutase activity and serum malondialdehyde levels 24% less and 78% higher, respectively, than those of controls. These findings suggest that occupational exposure to welding fumes among welders disturbs the homeostasis of trace elements in systemic circulation and induces oxidative stress.

34. Malecki EA, Cable EE, Connor JR. (2000) Short-term dietary manganese deficiency increases intestinal expression of DMT-1. Faseb Journal 14(4):A229-A229.

35. Malecki EA, Cook BM, Devenyi AG, Beard JL, Connor JR. (1999) Transferrin is required for normal distribution of Fe-59 and Mn-54 in mouse brain. Journal of the Neurological Sciences 170(2):112-118.

Hypotransferrinemia (hpx/hpx) is a genetic defect in mice resulting in <1% of normal plasma transferrin (Tf) concentrations; heterozygotes for this mutation (+/hpx) have low circulating Tf concentrations. These mice provide a unique opportunity to examine the role of Tf in Fe and Mn transport in the brain. Twenty weanling wild-type BALB/cJ mice, 15 + /hpx mice, and 12 hpx/hpx mice of both sexes were injected i.v. with either (MnCl2)-Mn-54, or (FeCl3)-Fe-59 either 1 h or 1 week before killing at 12 weeks of age. Total brain counts of Mn-54 and Fe-59 were measured, and regional brain distributions were assessed by autoradiography. Hypotransferrinemia did not affect total brain Mn uptake. However, 1 week after i.v. injection, hpx/hpx mice had less Mn-54 in forebrain structures including cerebral cortex, corpus callosum, striatum, and substantia nigra. The +/hpx mice had the highest total brain Fe-59 accumulation 1 h after i.v. injection. A striking effect of regional distribution of Fe-59 was noted I week after injection; in hpx/hpx mice, Fe-59 was located primarily in choroid plexus, whereas in +/+ and +/hpx mice Fe-59 was widely distributed, with relatively high amounts in cerebral cortex and cerebellum. We interpret these data to mean that Tf is necessary for the transport of Fe but not Mn across the blood-brain barrier, and that there is a Tf-independent uptake mechanism for iron in the choroid plexus. Additionally, these data suggest that endogenous synthesis of Tf is necessary for Fe transport from the choroid plexus.

36. Malecki EA, Devenyi AG, Connor JR. (1997) Manganese (Mn) transport in mice heterozygotic for hypotransferrinemia mutation: Effects of iron (Fe) deficiency. Gastroenterology 112(4):A891-A891.

37. Matsumoto K, Inagaki T, Hirunuma R, Enomoto S, Endo K. (2001) Contents and uptake rates of Mn, Fe, Co, Zn, and Se in Se-deficient rat liver cell fractions. Analytical Sciences 17(5):587-591.
The contents of manganese (Mn), iron (Fe), cobalt (Co), zinc (Zn), and selenium (Se) in nuclear (NU), mitochondrial (MT), microsomal (MC), and cytosolic (CS) fractions of liver homogenates of normal and selenium-deficient (SeD) rats were determined by instrumental neutron activation analysis (INAA). The uptake rates of these elements in the liver cell fractions of both groups of rats were determined by multitracer analysis (MTA). The results indicated that Se-deficiency caused a significant increase in the content of Fe in the MC fractions. The MTA showed that the uptake rate of Fe was highest in the MC fraction, and that the uptake rate in the fraction was similar between the SeD and normal rats.

38. Reaney SH, Kwik-Uribe CL, Smith DR. (2002) Manganese oxidation state and its implications for toxicity. Chemical Research in Toxicology 15(9):1119-1126.
Manganese (Mn) is ubiquitous in mammalian systems and is essential for proper development and function, though it can also be toxic at elevated exposures. While essential biologic functions of Mn depend on its oxidation state [e.g., Mn(II), Mn(III)], little is known about how the oxidation state of elevated Mn exposures affect cellular uptake, and function/toxicity. Here we report the dynamics of EPR measurable Mn(II) in fresh human plasma and cultured PC12 cell lysates as a function of exposure to either manganese(II) chloride or manganese(III) pyrophosphate, and the effects of exposure to Mn(II) versus Mn(III) on total cellular aconitase activity and cellular Mn uptake. The results indicate that Mn(II) or Mn(III) added in vitro to fresh human plasma or cell lysates yielded similar amounts of EPR measurable Mn(II). In

contrast, Mn added as Mn(III) was significantly more effective in inhibiting total cellular aconitase activity, and intact PC 12 cells accumulated significantly more Mn when exposures occurred as Mn(III)., Collectively, these data reflect the dynamic nature of Mn speciation in simple biological systems, and the importance of Mn oxidation/speciation state in mediating potential cellular toxicity. This study supports concern over increased environmental exposures to Mn in different oxidation states [Mn(II), Mn(III), and Mn(IV)] that may arise from combustion products of. the gasoline antiknock additive methycyclopentadienyl manganese tricarbonyl (MMT).

39. Slikker W, Keenan F. (1998) Toxicokinetics and bioavailability of manganese: Session II summary and research needs. Neurotoxicology 19(3):475-478.

40. Takeda A, Devenyi A, Connor JR. (1998) Evidence for non-transferrin-mediated uptake and release of iron and manganese in glial cell cultures from hypotransferrinemic mice. Journal of Neuroscience Research 51(4):454-462.
Transferrin (Tf) is accepted as the iron mobilization protein, but its role in transport of other metals is controversial, In this study, we used mixed glial cultures from hypotransferrinemic (Hp) mice to determine the dependence of these cells on transferrin for iron and manganese delivery and release, Hp mice have a splicing defect in the transferrin (Tf) gene, resulting in < 1% of the normal plasma levels of Tf, Cellular iron and manganese uptake increases over 24 hr in cultures of normal and Hp glial cells in the presence of standard concentrations of Tf in the media; although total (59)iron uptake in the Hp mouse cultures was 2X greater than normal, Mn-54 uptake was similar between the two groups, The absence of Tf in the media resulted in a significant increase in (59)iron uptake in both normal and Hp glial but did not affect Mn uptake, Elevated Tf (10X normal) in the media reduced both (59)iron and Mn-54 uptake, Efflux of (59)Iron and Mn-54 occurred in normal and Hp cultures, indicating the existence of a dynamic exchange of metals, and that intracellular Tf is not necessary for metal release, However, in the absence of Tf in the media, significantly more iron was retained in the cells than if Tf were present in both normal and Hp glial cultures. Mn-54 release was minimally affected by extracellular Tf. The data demonstrate that Tf is not required for iron and Mn uptake into glial cells, These data further demonstrate a dynamic metal exchange system for glial cells which is not dependent on intracellular Tf. (C) 1998 Wiley-Liss, Inc.

41. Tiffany-Castiglioni E, Qian YC. (2001) Astroglia as metal depots: Molecular mechanisms for metal accumulation, storage and release. Neurotoxicology 22(5):577-592.
The brain is an organ that concentrates metals, and these metals are often localized to astroglia. An examination of metal physiology of brain cells, particularly astroglia, offers insights into the developmental neurotoxicity of certain metals, including lead (Pb), mercury (Hg), manganese (Mn), and copper (Cu). Xenobiotic metals probably accumulate in cells by exploiting the normal functions of proteins that transport and handle essential metals. In addition, essential metals may become toxic by accumulating at levels that exceed the normal metal buffering capacity of the cell. This review considers the uptake, accumulation, storage, and release of two xenobiotic metals, Pb and Hg, as well as two essential nutrient metals that are neurotoxic in high amounts, Mn and Cu. Evidence that each metal accumulates in astroglia is evaluated, together with the mechanisms the host cell may invoke to protect itself from cytoxicity,

42. Wang X, Li JG, Zheng W. (2005) Overexpression Of Dmt1 In The Choroid Plexus Following Manganese (Mn) Exposure. Toxicol Sci 84(1-S):122.
Divalent Metal Transporter 1 (DMT1), whose mRNA possesses a 3'-UTR stemloop structure, has been identified in most organs and responsible for transport of various divalent metal ions. Previous work from this laboratory has shown that Mn exposure alters the function of iron regulatory protein (IRP) and increases iron (Fe) concentrations in blood-cerebrospinal fluid (CSF). This study aimed to test the hypothesis that Mn treatment, by acting on protein-mRNA binding between IRP and DMT1 mRNA, altered the expression of DMT1 in the choroid plexus (CP), where the blood-CSF barrier resides, leading to a compartmental shift of Fe from the blood to CSF. Western blot and real time PCR confirmed the presence of DMT1 in an immortalized choroidal epithelial Z310 cell line. Following in vitro exposure to Mn at 100 µM for 24 and 48 hrs, the expression of DMT1 mRNA in Z310 cells was significantly increased by 45.4% ($p < 0.05$) and 78.1% ($p < 0.01$), respectively, as compared to controls. Accordingly, Western blot analysis revealed a significant increase of DMT1 protein concentrations at 48 hr after Mn exposure (100 µM). When rats received, by oral gavage, 5 and 15 mg Mn/kg as MnCl2 per day for 30 consecutive days, the levels of DMT1 mRNA in choroids plexus tissues were significantly increased by 258% and 305% ($p < 0.05$), respectively. An electrophoretic mobility shift assay (EMSA), by using S100 cytosolic extracts from both in vitro cells and in vivo brain tissues, was conducted to investigate the effect of Mn exposure on the interaction between IRP and DMT1 mRNA. Results showed that Mn exposure increased binding of IRP to DMT1 mRNA in cultured choroidal Z310 cells, in animal CP, as well as in selected brain tissues. These data suggest that Mn appears to stabilize the binding of IRP to DMT1 mRNA, thereby increasing the expression of DMT1. The facilitated transport of Fe by DMT1 at the blood-CSF barrier may partly contribute to Mn-induced neurodegenerative Parkinsonism.

43. Yokel RA, Lasley SM, Dorman DC. (2006) The speciation of metals in mammals influences their toxicokinetics and toxicodynamics and therefore human health risk assessment. Journal of Toxicology and Environmental Health-Part B-Critical Reviews 9(1):63-85.
Chemical form (i.e., species) can influence metal toxicokinetics and toxicodynamics and should be considered to improve human health risk assessment. Factors that influence metal speciation (and examples) include: (1) carrier-mediated processes for specific metal species (arsenic, chromium, lead and manganese), (2) valence state (arsenic, chromium, manganese and mercury), (3) particle size (lead and manganese), (4) the nature of metal binding ligands (aluminum, arsenic, chromium, lead, and manganese), (5) whether the metal is an organic versus inorganic species (arsenic, lead, and mercury), and (6) biotransformation of metal species (aluminum, arsenic, chromium, lead, manganese and mercury). The influence of speciation on metal toxicokinetics and toxicodynamics in mammals, and therefore the adverse effects of metals, is reviewed to illustrate how the physicochemical characteristics of metals and their handling in the body (toxicokinetics) can influence toxicity (toxicodynamics). Generalizing from mercury, arsenic, lead, aluminum, chromium, and manganese, it is clear that metal speciation influences mammalian toxicity. Methods used in aquatic toxicology to predict the interaction among metal speciation, uptake, and toxicity are evaluated. A classification system is presented to show that the chemical nature of the metal can predict metal ion toxicokinetics and toxicodynamics. Essential metals, such as iron, are considered. These metals produce low oral toxicity under most exposure conditions but become toxic when biological processes that utilize or transport them

are overwhelmed, or bypassed. Risk assessments for essential and nonessential metals should consider toxicokinetic and toxicodynamic factors in setting exposure standards. Because speciation can influence a metal's fate and toxicity, different exposure standards should be established for different metal species. Many examples are provided which consider metal essentiality and toxicity and that illustrate how consideration of metal speciation can improve the risk assessment process. More examples are available at a website established as a repository for summaries of the literature on how the speciation of metals affects their toxicokinetics.

44. Zheng W, Aschner M, Ghersi-Egea JF. (2003) Brain barrier systems: a new frontier in metal neurotoxicological research. Toxicology and Applied Pharmacology 192(1):1-11.
The concept of brain barriers or a brain barrier system embraces the blood-brain interface, referred to as the blood-brain barrier, and the blood-cerebrospinal fluid (CSF) interface, referred to as the blood-CSF barrier. These brain barriers protect the CNS against chemical insults, by different complementary mechanisms. Toxic metal molecules can either bypass these mechanisms or be sequestered in and therefore potentially deleterious to brain barriers. Supportive evidence suggests that damage to blood-brain interfaces can lead to chemical-induced neurotoxicities. This review article examines the unique structure, specialization, and function of the brain barrier system, with particular emphasis on its toxicological implications. Typical examples of metal transport and toxicity at the barriers, such as lead (Pb), mercury (Hg), iron (Fe), and manganese (Mn), are discussed in detail with a special focus on the relevance to their toxic neurological consequences. Based on these discussions, the emerging research needs, such as construction of the new concept of blood-brain regional barriers, understanding of chemical effect on aged or immature barriers, and elucidation of the susceptibility of tight junctions to toxicants, are identified and addressed in this newly evolving field of neurotoxicology. They represent both clear challenges and fruitful research domains not only in neurotoxicology, but also in neurophysiology and pharmacology.

45. Zheng YX, Chan P, Pan ZF, Shi NN, Wang ZX, Pan J, Liang HM, Niu Y, Zhou XR, He FS. (2002) Polymorphism of metabolic genes and susceptibility to occupational chronic manganism. Biomarkers 7(4):337-346.
In this study we investigated genetic polymorphisms of five metabolizing genes and their association with occupational chronic manganism. We recruited 49 patients with chronic manganism and 50 unrelated healthy control subjects who were welders and ferromanganese smelters and occupationally exposed to manganese dust and fume in the same workshops from three metallurgical industries. The controls were matched to the cases by sex, age, cigarette and alcohol intake, as well as the manganese exposure duration. Polymerase chain reaction-restriction fragment length polymorphism (PCR-RFLP) was used to genotype the cytochrome P450 2D6L gene (CYP2D6L) and the NAD(P) H: quinone oxidoreductase gene (NQO1). Allele-specific PCR was used to detect the cytochrome P450 1A1 gene (CYP1A1), and the glutathione-S-transferase mu and theta genes (GSTM and GSTT). The frequency of polymorphic alleles, a mutation of CYP2D6L, was significantly lower in patients with chronic manganism (16.3%) than in controls (29.0%). Individuals with the homozygote polymorphism (L/L) of CYP2D6 had a 90% decreased risk of chronic manganism compared with the wild-type (Wt/Wt) (odds ratio =0.10, 95% confidence interval =0.01-0.82). A significant association between the CYP2D6 genotype subgroup and the latency of chronic manganese poisoning was also found. Patients

who had homozygous (L/L) or heterozygous (Wt/L) mutant alleles developed manganism an average of 10 years later than those who were homozygous wildtype (Wt/Wt). However, the allele and genotype frequencies of CYP1A1 and NQO1 genes were distributed similarly in cases and controls. In addition, no difference in the frequencies of GSTM1 and GSTT1 null genotypes were observed between cases and controls. The results suggest that CYP2D6L gene polymorphism might influence susceptibility to manganese-induced neurotoxicity. However, because of limited sample size, our results should be validated in large-scale studies.

3.2 PHYSIOLOGICALLY BASED TOXICOKINETIC MODELS

Key References (7)

1. Andersen ME, Gearhart JM, Clewell HJ. (1999) Pharmacokinetic data needs to support risk assessments for inhaled and ingested manganese. Neurotoxicology 20(2-3):161-171.
Manganese (Mn)-deficiency or Mn-excess can lead to adverse biological consequences. Central nervous system tissues, rich in dopaminergic neurons, are the targets whether the Mn gains entrance by inhalation, oral ingestion, or intravenous administration. Risk assessments with Mn need to ensure that brain concentrations in the globus pallidus and striatum stay within the range of normal. This paper first provides a critical review of the biological factors that determine the disposition of Mn in tissues within the body. Secondly, it outlines specific data needs for developing a physiologically based pharmacokinetic (PBPK) model for Mn to assist in conducting risk assessments for inhaled and ingested Mn. Uptake of dietary Mn appears to be controlled by several dose-dependent processes: biliary excretion, intestinal absorption, and intestinal elimination. Mn absorbed in the divalent form from the gut via the portal blood is complexed with plasma proteins that are efficiently removed by the liver. Absorption of Mn via inhalation, intratracheal instillation or intravenous infusions bypasses the control processes in the gastrointestinal tract. After absorption into the blood system by these alternate routes, Mn is apparently oxidized by ceruloplasmin and the trivalent Mn binds to the iron carrying protein, transferrin. Brain uptake of Mn occurs via transferrin receptors located in various brain regions. Transferrin-bound trivalent Mn is not as readily removed by the liver, as are protein complexes with divalent Mn. Thus, Mn delivered by these other dose routes would be available for uptake into tissues for a longer period of time than the orally administered Mn, leading to quantitative differences in tissue uptake for different dose routes. Several important data gaps impede organizing these various physiological factors into a multi-dose route PK model for Mn. They include knowledge of (1) oxidation rates of Mn in blood, (2) uptake rates of protein-bound forms of Mn by the liver, (3) neuronal transfer rates within the CNS, and (4) quantitative analyses of the control processes that regulate uptake of ingested Mn by the intestines and liver. These data gaps are the main obstacles to developing a risk assessment strategy for Mn that considers contributions of both inhalation and ingestion of this essential nutrient in determining brain Mn concentrations. (C) 1999 Inter Press, Inc.

2. Aschner M, Erikson KM, Dorman DC. (2005) Manganese dosimetry: Species differences and implications for neurotoxicity. Critical Reviews in Toxicology 35(1):1-32.
Manganese (Mn) is an essential mineral that is found at low levels in food, water, and the air. Under certain high-dose exposure conditions, elevations in tissue manganese levels can occur. Excessive manganese accumulation can result in adverse neurological, reproductive, and

respiratory effects in both laboratory animals and humans. In humans, manganese-induced neurotoxicity (manganism) is the overriding concern since affected individuals develop a motor dysfunction syndrome that is recognized as a form of parkinsonism. This review primarily focuses on the essentiality and toxicity of manganese and considers contemporary studies evaluating manganese dosimetry and its transport across the blood-brain barrier, and its distribution within the central nervous system (CNS). These studies have dramatically improved our understanding of the health risks posed by manganese by determining exposure conditions that lead to increased concentrations of this metal within the CNS and other target organs. Most individuals are exposed to manganese by the oral and inhalation routes of exposure; however, parenteral injection and other routes of exposure are important. Interactions between manganese and iron and other divalent elements occur and impact the toxicokinetics of manganese, especially following oral exposure. The oxidation state and solubility of manganese also influence the absorption, distribution, metabolism, and elimination of manganese. Manganese disposition is influenced by the route of exposure. Rodent inhalation studies have shown that manganese deposited within the nose can undergo direct transport to the brain along the olfactory nerve. Species differences in manganese toxicokinetics and response are recognized with nonhuman primates replicating CNS effects observed in humans while rodents do not. Potentially susceptible populations, such as fetuses, neonates, individuals with compromised hepatic function, individuals with suboptimal manganese or iron intake, and those with other medical states (e.g., pre-parkinsonian state, aging), may have altered manganese metabolism and could be at greater risk for manganese toxicity.

3. Dorman DC, Struve MF, Clewell HJ, Andersen ME. (2006) Application of pharmacokinetic data to the risk assessment of inhaled manganese. Neurotoxicology 27(5):752-764.
There is increased interest within the scientific community concerning the neurotoxicity of manganese owing in part to the use of methylcyclopentadienyl manganese tricarbonyl (MMT) as a gasoline fuel additive and an enhanced awareness that this essential metal may play a role in hepatic encephalopathy and other neurologic diseases. Neurotoxicity generally arises over a prolonged period of time and results when manganese intake exceeds its elimination leading to increases in brain manganese concentration. Neurotoxicity can occur following high dose oral, inhalation, or parenteral exposure or when hepatobiliary clearance of this metal is impaired. Studies completed during the past several years have substantially improved our understanding of the health risks posed by inhaled manganese by determining exposure conditions that lead to increased concentrations of manganese within the central nervous system and other target organs. Many of these studies focused on phosphates, sulfates, and oxides of manganese since these are formed and emitted following MMT combustion by an automobile. These studies have evaluated the role of direct nose-to-brain transport of inhaled manganese and have examined differences in manganese toxicokinetics in potentially sensitive subpopulations (e.g., fetuses, neonates, individuals with compromised hepatic function or sub-optimal manganese intake, and the aged). This manuscript reviews the U.S. Environmental Protection Agency's current risk assessment for inhaled manganese, summarizes these contemporary pharmacokinetic studies, and considers how these data could inform future risk assessments of this metal following inhalation.

4. Heilig E, Molina R, Donaghey T, Brain JD, Wessling-Resnick M. (2005) Pharmacokinetics of pulmonary manganese absorption: evidence for increased susceptibility to manganese loading

in iron-deficient rats. American Journal of Physiology-Lung Cellular and Molecular Physiology 288(5):L887-L893.
High levels of airborne manganese can be neurotoxic, yet little is known about absorption of this metal via the lungs. Intestinal manganese uptake is upregulated by iron deficiency and is thought to be mediated by divalent metal transporter 1 (DMT1), an iron-regulated factor known to play a role in dietary iron absorption. To better characterize metal absorption from the lungs to the blood and test whether iron deficiency may modify this process, the pharmacokinetics of pulmonary manganese and iron absorption by control and iron-deficient rats were compared. Levels of DMT1 expression in the lungs were determined to explore potential changes induced by iron deficiency that might alter metal absorption. The pharmacokinetic curves for intratracheally instilled Mn-54 and Fe-59 were significantly different, suggesting that pulmonary uptake of the two metals involves different mechanisms. Intratracheally instilled iron-deficient rats had significantly higher blood Mn-54 levels, whereas blood Fe-59 levels were significantly reduced compared with controls. The same trend was observed when radioisotopes were delivered by intravenous injection, indicating that iron-deficient rats have altered blood clearance of manganese. In situ analysis revealed the presence of DMT1 transcripts in airway epithelium; however, mRNA levels did not change in iron deficiency. Although lung DMT1 levels and metal absorption did not appear to be influenced by iron deficiency, the differences in blood clearance of instilled manganese identified by this study support the idea that iron status can influence the potential toxicity of this metal.

5. Teeguarden JG, Dorman DC, Covington TR, Clewell HJ, 3rd, Andersen ME. (2007) Pharmacokinetic modeling of manganese. I. Dose dependencies of uptake and elimination. J Toxicol Environ Health A 70(18):1493-1504.
Homeostatic mechanisms controlling uptake, storage, and elimination of dietary manganese (Mn) afford protection against fluctuations in tissue manganese (Mn) levels. Homeostatic control of inhaled Mn is less well understood, but important in assessing likely risks of Mn inhalation. Two compartmental kinetic models were used to characterize the influence of Mn exposure level and route (oral, inhalation) on uptake, elimination, and transport of Mn. The models were fitted to or used to interpret data from five whole-body Mn elimination studies: one dietary Mn balance study, two biliary elimination studies, and one acute and one chronic. As dietary Mn concentrations increased from low sufficiency (1.5 ppm) to sufficiency (20 ppm), control of Mn uptake shifts from the intestine (principally) to more proportional control by both intestinal tissues and liver. Using a two-compartment distribution model, the increased elimination of 54Mn tracer doses in response to increases in dietary Mn (rats and mice) or inhaled Mn (rats) resulted from elevation in Mn elimination rate constants rather than changes in intercompartmental transfer rate constants between a central compartment and deep compartment. The pharmacokinetic (PK) analysis also indicated differential control of absorption in single gavage oral dose studies versus continuous high oral doses in the feed. The gavage study indicated increased elimination rate constants, and the chronic study showed reduced rate constants for absorption. These dose dependencies in uptake and elimination are necessary inputs for comprehensive PK models guiding human health risk assessments with Mn.

6. Teeguarden JG, Dorman DC, Nong A, Covington TR, Clewell HJ, 3rd, Andersen ME. (2007) Pharmacokinetic modeling of manganese. II. Hepatic processing after ingestion and inhalation. J Toxicol Environ Health A 70(18):1505-1514.

Current concerns regarding inhalation exposure to Mn, a component from oxidation of the gasoline antiknock agent MMT, have stimulated interest in developing kinetic tools for describing the inhalation and combined inhalation/oral route kinetics of Mn. Kinetic approaches were integrated kinetic for (1) bulk tissue Mn kinetics and (2) hepato-intestinal control of oral-route Mn uptake into a integrated model structure connecting systemic and oral Mn. Linkages were developed between the hepato-intestinal and systemic tissues in order to evaluate differences in hepatic processing of orally absorbed Mn and systemic Mn. The integrated, unified model described the uptake, net absorption, and elimination of ingested Mn and the elimination kinetics of i.v. administered (systemic) Mn by treating Mn arriving at the liver from systemic versus portal blood differently. Hepatic extraction of orally absorbed Mn in rats predicted through simulation of the oral uptake data was 19, 54, and 78% at dietary exposures of 1.5, 11.2, and 100 ppm, respectively. In contrast, hepatic extraction of systemic Mn predicted through simulation of elimination kinetics i.v. tracer Mn was much less, 0.004, 0.005, or 0.009% at dietary levels of 2, 10, and 100 ppm, respectively. These differences in hepatic processing of blood Mn derived from different dose routes need to be accounted for in more complete PK models for Mn that are intended to support human health risk assessments.

7. Teeguarden JG, Gearhart J, Clewell HJ, 3rd, Covington TR, Nong A, Andersen ME. (2007) Pharmacokinetic modeling of manganese. III. Physiological approaches accounting for background and tracer kinetics. J Toxicol Environ Health A 70(18):1515-1526.
Manganese (Mn), an essential metal nutrient, produces neurotoxicity in workers exposed chronically to high concentrations of Mn-containing dusts. Our long-term goal was to develop a physiologically based pharmacokinetic (PBPK) model to support health risk assessments for Mn. A PK model that accounts for Mn-tracer kinetics and steady-state tissue Mn in rats on normal diets (about 45 ppm Mn) is described. The focus on normal dietary intakes avoids inclusion of dose-dependent processes that maintain Mn homeostasis at higher dose rates. Data used for model development were obtained from published literature. The model represents six tissues: brain, respiratory tract, liver, kidneys, bone, and muscle. Each of these has a shallow tissue pool in rapid equilibration with blood and a deep tissue store, connected to the shallow pool by transfer rate constants. Intraperitoneal (i.p.) tracer Mn is absorbed into systemic blood and equilibrated with the shallow and deep pools of tissue Mn. The model was calibrated to match steady-state tissue concentrations and radiotracer kinetics following an i.p. dose of 54Mn. Successful simulations showed uptake of 0.8% of dietary Mn, and estimated tissue partition coefficients and transfer rate constants in the tissues. Inhalation tracer 54Mn studies could only be adequately modeled by assuming that deposited Mn was absorbed into deep tissue stores in the lung before becoming available to move via blood to other tissues. In summary, this present effort provides the basic structure of a multiroute PBPK model for Mn that should now be easily extended to include homeostatic control and inhalation exposures in order to support risk assessment calculations for Mn.

Supporting References (0)

There were no supporting references identified for this section.

3.3 LIVER/GI FUNCTION

Key References (0)

There were no key references identified for this section.

Supporting References (12)

1. Agte V, Jahagirdar M, Chiplonkar S. (2005) Apparent absorption of eight micronutrients and phytic acid from vegetarian meals in ileostomized human volunteers. Nutrition 21(6):678-685. Objectives: Apparent absorption of eight micronutrients and degradation of phytic acid were studied in human subjects who underwent ileostomy. The prominent factors affecting micronutrient absorption from vegetarian Indian meals (n = 11) were identified. Methods: Levels of β-carotene, ascorbic acid, riboflavin, and thiamine in food and ileostomy contents were estimated by spectrophotometry and spectrofluorometry. Contents of zinc iron, copper, and manganese were estimated by atomic absorption spectrometry and that of phytic acid by gradient elution ion exchange chromatography. Statistical analyses were done with SPSS 10.0. Results: Absorption of β-carotene,. ascorbic acid, riboflavin, and thiamine was 63% to 75.6%. There was a negative non-significant trend in values of β-carotene absorption with increased intake of 0-carotene (r = -0.51, P > 0.1) and iron (r = -0.67, P = 0.1) but a positive significant trend with riboflavin intakes (r = 0.84, P = 0.018). Percentage of absorption of ascorbic acid showed weak positive associations with intakes of riboflavin (r = 0.71) and ascorbic acid (r = 0.5). Percentage of absorption of ascorbic acid was positively correlated. with percentage of absorption of β-carotene (r = 0.80, P < 0.05), iron, and riboflavin (r = 0.64, P = 0.086), indicating some common influencing factors. Percentages of absorption for zinc (20.2), iron (9.9), and copper (17.6) was comparable with those reported for soy. protein-based, high phytate diets. Pattern of phytic acid in the meals and output indicated partial degradation and absorption (34%). Conclusions: For vegetarian Indian meals, apparent absorptions of β-carotene and ascorbic acid were 76% and 73.5% and of riboflavin and thiamine was 63%. Zinc, copper, and iron showed a lower absorption (10% to 20%). © 2005 Elsevier Inc. All rights reserved.

2. Aschner JL, Furlong H, Daily D, Aschner M. (2006) Neuroimaging and neurodevelopmental correlates of intravenous manganese exposure in parente rally-fed infants: A clinical trial in the neonatal intensive care unit (NICU). Neurotoxicology 27(6):1168-1168.

3. Davis CD, Schafer DM, Finley JW. (1998) Effect of biliary ligation on manganese accumulation in rat brain. Biological Trace Element Research 64(1-3):61-74.
Neurologic and radiologic disorders have been reported to occur in miners inhaling manganese (Mn)-laden dust and in humans receiving long-term parenteral nutrition. These abnormalities have been attributed to Mn intoxication because of elevated serum Mn concentrations. Because the liver, by way of the bile, is the major route of Mn excretion, it is possible that anything that decreases biliary excretion could increase accumulation of Mn in the brain. The purpose of this study was to determine whether biliary ligation would increase Mn accumulation in the brain of rats that were exposed to deficient or adequate amounts of dietary manganese. The first experiment had a 2 x 3 factorial design, two levels of Mn (0 or 45 mu g/g diet) and three surgical

treatments (control, sham, or bile-ligation). Animals were sacrificed 10 d after being fed Mn-54. In experiment 2, animals that had a sham operation or bile-ligation were sacrificed at 8 time points after being injected intraportally with 54Mn complexed to albumin. The biliary-ligated animals had a significantly ($p < 0.001$) smaller percentage of the 54Mn in their brains (when expressed as a percentage of whole animal 54Mn) than the sham-operated animals. Mn deficiency had a similar effect. However, we did observe an increased accumulation of the radioisotope in the brain over time. Therefore, in short-term studies, biliary-ligated rats do not appear to be a good model for Mn accumulation in the brains of people with cholestatic liver disease.

4. Fell JME, Reynolds AP, Meadows N, Khan K, Long SG, Quaghebeur G, Taylor WJ, Milla PJ. (1996) Manganese toxicity in children receiving long-term parenteral nutrition. Lancet 347(9010):1218-1221.
Background In patients receiving long-term parenteral nutrition (PN), cholestatic disease acid nervous system disorders have been associated with high blood concentrations of manganese. In such patients, the normal homoeostatic mechanisms of the liver and gut ate bypassed and the requirement for this trace element is not known; nor has it been certain whether hypermanganesaemia causes the cholestasis or vice versa. We explored the direction of effect by serial tests of liver function after withdrawal of manganese supplements from children receiving long-term PN. We also examined the relation between blood manganese concentrations and brain lesions, as indicated by clinical examination and magnetic resonance imaging (MRI). Methods From a combined group of 57 children receiving PN we identified 11 with the combination of hypermanganesaemia and cholestasis; one also had a movement disorder. Manganese supplements were reduced in the first three and withdrawn in the remainder. MRI was done in two of these children. We also looked at manganese concentrations and MRI scans in six children who had received PN for more than 2 years without developing liver disease. Findings In the hypermanganesaemia/cholestasis group, four of the 11 patients died. In the seven survivors baseline whole-blood manganese was 615-1840 nmol/L, and after 4 months it had declined by a median of 643 nmol/L ($p<0 . 01$). Over the same interval total bilirubin declined by a median of 70 mu mol/L ($p<0 . 05$). Two of these children had movement disorders, one of whom survived to have an MRI scan; this showed, with T1 weighted images, bilateral symmetrically increased signal intensity in the globus pallidus and subthalamic nuclei. Such changes were also seen in five other children-one from the hypermanganesaemia/cholestasis group and four of six in the long-term PN group without liver disease (in all of whom blood manganese was above normal). Interpretation The cholestasis complicating PN is multifactorial, but these results add to the evidence that manganese contributes. In view of the additional hazard of basal ganglia damage from high manganese levels in children receiving long-term PN, we recommend a low dose regimen of not more than 0 . 018 mu mol/kg per 24 h together with regular examination of the nervous system.

5. Finley JW, Penland JG, Pettit RE, Davis CD. (2003) Dietary manganese intake and type of lipid do not affect clinical or neuropsychological measures in healthy young women. Journal of Nutrition 133(9):2849-2856.
Because manganese (Mn) is potentially toxic, and because dietary fat type may affect Mn absorption, the objectives of the current study were to determine whether diets containing very low or very high amounts of Mn and enriched in either saturated or unsaturated fats affected

measures of neuropsychological and basic metabolic function. Healthy young women were fed for 8 wk each, in a crossover design, diets that provided 0.8 or 20 mg of Mn/d. One half of the subjects received 15% of energy as cocoa butter, and one half received 15% of energy as corn oil. A meal containing Mn-54 was fed after 4 wk, and subjects underwent whole-body counting for the next 21 d. Blood draws and neuropsychological tests were administered at regular intervals during the dietary periods. When subjects consumed the diets low in Mn, compared with the high Mn diets, they absorbed a significantly higher percentage of Mn-54, but had a significantly longer biological half-life of the absorbed Mn-54. Manganese intake did not affect any neurological measures and only minimally affected psychologic variables. These data show that efficient mechanisms operate to maintain Mn homeostasis over the range of intakes that may be encountered in a mixed Western diet. Thus, dietary intakes of Mn from 0.8 to 20 mg for 8 wk likely do not result in Mn deficiency or toxicity signs in healthy adults.

6. Fitzgerald K, Mikalunas V, Rubin H, McCarthy R, Vanagunas A, Craig RM. (1999) Hypermanganesemia in patients receiving total parenteral nutrition. Journal of Parenteral and Enteral Nutrition 23(6):333-336.
Background: Manganese is one of the trace elements that is routinely administered to total parenteral nutrition (TPN) patients. The recommended daily IV dosage ranges from 100 to 800 mu g. We have used 500 mu g daily. Recent reports have suggested neurologic symptoms seen in some patients receiving home parenteral nutrition (HPN) may be due to hypermanganesemia. Therefore, HPN patients and some short-term inpatients receiving TPN were studied to ascertain the relationship between dose and blood levels. Methods: Red blood cell manganese levels were obtained by atomic absorptiometry. Results: The levels in 36 hospitalized, short-term patients obtained within 48 hours of initiating TPN were all normal. The 30 patients receiving TPN from 3 to 30 days had levels that ranged from 4.8 to 28 mu g/L (normal, 11 to 23 mu g/L). Two patients had abnormal levels, at days 14 and 18. Fifteen of the 21 patients receiving inpatient TPN or HPN for 36 to 5075 days had elevated Mn levels. Only one patient with hypermanganesemia, an inpatient, had abnormal biochemical liver tests (bilirubin and alkaline phosphatase). One of the patients with a high level had some vestibular symptoms attributed to aminoglycoside use and had increased signal density in the globus pallidus on T1-weighted images on magnetic resonance imaging (MRI). A second patient with Mn levels twice normal had no neurologic symptoms, but had similar MRI findings. A third had some basal ganglia symptoms, confirmed by a neurologic evaluation, seizures, and very high Mn levels. The MRI showed no signal enhancement, but motion artifacts limited the study technically. Conclusions: Hypermanganesemia is seen in HPN patients receiving 500 mu g manganese daily and may have resulted in some neurologic damage in three patients. Hypermanganesemia is sometimes seen after a short course of TPN in inpatients, as early as 14 days. Patients should be monitored for hypermanganesemia if they receive Mn in their TPN for >30 days. A 500 mu g/d dose of Mn is probably excessive, and 100 mu g/d should probably never be exceeded. Mn should be eliminated from the solution if the Mn level is elevated and should not be readministered unless the level returns to normal or subnormal. Mn should not be supplemented if the patient has liver disease with an elevated bilirubin.

7. Ikeda S, Yamaguchi Y, Sera Y, Ohshiro H, Uchino S, Yamashita Y, Ogawa M. (2000) Manganese deposition in the globus pallidus in patients with biliary atresia. Transplantation 69(11):2339-2343.

Background. Chronic liver diseases may alter trace element contents in the brain. Among these trace elements, manganese is a ubiquitous transition metal excreted by the liver into the bile. Blood concentrations of manganese are elevated in patients with biliary atresia who have undergone hepatic portoenterostomy. The present study investigated the effects of liver transplantation on manganese deposition in the brain in such patients. Methods. The signal intensity of the globus pallidus was calculated as an index defined as the percentile ratio of signal intensity in the globus pallidus to the subcortical frontal white-matter in sagittal T1-weighted magnetic resonance imaging planes. Results. Brain magnetic resonance imaging revealed hyperintense signals in the globus pallidus due to manganese deposition in biliary atresia patients. Few neurologic symptoms related to manganese intoxication were observed. However, one 23-year-old female with biliary atresia had depressive symptoms and dyskinesia; she improved after oral administration of the dopamine precursor, L-DOPA. Manganese deposition disappeared in two patients after living-related reduced-size hepatic transplantation. Conclusions. Manganese accumulates in the brain during cholestasis associated with biliary atresia and disappears after hepatic transplantation. Manganese deposition is likely to be subclinical and reversible but may be associated with some age-related neurologic symptoms.

8. Kafritsa Y, Fell J, Long S, Bynevelt M, Taylor W, Milla P. (1998) Long term outcome of brain manganese deposition in patients in home parenteral nutrition. Archives of Disease in Childhood 79(3):263-265.
BIOSIS COPYRIGHT: BIOL ABS. Manganese intoxication has been described in children on long term parenteral nutrition presenting with liver and nervous system disorders. Cases are reported of a brother and sister on long term parenteral nutrition with hypermanganesaemia and basal ganglia manganese deposition, detected by magnetic resonance imaging (MRI), without overt neurological signs. Following reduction of manganese intake, basal ganglia manganese was monitored by repeated MRI, and neurological and developmental examinations. An MRI intensity index of the globus pallidus declined over a three year period from 0.318 and 0.385 to 0.205 and 0.134 with concomitant falls in whole blood manganese from 323 and 516 to 226 and 209 nmol/l (normal range, 73-210 nmol/l). Unlike adult experience these children developed normally without neurological signs. In conclusion, deposited manganese is removed from neural tissue over time and the prognosis is good when neurological manifestations and liver disease ar

9. Krieger D, Krieger S, Jansen O, Gass P, Theilmann L, Lichtnecker H. (1995) Manganese and Chronic Hepatic-Encephalopathy. Lancet 346(8970):270-274.
Clinical observations and animal studies have raised the hypothesis that increased concentrations of manganese (Mn) in whole blood might lead to accumulation of this metal within the basal ganglia in patients with end-stage liver disease. We studied ten patients with liver failure (and ten controls) by magnetic resonance imaging (MRI) and measurement of Mn in brain tissue of three patients who died of progressive liver failure (and three controls) was also done. Whole blood Mn concentrations in patients with liver cirrhosis were significantly increased (median 34.4 mu g/L vs 10.3 mu g/L in controls; p=0.0004) and pallidal signal intensity indices correlated with blood Mn (R(s)=0.8, p=0.0058). Brain tissue samples reveal highest Mn concentrations in the caudate nucleus, followed by the quadrigeminal plate and globus pallidus. Mn accumulates within the basal ganglia in liver cirrhosis. Similarities between Mn neurotoxicity and chronic hepatic encephalopathy suggest that this metal may have a role in the

pathogenesis of chronic hepatic encephalopathy. Further studies are warranted because the use of chelating agents could prove to be a new therapeutic option to prevent or reverse this neuropsychiatric syndrome.

10. Malecki EA, Devenyi AG, Barron TF, Mosher TJ, Eslinger P, Flaherty-Craig CV, Rossaro L. (1999) Iron and manganese homeostasis in chronic liver disease: Relationship to pallidal T1-weighted magnetic resonance signal hyperintensity. Neurotoxicology 20(4):647-652.
The hyperintense signal in the globus pallidus of cirrhotic patients on T1-weighted magnetic resonance (MR) imaging has been postulated to arise from deposition of paramagnetic manganese(2+) (Mn). Intestinal absorption of both iron and Mn are increased in iron deficiency; iron deficiency may therefore increase susceptibility to Mn neurotoxicity. To investigate the relationships between MR signal abnormalities and Mn and Fe status, 21 patients with chronic liver disease were enrolled (alcoholic liver disease, 5; primary biliary cirrhosis, 9; primary sclerosing cholangitis, 3; hepatitis B virus, 2; hepatitis C virus, 1; alpha 1-antitrypsin deficiency 1). Signal hyperintensity in the pallidum on axial T1 weighted images repetition time/evolution time: 500 ms/15ms was observed in 13 of 21 subjects: four patients had mild hyperintensity, three moderate, and six exhibited marked hyperintensity. Erythrocyte Mn concentrations were positively correlated with the degree of the MR hyperintensity (Kendall's tau-b=0.52, P<0.005). The log of erythrocyte Mn concentration was also inversely correlated with all measures of iron status: hemoglobin (Pearson's R=-0.73, P<0.0005); hematocrit (R=-0.62, P<0.005); serum Fe concentrations (R=-0.65, P<0.005); and TIBC saturation (R=-0.62, P<0.005). These findings confirm the association of Mn with the development of pallidal hyperintensity in patients with liver disease. We further found that iron deficiency is an exacerbating factor probably because of increased intestinal absorption of Mn. We therefore recommend that patients with chronic liver disease avoid Mn supplements without concurrent iron supplementation. (C)1999 Intox Press, Inc.

11. Ono J, Harada K, Kodaka R, Sakurai K, Tajiri H, Takagi Y, Nagai T, Harada T, Nihei A, Okada A and others. (1995) Manganese deposition in the brain during long-term total parenteral nutrition. Journal of Parenteral and Enteral Nutrition 19(4):310-312.
BIOSIS COPYRIGHT: BIOL ABS. Background: Manganese deposition was suspected in a pediatric patient who received long-term total parenteral nutrition. T1-weighted magnetic resonance images revealed high intensity areas in the globus pallidus. This study was designed to clarify if these abnormal findings were related to manganese deposition and clinical neurological manifestations. Methods: Whole-blood manganese concentrations were measured during manganese supplementation to total parenteral nutrition and after 5 months without manganese. Magnetic resonance images were also examined on each occasion and compared with the blood level of manganese. Results: The whole-blood manganese level during supplementation was 135 mug (normal range 14.6 | 4.7 mug/L), whereas the level was 20 mug/L after a manganese-free period of 5 months. Accompanied with normalization of manganese level, abnormal high intensity lesions in the globus pallidus on T1-weighted images also disappeared. No neurological manifestation

12. Reynolds N, Blumsohn A, Baxter JP, Houston G, Pennington CR. (1998) Manganese requirement and toxicity in patients on home parenteral nutrition. Clinical Nutrition 17(5):227-230.

Two patients who were receiving home parenteral nutrition complained of vague neurological symptoms of such severity that they underwent full clinical appraisal. The only positive finding was that plasma manganese concentrations were greater than twice the upper 95% confidence interval of normal (7-27 nmol/l). In the light of this result all nine patients receiving home parenteral nutrition underwent evaluation for possible manganese toxicity. One other patient had serum manganese concentrations exceeding twice the upper limit (127 nmol/l). The three patients with elevated serum Mn had evidence of manganese deposition in the brain on magnetic resonance imaging scanning. In contrast two patients with normal plasma results had negative scans. Patient susceptibility appears very variable. We suggest that current amounts of trace elements provided in nutrition solutions may be a potential source of nutrient activity. The fine tuning of supply and demand may be difficult on account of a limited range of commercially available trace element solutions.

4.1 STUDIES IN HUMANS—EPIDEMIOLOGY, CASE REPORTS, CLINICAL CONTROLS

Key References (34)

1. Beuter A, Lambert G, MacGibbon B. (2004) Quantifying postural tremor in workers exposed to low levels of manganese. Journal of Neuroscience Methods 139(2):247-255.
The aim of this study was: (1) To determine the minimum number of characteristics necessary to discriminate between postural tremor recorded in control subjects (CO), in subjects exposed to manganese (MN), and in patients with Parkinson's disease (PD), and (2) to examine the continuum of changes between the three groups examined. Workers previously exposed to Mn (n = 10), patients with PD (n = 10), and control subjects (CO) (n = 11) underwent a clinical examination. Blood Mn was measured at the end of exposure time for the MN group and 12 months later at the beginning of the experiment for all groups. Postural tremor with visual feedback was recorded in the index finger with a laser system. Statistical criteria were used to reduce computed tremor characteristics to a minimal set of reliable discriminating variables. Two variables were retained namely corrected wobble (CW), describing the morphology of the tremor oscillations, and variability ratio (VR), describing proportional power of tremor. Both variables had an overall correct classification rate of 77.4%. Blood Mn levels at the time of the experiment were similar for all groups and had insignificant correlation with tremor variables. However, blood Mn levels in workers which were also measured at the end of exposure time (i.e., 12 months before) showed significant correlation (Spearman's rank coefficient) with both harmonic index ($p = 0.70$, $P = 0.03$) and first maximum of the autocorrelation function ($p = 0.89$, $P = 0.001$). We conclude that (1) the tremor of workers exposed to Mn could be adequately described with only two variables; (2) a continuum of changes between tremor recorded in control subjects, in subjects exposed to Mn and in patients with PD was observed, with the MN group always found in between the control (CO) and the PD groups; (3) while blood Mn levels in workers were back at control levels at the time of the experiment, the effect of Mn on postural tremor was still detected. Thus our method has the potential to detect the effect of Mn on tremor with only two variables even after Mn level in the blood is back to normal values.

2. Boojar MMA, Goodarzi F. (2002) A longitudinal follow-up of pulmonary function and respiratory symptoms in workers exposed to manganese. Journal of Occupational and Environmental Medicine 44(3):282-290.
The purpose of the investigation was to study the effects on the respiratory system in mine workers with long-term exposure to manganese (Mn) in the workplace. The study included a follow-up Of pulmonary Junction and respiratory symptoms among 145 workers employed in a large Mn mine an 5 matched controls, and the assessment of Mn concentrations in environment and biological samples. Lung function was measured by recording spirometric parameters. The Mn-exposed workers reported more respiratory symptoms and a significantly higher prevalence of all grades of pulmonary function impairment. All predicted symptoms except for asthma increased significantly in the current smoking group compared with the non-smoking group. There was a significant decrease in FEV1, FVC, and FEV1% values in exposed workers compared with controls at stages 2 and 3, with an additive effect of the smoking habit. The Mn concentrations in blood, urine, and hair were significantly higher in the exposed workers than in the controls. The level of cumulative exposure index of workplace Mn was notable and did not change significantly over this study. The respiratory effects found in Mn-exposed workers were probably caused by the Mn in the workplace and the synergistic effect of smoking. These effects indicate a need for respiratory protection and improvements in the work environment.

3. Bouchard M, Laforest F, Vandelac L, Bellinger D, Mergler D. (2007) Hair manganese and hyperactive behaviors: Pilot study of school-age children exposed through tap water. Environmental Health Perspectives 115(1):122-127.
BACKGROUND: Neurotoxic effects are known to occur with inhalation of manganese particulates, but very few data are available on exposure to Mn in water. We undertook a pilot study in a community in Quebec (Canada) where naturally occurring high Mn levels were present in the public water system. Our objective was to test the hypothesis that greater exposure to Mn via drinking water would be reflected in higher Mn content in hair which, in turn, would be associated with increased level of hyperactive behaviors. METHODS: Forty-six children participated in the study, 24 boys and 22 girls, 6-15 years of age (median, 11 years). Their homes received water from one of two wells M with different Mn concentrations: W1: mean 6 10 mu g/L; W2: mean 160 mu g/L. The Revised Conners' Rating Scale for parents (CPRS-R) and for teachers (CTRS-R) were administered, providing T-scores on the following subscales: Oppositional, Hyperactivity, Cognitive Problems/Inattention, and ADHD Index. RESULTS: Children whose houses were supplied by W1 had higher hair Mn (MnH) than those supplied by W2 (mean 6.2 +/- 4.7 mu g/g vs. 3.3 +/- 3.0 mu g/g, p = 0.025). MnH was significantly associated with T-scores on the CTRS-R Oppositional (p = 0.020) and Hyperactivity (p = 0.002) subscales, after adjustment for age, sex, and income. All children with Oppositional and Hyperactivity T-scores >= 65 had MnH > 3.0 mu g/g. CONCLUSIONS: The findings of this pilot study are sufficiently compelling to warrant more extensive investigations into the risks of Mn exposure in drinking water.

4. Bowler RM, Gysens S, Diamond E, Nakagawa S, Drezgic M, Roels HA. (2006) Manganese exposure: Neuropsychological and neurological symptoms and effects in welders. Neurotoxicology 27(3):315-326.
Manganese exposure reportedly may have an adverse effect on CNS function and mood. Sixty-two welders with clinical histories of exposure to manganese were compared to 46 matched

regional controls chosen at random from a telephone directory. The following tests were given: Wechsler Adult Intelligence Scale (WAIS-III), Wechsler Memory Scale (WMS-III), Boston Naming, WRAT-3, Cancellation H, Trail Making Tests A and B, Auditory Consonant Trigrams, Stroop, Rey-Osterreith, Animal Naming, Controlled Oral Word Association (COWAT), Test of Memory Malingering, Rey 15-item, Fingertapping, Grooved Pegboard, Dynamometer, Visual Attention Test. Lanthony d-15 Color Vision, Vistech Contrast Sensitivity, and Schirmer strips. The controls were administered a shorter battery of tests and the Rey-Osterreith, Animal Naming and some of the subtests of the WAIS-III, WMS-III were not administered. Mood tests, given to both groups, included the Symptom Checklist-40, Symptom Checklist-90-R, Profile of Mood Scale, Beck Depression Inventory II, and Beck Anxiety Inventory. Forty-seven welders and 42 controls were retained for statistical analysis after appropriate exclusions. Results showed a high rate of symptom prevalence and pronounced deficits in motor skills, visuomotor tracking speed and information processing, working memory, verbal skills (COWAT), delayed memory, and visuospatial skills. Neurological examinations compared to neuropsychological test results suggest that neuropsychologists obtain significantly more mood symptoms overall. Odds ratios indicate highly elevated risk for neuropsychological and neurological symptomatology of manganism. Mood disturbances including anxiety, depression, confusion, and impaired vision showed very high odds ratios. Neurological exams and neuropsychological tests exhibit complementarity and differences, though neuropsychological methods may be more sensitive in detecting early signs of manganism. The present study corroborates the findings of our previous study in another group of welders.

5. Bowler RM, Koller W, Schulz PE. (2006) Parkinsonism due to manganism in a welder: Neurological and neuropsychological sequelae. Neurotoxicology 27(3):327-332.
A 33-year-old welder with 3 years of exposure to manganese (Mn) bearing welding fumes was seen by neurologists for cognitive and motor complaints. He exhibited signs and symptoms of Parkinson's disease, including tremor, bradykinesia, gait disturbance and cogwheel rigidity. However, he was young and had significant inattention and forgetfulness, had found levodopa unhelpful and moved with a cock-walk gait, all of which suggested manganism. His serum and urine levels of Mn were, in fact, elevated, and his brain MRI had increased T1-weighted signal intensities in the basal ganglia bilaterally (globus pallidus) consistent with Mn deposition. Two years later, he underwent comprehensive neuropsychological testing. Clinical history indicated a mild tremor and emotional dysfunction with irritability, anxiety, and depression with psychotic features. He showed deficits in cognitive flexibility, information processing and speed, and greatly reduced motor speed, which are consistent with a fronto-subcortical process. These findings support a diagnosis of early onset parkinsonism from welding,

6. Bowler RM, Nakagawa S, Drezgic M, Roels HA, Park RM, Diamond E, Mergler D, Bouchard M, Bowler RP, Koller W. (2007) Sequelae of fume exposure in confined space welding: A neurological and neuropsychological case series. NeuroToxicology 28(2):298-311.
Welding fume contains manganese (Mn) which is known to be bio-available to and neurotoxic for the central nervous system. Although an essential metal, Mn overexposure may cause manganism, a parkinsonian syndrome. The present welder study sought to improve the clinical portrait of manganism and to determine dose-effect relationships. The welders were employed in the construction of the new Bay Bridge (San Francisco) and welded in confined spaces for up to

2 years with minimal protection and poor ventilation. Neurological, neuropsychological, neurophysiological, and pulmonary examinations were given to 49 welders. Clinical cases were selected on the basis of apriori defined criteria pertaining to welding history and neurological/neuropsychological features. Among the 43 eligible welders, 11 cases of manganism were identified presenting with the following symptoms: sleep disturbance, mood changes, bradykinesia, headaches, sexual dysfunction, olfaction loss, muscular rigidity, tremors, hallucinations, slurred speech, postural instability, monotonous voice, and facial masking. Significant associations between outcome variables and cumulative exposure index (CEI) or blood Mn (MnB) were obtained with CEI for variables implicating attention and concentration, working and immediate memory, cognitive flexibility, and verbal learning; and with MnB for executive function, cognitive flexibility, visuo-spatial construction ability, and visual contrast sensitivity. This study strongly suggests that neuropsychological features contribute in a dose-effect related way to the portrait of manganism usually characterized by tremor, loss in balance, diminished cognitive performance, and signs and symptoms of parkinsonism.

7. Bowler RM, Roels HA, Nakagawa S, Drezgic M, Diamond E, Park R, Koller W, Bowler RP, Mergler D, Bouchard M and others. (2007) Dose-effect relationships between manganese exposure and neurological, neuropsychological and pulmonary function in confined space bridge welders. Occupational and Environmental Medicine 64(3):167-177.
Background: Although adverse neuropsychological and neurological health effects are well known among workers with high manganese (Mn) exposures in mining, ore-processing and ferroalloy production, the risks among welders with lower exposures are less well understood. Methods: Confined space welding in construction of a new span of the San Francisco-Oakland Bay Bridge without adequate protection was studied using a multidisciplinary method to identify the dose-effect relationship between adverse health effects and Mn in air or whole blood. Bridge welders (n = 43) with little or no personal protection equipment and exposed to a welding fume containing Mn, were administered neurological, neuropsychological, neurophysiological and pulmonary tests. Outcome variables were analysed in relation to whole blood Mn (MnB) and a Cumulative Exposure Index (CEI) based on Mn-air, duration and type of welding. Welders performed a mean of 16.5 months of welding on the bridge, were on average 43.8 years of age and had on average 12.6 years of education. Results: The mean time weighted average of Mn-air ranged from 0.11-0.46 mg/m(3) (55% > 0.20 mg/m(3)). MnB > 10 mu g/l was found in 43% of the workers, but the concentrations of Mn in urine, lead in blood and copper and iron in plasma were normal. Forced expiratory volume at 1s: forced vital capacity ratios (FEV1/FVC) were found to be abnormal in 33.3% of the welders after about 1.5 years of welding at the bridge. Mean scores of bradykinesia and Unified Parkinson Disease Rating Scale exceeded 4 and 6, respectively. Computer assisted tremor analysis system hand tremor and body sway tests, and University of Pennsylvania Smell Identification Test showed impairment in 38.5/61.5, 51.4 and 88% of the welders, respectively. Significant inverse dose-effect relationships with CEI and/or MnB were found for IQ ($p <= 0.05$), executive function ($p <= 0.03$), sustaining concentration and sequencing ($p <= 0.04$), verbal learning ($p <= 0.01$), working ($p <= 0.04$) and immediate memory ($p <= 0.02$), even when adjusted for demographics and years of welding before Bay Bridge. Symptoms reported by the welders while working were: tremors (41.9%); numbness (60.5%); excessive fatigue (65.1%); sleep disturbance (79.1%); sexual dysfunction (58.1%); toxic hallucinations (18.6%); depression (53.5%); and anxiety (39.5%). Dose-effect associations between CEI and sexual function ($p < 0.05$), fatigue ($p < 0.05$), depression ($p < 0.01$) and

headache ($p < 0.05$) were statistically significant. Conclusions: Confined space welding was shown to be associated with neurological, neuropsychological and pulmonary adverse health effects. A careful enquiry of occupational histories is recommended for all welders presenting with neurological or pulmonary complaints, and a more stringent prevention strategy should be considered for Mn exposure due to inhalation of welding fume.

8. Cersosimo MG, Koller WC. (2006) The diagnosis of manganese-induced parkinsonism. Neurotoxicology 27(3):340-346.
Parkinsonism is a clinical syndrome consisting of tremor, bradykinesia, rigidity, gait, balance problems, in addition to various non-motor symptoms. There are many causes of parkinsonism such as neurodegenerative disease, drugs, vascular causes, structural lesions, infections, and toxicants. Parkinson's disease, or idiopathic parkinsonism, is the most common form of parkinsonism observed in the clinic. There is degeneration of the substantia nigra, pars compacta, which results in loss of striatal dopamine. Parkinson's disease is a slowly progressive condition in which there is a dramatic and sustained responsiveness to levodopa therapy. Manganese is an essential trace element that can be associated with neurotoxicity. Hypermanganism can occur in a variety of clinical settings. The clinical symptoms of manganese intoxication include non-specific complaints, neurobehavioral changes, parkinsonism, and dystonia. Although the globus pallidus is the main structure of damage, other basal ganglia areas can also be involved. MRI scans may show globus pallidus changes during (and for a short period after) exposure. Fluorodopa PET scans that assess the integrity of the substantia nigra. dopaminergic system are abnormal in Parkinson's disease. However, these scans re-reported to be normal in a few cases studied with manganese-induced parkinsonism. The parkinsonism due to manganese may have some clinical features that occur less commonly in Parkinson's disease, such as kinetic tremor, dystonia, specific gait disturbances, and early mental, balance and speech changes. The clinical signs tend to be bilateral whereas Parkinson's disease begins on one side of the body. Patients with manganese-induced parkinsonism may be younger at the onset of the disease than with Parkinson's disease. Lastly, there appears to be a lack of response to levodopa therapy in manganese-induced parkinsonism. In summary it may be possible to differentiate manganese-induced parkinsonism from Parkinson's disease using clinical and imaging studies.

9. Deschamps FJ, Guillaumot A, Raux S. (2001) Neurological effects in workers exposed to manganese. Journal of Occupational and Environmental Medicine 43(2):127-132.
The purpose of this study was to examine the effects on the nervous system in enamels-production workers who have low levels of and long exposure to manganese (Mn). The study included 138 Mn-exposed workers and 137 controls who received questionnaires on symptoms, a batter of psychological tests, and assessments of blood concentrations of metal. The exposure levels to airborne Mn concentrations were determined by personal and stationary samplings. The mean duration exposure to Mn was 19.87 years (SD +/- 9). The workers exposed to Mn reported more nonspecific subjective complaints than the control group. No effect of Mn exposure was indicated by the results of any of the neuropsychological tests. The Mn workers did not have higher concentrations of Mn in blood than the controls. Exposures of workers currently working with Mn averaged 57 mug/m(3) respirable (personal samplings) and 12 g/m(3) (stationary samplings). In conclusion, long exposure to low levels of Mn (approximately 200 mug/m(3)), as induced in our study, showed no significant disturbance of neurological performance.

10. Finley BL, Santamaria AB. (2005) Current evidence and research needs regarding the risk of manganese-induced neurological effects in welders. Neurotoxicology 26(2):285-289.

11. Fored CM, Fryzek JP, Brandt L, Nise G, Sjogren B, McLaughlin JK, Blot WJ, Ekbom A. (2006) Parkinson's disease and other basal ganglia or movement disorders in a large nationwide cohort of Swedish welders. Occupational and Environmental Medicine 63(2):135-140.
Introduction: Although it has been hypothesised that metal welding and flame cutting are associated with an increased risk for Parkinson's disease due to manganese released in the welding fume, few rigorous cohort studies have evaluated this risk. Methods: The authors examined the relation between employment as a welder and all basal ganglia and movement disorders (ICD-10, G20-26) in Sweden using nationwide and population based registers. All men recorded as welders or flame cutters (n=49 488) in the 1960 or 1970 Swedish National Census were identified and their rates of specific basal ganglia and movement disorders between 1964 and 2003 were compared with those in an age and geographical area matched general population comparison cohort of gainfully employed men (n=489 572). Results: The overall rate for basal ganglia and movement disorders combined was similar for the welders and flame cutters compared with the general population (adjusted rate ratio (aRR)=0.91 (95% Cl 0.81 to 1.01). Similarly, the rate ratio for PD was 0.89 (95% Cl 0.79 to 0.99). Adjusted rate ratios for other individual basal ganglia and movement disorders were also not significantly increased or decreased. Further analyses of Parkinson's disease by attained age, time period of follow up, geographical area of residency, and educational level revealed no significant differences between the welders and the general population. Rates for Parkinson's disease among welders in shipyards, where exposures to welding fumes are higher, were also similar to the general population (aRR=0.95; 95% Cl 0.70 to 1.28). Conclusion: This nationwide record linkage study offers no support for a relation between welding and Parkinson's disease or any other specific basal ganglia and movement disorders.

12. Fryzek JP, Hansen J, Cohen S, Bonde JP, Llambias MT, Kolstad HA, Skytthe A, Lipworth L, Blot W, Olsen JH. (2005) A cohort study of Parkinson's disease and other neurodegenerative disorders in Danish welders. Journal of Occupational and Environmental Medicine 47(5):466-472.
Objective. We sought to evaluate rates of hospitalizations for neurode-generative disorders in a cohort of Danish metal manufacturing employees. Methods: A retrospective cohort study was conducted from 1977 to 2002 among 27,839 mate Danish metal-manufacturing employees, with 9,817 of those employed in departments engaged in mild or stainless-steel welding and 6,163 welders. Results: The standardized hospitalization ratio and 95 % confidence intervals (Q) for Parkinson's disease were 0.9 (CI = 0.7-1.2) for men in steel-manufacturing companies, 1.0 (CI = 0.7-1.5) for men in welding departments, and 0.9 (CI = 0.4 -1.5) for welders. Observed numbers for other neurological conditions were small and not above population expectations. Analyses for time period worked, age, and duration of welding were unremarkable. Conclusions: This relatively large cohort study with long-term follow-up provides no support for the hypothesis that rates of hospitalization for Parkinson's disease or other neurological conditions are elevated under the exposure circumstances of these Danish workers.

13. Gibbs JP, Crump KS, Houck DP, Warren PA, Mosley WS. (1999) Focused medical surveillance: A search for subclinical movement disorders in a cohort of U.S. workers exposed to low levels of manganese dust. Neurotoxicology (Little Rock) 20(2-3):299-314.
BIOSIS COPYRIGHT: BIOL ABS. Seventy-five workers with recent and/or historical exposure to manganese (Mn) at a metal producing plant in northern Mississippi were closely matched with 75 control workers who had no known history of occupational exposure to Mn. Both plants are OSHA STAR work sites and share common medical, safety, and industrial hygiene services. Airborne Mn levels were assessed for each of twelve job categories at the Mn facility by collecting 63 side-by-side full-shift personal samples of both total and res n was estimated for the preceding 30 days, preceding year, and for the worker's entire employment history. Both Mn and control workers were administered multiple neuropsychological tests including tests of hand-eye coordination, hand steadiness, complex reaction time, and rapidity of finger tapping. A questionnaire was used to evaluate a worker's neuropsychological status. Performance decreased sign)ficantly with increasing age in tests of hand-eye coordination, complex reaction

14. Hernandez EH, Discalzi G, Valentini C, Venturi F, Chio A, Carmellino C, Rossi L, Sacchetti A, Pira E. (2006) Follow-up of patients affected by manganese-induced Parkinsonism after treatment with CaNa(2)EDTA. Neurotoxicology 27(3):333-339.
In the period of 1998-2004, seven workers affected by manganese-induced Parkinsonism were diagnosed, studied and treated with CaNa(2)EDTA at our Occupational Health Ward. Biological markers, as well as magnetic resonance imaging and clinical examinations, were used to assess the disease trend. Those workers still employed were immediately removed from exposure. Our results seem to confirm that very good clinical, biological and neuroradiological results can be obtained by timely removal from exposure and chelating treatment, and that amelioration can persist in time. Manganism is, however, a severe condition that can also progress independent of further exposure. Therefore, chelating treatment can be a great aid in overt manganism, but particular attention must be paid to primary prevention, as this disease should now be totally preventable and definitely merits eradication. (c) 2005 Elsevier Inc. All rights reserved.

15. Hochberg F, Miller G, Valenzuela R, McNelis S, Crump KS, Covington T, Valdivia G, Hochberg B, Trustman JW. (1996) Late motor deficits of Chilean manganese miners: A blinded control study. Neurology 47(3):788-795.
BIOSIS COPYRIGHT: BIOL ABS. High-level chronic manganese (Mn) exposure produces dystonic rigidity and proximal tremor. The late effects of asymptomatic exposure are uncertain. To evaluate hand movements of asymptomatic Chilean miners, we utilized a manual tremormeter (EAP) and a digitizing tablet (MOVEMAP). In Andacollo, Chile, we examined 59 individuals aged > 50 years (mean age, 64.4 years). Twenty-seven exposed miners had heavy Mn dust exposure in Mn mines for more than 5 years (mean duration, 20.25 years), ending at least 5 years previously. Thirty-two control miners had never worked in Mn mines or had short-term Mn employment. Tests of resting tremor (EAP Tremormeter, MOVEMAP Steady paradigm), action tremor (MOVEMAP Square paradigm), and repetitive hand movements (EAP Tapping Test and Orthokinesimeter) differentiated performance of exposed miners from that of controls. Chronic asymptomatic Mn exposure results in detectable late-life abnormalities of movement.

16. Hudnell HK. (1999) Effects from environmental Mn exposures: A review of the evidence from non-occupational exposure studies. Neurotoxicology 20(2-3):379-397.
Objective: The risk posed to human health by environmental manganese exposure is unknown. Occupational-exposure outcomes may not extrapolate to environmental exposures due to the healthy worker effect and differences in dosage parameters which may affect the biological response. This paper attempts to combine the existing literature on non-occupational Mn exposures with results from our current study in SW Quebec on environmental Mn exposure (Mergler et al., this issue) within the framework of a biologically-based, dose-response (BBDR) model. BBDR Model: The basic BBDR model consists of seven stages relating exposure to health effects. The stages are: 1) sources, 2) applied dose, 3) absorbed dose, 4) target-site dose, 5) toxic event, 6) measurable change, and 7) health outcome. Results: Several air monitoring programs, such as the PTEAM study (Riverside, CA, 1990, mean PM10 Mn outdoor-airborne 24h average=0.045 mu g/m(3)) provided data relevant to the estimation of Mn applied dose, but did not include measures of body burden. Data from the SW Quebec study showed a mean total particulate airborne Mn concentration of 0.022 mu g/m(3) with a range of 0.009 to 0.035 mu g/m(3) across four sampling sites, whereas the EPA reference concentration (RfC) is 0.05 mu g/m(3). EPA has considered tap water levels to be safe below 200 mu g/l Mn, and mean Mn tap-water (MnW) level in the participants' homes was 6.38+/-11.95 mu g/l with a range from 0.1 to 158.9 mu g/l Mn. A previous study of MnW exposure in Greece reported Mn levels in areas with low, medium and high MnW ranging from 4 to 2,300 mu g/l and a significant association with Mn in hair but not Mn in blood (MnB). The mean absorbed dose of the SW Quebec study participants, as indicated by MnB, was 7.5+/-2.3 mu g/l with a range of 2.5 to 15.9 mu g/l. Our study and others on environmental Mn exposure did not provide an estimate of target-site dose. However, a significant correlation (r=0.65) between MnB and signal intensify in TI-weighted MRI images has been reported in liver-disease patients with Parkinson-like signs who had MnB levels as low as 6.6 mu g/l. Only animal and in vitro studies ha ve provided evidence on the mechanisms of toxicity caused by Mn in the CNS. Several studies reported measurable changes in endpoints suggestive of a Parkinson-like syndrome in subjects with MnB levels ranging from 7.5 to 25.0 mu g/l. Among other effects on neurobehavioral function observed in the current study was a significant relationship between MnB and the direction and speed of body-sway in men. The effects observed in these participants are sub-clinical and no health outcomes have been diagnosed. However, the Parkinson's disease incidence in the study area was previously reported to be 2-5 times higher than in the rest of Quebec, and several studies indicate that 25-35% of idiopathic Parkinson disease diagnoses are incorrect. Our study, the Greek study, and some clinical studies suggest that the risk of a Parkinson-like syndrome diagnosis may increase with continued Mn exposure and aging. Conclusion: The limited data available for the BBDR model point to the need for evidence, particularly on relationships between Mn species, exposure route, MnB with chronic environmental exposure, ageing, and susceptibility factors, to improve human-health risk assessments for chronic, environmental Mn exposure. (C) 1999 Inter Press, Inc.

17. Iregren A. (1999) Manganese neurotoxicity in industrial exposures: Proof of effects, critical exposure level, and sensitive tests. Neurotoxicology 20(2-3):315-323.
Manganese neurotoxicity has been known for more than 150 years, since Couper(1837) described a syndrome, similar to Parkinsonis disease, in Scottish workers exposed to high levels of dust while grinding "black oxide of manganese" at a chemical industry. Since then, the

syndrome has been described in several groups of highly exposed miners and other workers. A thorough review of manganese neurotoxicity was provided by the WHO (1981) and a recent update was written by Mergler and Baldwin (1997). From these reviews it is evident that the critical effect from manganese exposure is damage to the central nervous system, and that the effects, once established, are generally irreversible. Therefore, the early detection of symptoms of manganese neurotoxicity in populations at risk is of the utmost importance. In spite of this fact, only about a dozen studies of manganese exposed groups of workers have been performed using psychological test methods. These studies are briefly presented, the preponderance of proof for Mn neurotoxicity even in present industrial settings is demonstrated, the critical exposure level is briefly discussed, the test methods are evaluated, and recommendations for a test battery useful for studies of manganese neurotoxicity, are presented. (C) 1999 Inter Press, Inc.

18. Jiang YM, Zheng W. (2005) Cardiovascular toxicities upon manganese exposure. Cardiovascular Toxicology 5(4):345-354.
Manganese (Mn)-induced Parkinsonism has been well documented; however, little attention has been devoted to Mn-induced cardiovascular dysfunction. This review summarizes literature data from both animal and human studies on Mn's effect on cardiovascular function. Clinical and epidemiological evidence suggests that the incidence of abnormal electrocardiogram (ECG) is significantly higher in Mn-exposed workers than that in the control subjects. The main types of abnormal ECG include sinus tachycardia, sinus bradycardia, sinus arrhythmia, sinister megacardia, and ST-T changes. The accelerated heartbeat and shortened P-R interval appear to be more prominent in female exposed workers than in their male counterparts. Mn-exposed workers display a mean diastolic blood pressure that is significantly lower than that of the control subjects, especially in the young and female exposed workers. Animal studies indicate that Mn is capable of quickly accumulating in heart tissue, resulting in acute or sub-acute cardiovascular disorders, such as acute cardio-depression and hypotension. These toxic outcomes appear to be associated with Mn-induced mitochondrial damage and interaction with the calcium channel in the cardiovascular system.

19. Kim Y, Kim KS, Yang JS, Park IJ, Kim E, Jin YW, Kwon KR, Chang KH, Kim JW, Park SH and others. (1999) Increase in signal intensities on T1-weighted magnetic resonance images in asymptomatic manganese-exposed workers. Neurotoxicology 20(6):901-907.
Objectives. To clarify the clinical significance of increased signal intensities on T1 weighted magnetic resonance imaging (MRI) we performed a large-scale epidemiological study on asymptomatic manganese (Mn)-exposed workers with its focus on MRI. Methods: We randomly selected 121 male workers out of a total of 750 workers including Mn-exposed, non-exposed manual, and non-exposed clerical workers in the factories. We studied environmental and biological monitoring, neurological examination, and MRI. Results: The proportion of workers with increased signal intensities among the exposed the non-exposed manual workers, and the non-exposed clerical workers was 46.1%, 18.8%, and 0%, respectively. Especially, 73.5% of the welders showed increased signal intensities. In no subject, were clinical signs of manganism observed. The pallidal index correlated with blood Mn concentration. Conclusion: Increase in signal intensities on the T1-weighted image reflect recent exposure to Mn, but not necessarily manganism. At which increase of signal intensity, the progression of manganism from Mn exposure occurs, remains to be solved. (C) 1999 Intox Press, Inc.

20. Klos KJ, Chandler M, Kumar N, Ahlskog JE, Josephs KA. (2006) Neuropsychological profiles of manganese neurotoxicity. European Journal of Neurology 13(10):1139-1141.
The etiology of manganese neurotoxicity is heterogenous and includes exposure to welding fumes, chronic liver failure, and chronic total parental nutrition (TPN). We recently reported that cognitive impairment occurs in welders and patients with chronic liver failure who had evidence of manganese neurotoxicity including abnormal magnetic resonance imaging (MRI) basal ganglia T1 hyperintensity. In this study, we compared the neuropsychological profiles of patients with manganese neurotoxicity and basal ganglia T1 hyperintensities from three different etiologies: welding, chronic liver failure, and chronic TPN. Across all three groups, the neuropsychological profiles suggest frontal and subcortical cognitive impairment, with more widespread abnormalities occurring in the non-welding groups.

21. Lees-Haley PR, Greiffenstein MF, Larrabee GJ, Manning EL. (2004) Methodological problems in the neuropsychological assessment of effects of exposure to welding fumes and manganese. Clinical Neuropsychologist 18(3):449-464.
Recently, Kaiser (2003) raised concerns over the increase in brain damage claims reportedly due to exposure to welding fumes. In the present article, we discuss methodological problems in conducting neuropsychological research on the effects of welding exposure, using a recent paper by Bowler et al. (2003) as an example to illustrate problems common in the neurotoxicity literature. Our analysis highlights difficulties in conducting such quasi-experimental investigations, including subject selection bias, litigation effects on symptom report and neuropsychological test performance, response bias, and scientifically inadequate casual reasoning.

22. Levy BS, Nassetta WJ. (2003) Neurologic effects of manganese in humans: A review. International Journal of Occupational and Environmental Health 9(2):153-163.
Manganese, which enters the body primarily via inhalation, can damage the nervous system and respiratory tract, as well as have other adverse effects. Occupational exposures occur mainly in mining, alloy production, processing, ferro-manganese operations, welding, and work with agrochemicals. Among the neurologic effects is an irreversible parkinsonian-like syndrome. An estimated 500,000 to 1.5 million people in the United States have Parkinson's disease, and physicians need to consider manganese exposure in its differential diagnosis. Since 1837, there have been many reports of cases and case series describing manganese toxicity. More recently, there have been epidemiologic studies of its adverse effects on health. Occupational medicine physicians can play critical roles in preventing the adverse health effects of manganese.

23. Levy LS, Aitken R, Holmes P, Hughes J, Hurley F, Rumsby PC, Searl A, Shuker LK, Spurgeon A, Warren FC. (2004) The derivation of a health-based occupational exposure limit for maganese using human neurobehaviour/neurotoxicity data. Toxicology 202(1-2):133-134.

24. Lucchini R, Selis L, Folli D, Apostoli P, Mutti A, Vanoni O, Iregren A, Alessio L. (1995) Neurobehavioral Effects of Manganese in Workers from a Ferroalloy Plant after Temporary Cessation of Exposure. Scandinavian Journal of Work Environment & Health 21(2):143-149.
Objectives The goal of this study was to assess long-term neurobehavioral effects associated with low airborne concentrations of manganese in a ferroalloy plant. Methods During a period of

forced cessation of work (1 to 42 d) neurobehavioral performance on tests of simple reaction time, finger tapping, digit span, additions, symbol digit, and shapes comparison was evaluated for 58 workers exposed from 1 to 28 (mean 13, SD 7) years to manganese. Airborne manganese concentrations in total dust had been reduced in the last 10 years from 70-1590 mu g . m(-3) (geometric means in different areas) to 27-270 mu g . m(-3). For each worker, manganese concentrations in blood and urine were measured, and a cumulative exposure index was also calculated. Results Blood manganese and urinary manganese ranged from 4 to 18 mu g . l(-1) (0.07 to 0.03 mu mol . l(-1)) and from 0.7 to 7 mu g . l(-1) (0.01 to 0.13 mu mol . l(-1)), respectively. Significant relationships were found between the blood manganese and urinary manganese levels and between these biological measures and the cumulative exposure index. Correlations were also found between the blood manganese level, the urinary manganese level, and the cumulative exposure index and the following tests: finger tapping, symbol digit, digit span, and additions. The correlation coefficients increased as the latency time after the cessation of exposure and work seniority increased. Conclusions The results support the hypothesis that the neurobehavioral effects observed at exposure levels well below current occupational standards are related to manganese body burden, which is better reflected by the blood manganese level after the cessation of exposure.

25. Myers JE, Thompson ML, Ramushu S, Young T, Jeebhay MF, London L, Esswein E, Renton K, Spies A, Boulle A and others. (2003) The nervous system effects of occupational exposure on workers in a South African manganese smelter. Neurotoxicology 24(6):885-894. Five hundred and nine production workers at a manganese (Mn) smelting works comprising eight production facilities and 67 external controls were studied cross-sectionally for Mn related neurobehavioural effects. Exposure measures from personal sampling included Mn in inhalable dust as cumulative exposure indices (CEI) and average intensity (INT). Biological exposure and biological effect measures included blood (MnB), urine (MnU) manganese and serum prolactin. Endpoints included items from the Swedish nervous system questionnaire (Q16), World Health Organisation neurobehavioural core test battery (WHO NCTB), Swedish performance evaluation system (SPES), Luria-Nebraska (IN), and Danish product development (DPD) test batteries, and a brief clinical examination. Potential confounders and effect modifiers included age, educational level, alcohol and tobacco consumption, neurotoxic exposures in previous work, past medical history, previous head injury and home language. Associations were evaluated by multiple linear and logistic regression modelling. Modelling assumptions were tested. Average exposure intensity across all jobs ranged from near 0 (0.06 mug/m(3)) for external controls to 5.08 mg/m(3) for inhalable Mn, and was greater than the ACGIH TLV for 69% of subjects. Results from the large number of tests performed resolved into three groups. Group I shows differences between external unexposed referents and all the exposed and/or differences between internal low exposed referents and the rest of the exposed but no further exposure-response relationships. It includes the Santa Ana, Benton and digit-span tests from the WHO NCTB; the hand tapping and endurance tapping tests from the SPES; Luria-Nebraska item 2L; questionnaire items tired, depressed, irritated, having to take notes in order to remember things, and subjects' perception that they had sex less often than normal; a test of clinical abnormality; and increased sway under two conditions (eyes open without foot insulation, eyes open with foot insulation). Group 2 shows the presence of a more substantive exposure-response relationship. It consists of only two tests: and includes the WHO digit-symbol test (although the major impact is at low exposure and therefore counterintuitive, arguably placing this test in group 3) and the LN item

IR which has a step to a poorer score at high exposure. Group 3 contains the overwhelming majority of test results (almost all the questionnaire items, almost all the DPD tests including tremor, sway and diadochokinesia, and serum prolactin) which were either null or counterintuitive (did not make sense). The CEI was the strongest predictor of test abnormalities, except for the clinical test which was more strongly associated with blood manganese. Despite a comprehensive range of endpoints, and levels of exposure ranging from environmental to industrial, this large study of Mn workers found little convincing

26. Nagatomo S, Umehara F, Hanada K, Nobuhara Y, Takenaga S, Arimura K, Osame M. (1999) Manganese intoxication during total parenteral nutrition: report of two cases and review of the literature. Journal of the Neurological Sciences 162(1):102-105.
We report two cases of manganese (Mn) intoxication during total parenteral nutrition including manganese (Mn). Both patients showed parkinsonism with psychiatric symptoms and elevated serum Mn levels. Tl-weighted magnetic resonance images (MRI) revealed symmetrical high intensity lesions in the globus pallidus. Discontinuation of Mn supplementation and levodopa treatment improved the symptoms and MRI abnormalities in the both patients. Thus, careful attention should be paid to the long-term intravenous administration of Mn. (C) 1999 Elsevier Science B.V. All rights reserved.

27. Ohtake T, Negishi K, Okamoto K, Oka M, Maesato K, Moriya H, Kobayashi S. (2005) Manganese-induced parkinsonism in a patient undergoing maintenance hemodialysis. American Journal of Kidney Diseases 46(4):749-753.
We report a rare case of manganese (Mn)-induced parkinsonism in a patient on maintenance hemodialysis therapy who complained of gait disturbance and dysarthria. His symptoms and abnormal magnetic resonance imaging (MRI) findings of the brain were thought to be caused, at least in part, by long-term ingestion of a health supplement (Chlorella extract) that contained 1.7 mg of Mn in the usual daily dose. Elevated serum and cerebrospinal fluid Mn levels were detected, and brain MRI showed areas of abnormal intensity in the bilateral basal ganglia (low intensity on T1-weighted images and high intensity on T2-weighted images). Edetic acid infusion therapy dramatically improved the MRI abnormalities, after which his symptoms gradually improved 4 months later.

28. Pal PK, Samii A, Calne DB. (1999) Manganese neurotoxicity: A review of clinical features, imaging and pathology. Neurotoxicology 20(2-3):227-238.
Manganese intoxication can result in a syndrome of parkinsonism and dystonia. If these extrapyramidal findings are present, they are likely to be irreversible and even progress after termination of the exposure to manganese. Clinical features are usually sufficient to distinguish these patients from those with Parkinson's disease. The neurological syndrome does not respond to levodopa. Imaging of the brain may reveal MRI signal changes in the globus pallidus, striatum, and midbrain. Positron emission tomography reveals normal presynaptic and postsynaptic nigrostriatal dopaminergic function. The primary site of neurological damage has been shown by pathological studies to be the globus pallidus. The mechanism of toxicity is not clear. (C) 1999 Inter Press, Inc.

29. Roels HA, Eslava MIO, Ceulemans E, Robert A, Lison D. (1999) Prospective study on the reversibility of neurobehavioual effects in workers exposed to manganese dioxide. Neurotoxicology 20(2-3):255-271.
In 1987, a cross-sectional study in a dry-alkaline battery plant in Belgium revealed subclinical neurobehavioral dysfunctions associated with inhalation exposure to manganese dioxide (MnO2) particulate. The overall geometric mean of the time-weighted average concentration of manganese (Mn) in "total" dust (MnT) amounted, at that time, to 1 mg Mn/m(3) and the duration of exposure was 5.5 years on average. An 8-year longitudinal investigation was conducted in this cohort (n = 92) in order to iind out whether early effects on eye-hand coordination (EHC), hand steadiness (HST), and simple visual reaction time (VRT) were reversible when the airborne manganese concentration at the workplace was abated. During the observation period from 1988 to 1995, MnT monitoring was implemented on a monthly basis producing more than 1300 personal air samples, EHC tests were given yearly to assess the precision of the hand-forearm movement (PN1), and HST and VRT tests were carried out yearly since 1991. By the end of the study, the cohort size had dropped to 34 subjects. The model of unbalanced repeated measurements with unstructured covariance matrix and a time-varying covariate (log MnT) was the most appropriate to analyze the data. Wald chi(2) statistic was used for testing time-trends. The reduction of MnT over time was significantly associated with an improvement of the PN1 values (total cohort: Wald chi(2) = 8.5, p=0.004; beta(log MnT) = -6.098 +/- 2.096). Like in the total cohort, time-trends were also found in the three exposure subgroups which could be identified in the cohort (average MnT over 1987-1992 were about 400, 600, and 2000 mu g Mn/m(3) for the low, medium, and high exposure subgroups, respectively). Only in the low exposure subgroup the PN 1 value normalized when MnT(provisional estimates) decreased from about 400 to 130 mu g Mn/m3 by the end of the study. Solely the reduction in MnT explained these findings on PN1, while a "healthy-worker-effect" mechanism was unlikely to have operated. The prognosis for the medium and high exposure subgroups remains uncertain as the improvement of their EHC performance may have been affected by past MnO2 exposure to such an extent that the persistence of a partial loss of EHC ability is suggested. The time courses of the HST and VRT test results, however, indicated the absence of any improvement, suggesting irreversible impairment of hand stability (postural tremor) and simple visual reaction time. A separate examination in a group of 39 control subjects, re-tested 10 years alter the first test in 1987, virtually precluded age as confounding factor in this prospective study. The findings of the longitudinal study are corroborated by the outcome of a separate follow-up study in a group of 24 ex-Mn employees, who showed in 1996 a significant improvement of eye-hand coordination alter at least three years with no MnO2 exposure; as to HST and VRT; there was no significant change in the deficit of these two neurobehavioral markers. (C) 1999 Inter Press, Inc.

30. Vieregge P, Heinzow B, Korf G, Teichert HM, Schleifenbaum P, Mosinger HU. (1995) Long-Term Exposure to Manganese in Rural Well Water Has No Neurological Effects. Canadian Journal of Neurological Sciences 22(4):286-289.
Background: There is debate on the neurological impact of chronic exposure to Manganese (MN), Methods: MN burden from rural well water was studied cross-sectionally in two proband cohorts from rural dwellings located in northern Germany. Both cohorts had exposure times for up to 40 years and were separated on the basis of well water MN content, Group A (41 subjects; mean age 57.5 years) was exposed to MN water contents of at least 0.300 mg/l (range 0.300 to 2.160), while group B (74 subjects; mean age 56.9 years) was exposed to concentrations of less

than 0.050 mg/l. Both proband groups were homogenous with regard to age, sex, nutritional habits, and drug intake. Neurological assessments by clinical investigators blinded for proband's exposure status was done using structured questionnaires, standardized neurological examination with assessment of possible Parkinsonian signs by the Columbia University Rating Scale, and instrumental tests of fine motor coordination. Results: No significant difference in any neurological measure was found between groups. Results were not confounded by demographic and dietary features. Conclusion: Exposure to high body burden of MN does not result in detectable neurological impairment, Exposure to MN in drinking water does not seem to be a risk factor for idiopathic Parkinson's disease.

31. Walczak, Jakubowski M, Matczak W. (2001) Neurological and neurophysiological examinations of workers occupationally exposed to manganese. International Journal of Occupational Medicine and Environmental Health 2001, Vol. 14, No. 4, p. 329-337. 16 ref.
To assess the effects of manganese on the functions of the nervous system in exposed workers in the shipbuilding and electrical industries, 75 male workers, 62 welders and fitters and 13 workers involved in battery production, were studied. The control group consisted of 62 non-exposed men matched by age and work shift distribution. Of the 62 welding workers, 30 worked in the area with Mn concentrations exceeding the MAC value of 0.3mg/m3. In battery production, six subjects were subject to concentrations exceeding MAC values. Clinically, the increased emotional irritability, dysmnesia, concentration difficulties, sleepiness and limb paresthesia predominated among the disorders of the nervous system functions in exposed workers. Generalized and paroxysmal changes were the most common recordings in the abnormal electroencephalography. Visual evoked potentials examinations showed abnormalities which could be a signal of the optic neuron disorders. The results show that manganese exposures within the range of < 0.01-2.67mg/m3 can induce sub-clinical effects on the nervous system.

32. Wirth JJ, Rossano MG, Daly DC, Paneth N, Puscheck E, Potter RC, Diamond MP. (2007) Ambient manganese exposure is negatively associated with human sperm motility and concentration. Epidemiology 18(2):270-273.
Background: Occupational and experimental animal studies indicate that exposure to high levels of manganese impairs male fertility, but the effects of ambient manganese in humans are not known. Methods: We measured blood levels of manganese and selenium in 200 infertility clinic clients in a cross-sectional study. Correlations between metals and semen variables were determined, adjusting for other risk factors. Outcomes were low motility (< 50% motile), low concentration (< 20 million/mL), or low morphology (< 4% normal). We also investigated dose-response relationships between quartiles of manganese exposure and sperm parameters. Results: High manganese level was associated with increased risk of low sperm motility (odds ratio = 5.4; 95% confidence interval = 1.6-17.6) and low sperm concentration (2.4; 1.2-4.9). We saw a U-shaped dose-response pattern between quartiles of manganese exposure and all 3 sperm parameters. Conclusion: Ambient exposure to manganese levels is associated with a reduction in sperm motility and concentration. No adverse effects were seen for high selenium.

33. Young T, Myers JE, Thompson ML. (2005) The nervous system effects of occupational exposure to manganese - Measured as respirable dust - in a South African manganese smelter. Neurotoxicology 26(6):993-1000.

Objectives: A major recent review of occupational exposure limits for manganese (Mn) has proposed a respirable dust level of 0.1 mg/m(3). There is, however no theoretical basis for using this exposure metric to estimate the systemic effects of Mn, and little in the way of empirical data relating respirable Mn to neurobehavioural and other non-pulmonary effects. Cross-sectional data from a study showing few and unconvincing neurobehavioural effects of inhalable dust in Mn smelter workers published just prior to this review were reanalyzed here using respirable Mn. The hypotheses tested were that respirable Mn exposure is a more appropriate predictor of neurobehavioural effects than inhalable Mn where such effects exist, and that there should be no observed effects at respirable dust levels below 0.1 mg/m(3). Methods: Five hundred and nine production workers and 67 external referents were studied. Exposure measures from personal sampling included the Mn content of respirable dust as a concentration-time integrated cumulative exposure index (CEI) and as average intensity (INT) over a working lifetime. Neurobehavioural endpoints included items from the Swedish nervous system questionnaire (Q16), World Health Organisation neurobehavioural core test battery (WHO NCTB), Swedish performance evaluation system (SPES), Luria-Nebraska (LN), and Danish product Development (DPD) test batteries, and a brief clinical examination. Results: The median respirable Mn exposure was 0.058 mg/m(3) (range = 0-0.51; IQR = 0.02-0.16) amongst the exposed, with 30% having average intensities above the proposed 0.1 mg/m(3) and 44% above the proposed supplemental limit of 0.5 mg/m(3) inhalable dust. As in the study of inhalable Mn effects, there were few respirable Mn effects showing clear continuity of response with increasing exposure. Conclusion: These data did not provide empirical support for a respirable, as opposed to an inhalable, dust metric being more sensitive in the identification of Mn effects. Neither metric showed convincing effects within the exposure range studied. Further study is needed to determine a threshold for respirable Mn effects, if such exist, and to verify our findings.

34. Yuan H, He SC, He MW, Niu Q, Wang L, Wang S. (2006) A comprehensive study on neurobehavior, neurotransmitters and lymphocyte subsets alteration of Chinese manganese welding workers. Life Sciences 78(12):1324-1328.

The neurotoxicity of manganese has been demonstrated by many researches. But few reports have been found on its immunotoxicity in manganese-exposed workers. Here we selected welding workers (aged 34 years) as Mn-exposed subjects. They have been exposed to manganese for 16 years. The control group was from a flour plant. The average concentrations of Mn, Cd, Fe and Ni in work place were 138.40 +/- 11.60 mu g/m(3), 581.40 +/- 45.32 mu g/m(3), 3.84 +/- 0.53 mu g/m(3) and 12.64 +/- 2.80 ng/m(3), respectively. Blood Mn (4.84 mu g/dl) of welding workers was higher than that of the control group (1.92 mu g/dl). Neurobehavioral core test battery (NCTB) recommended by WHO was conducted on the subjects and found that the scores of negative emotions, such as confusion-bewilderment, depression-dejection, fatigue-inertia, and tension-anxiety, were higher in welding workers. Visual simple reaction time and the fast simple reaction time were shorter than that of the control group. The numbers of digital span, forward digital span, backward digital span and digital symbol decreased in welding workers compared with control group. Monoamine neurotransmitters and their metabolism substances in urine were tested by HPLC-ultraviolet. NE, E, MHPG, HVA, DA, DOPAC and 5-HT in the urine of Mn-exposed group had no significant changes while 5-HIAA in Mn-exposed group had significantly decreased compared with that of the control group. Lymphocyte subsets of the subjects were determined by Flow Cytometer. CD3(+) T cell, CD4(+)CD8(-) T cell,

CD4(-)CD8(+) T cell, CD4(+)CD45RO(-) "virgin" lymphocytes, CD4(+)CD45RO(+) "memory" lymphocytes, and CD3(-)CD19(+) B cell had no significant changes compared with the control group. The results showed that long-term exposure to manganese in welding might have adverse effects on mood state, neurobehavior, and peripheral neurotransmitters. However, they had no effects on lymphocyte subsets parameters.

Supporting References (57)

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2. Azin F, Raie RM, Mahmoudi MM. (1998) Correlation between the levels of certain carcinogenic and anticarcinogenic trace elements and esophageal cancer in northern Iran. Ecotoxicology and Environmental Safety 39(3):179-184.
Levels of four carcinogenic (Ni, Fe, Cu, Pb) and four anticarcinogenic (Zn, Se, Mn, Mg) trace elements were measured in hair samples from esophageal cancer patients, their unaffected family members, and members of families with no history of cancer. Measurements were also made in non-esophageal cancer patients, using atomic absorption spectroscopy, inductively coupled plasma-emission spectroscopy, and neutron activation analysis. The results showed that Ni and Cu concentrations were significantly higher and Mg and Mn concentrations were significantly lower in all cancer cases. Levels of Zn, Fe, Se, and Pb were not significantly different in the above-mentioned groups. In addition, the serum albumin fraction, which is reported to have antioxidant activity, was found to be significantly lower among esophageal cancer patients. (C) 1998 Academic Press.

3. Barbee JY, Prince TS. (1999) Acute respiratory distress syndrome in a welder exposed to metal fumes. Southern Medical Journal 92(5):510-512.
A 43-year-old man began having malaise, chills, and fever 12 hours after cutting a galvanized steel grating with an acetylene torch at work. Over the next 72 hours, his symptoms persisted and became worse with progressive shortness of breath. We was admitted to the hospital and begun on antibiotics and steroids. The next day his condition had deteriorated to the point that he had to he intubated, Chest x-ray film and computed tomography showed patchy and interstitial infiltration bilaterally, consistent with acute respiratory distress syndrome. Open lung biopsy showed focal mild interstitial pneumonia. Multiple laboratory studies were negative for an infectious or an immune process. The patient remained on mechanical ventilation for 10 days and was discharged from the hospital 2 days after extubation. He continued to improve, with minimal symptoms and a return to normal activity levels several months after the incident with no continued treatment. Re-creation of his exposure was done under controlled circumstances, with air sampling revealing elevated air levels for cadmium and zinc and borderline levels of arsenic, manganese, lead, and iron.

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The observation of orthostatic hypotension in an index case of manganese toxicity lead to this prospective attempt to evaluate cardiovascular autonomic function and cognitive and emotional

neurotoxicity in eight manganese alloy welders and machinists. The subjects consisted of a convenience sample consisting of an index case of manganese dementia, his four co-workers in a "frog shop" for gouging, welding, and grinding repair of high manganese railway track and a convenience sample of three mild steel welders with lesser manganese exposure also referred because of cognitive or autonomic symptoms. Frog shop air manganese samples 9.6-10 years before and 1.2-3.4 years after the diagnosis of the index case exceeded 1.0 mg/m(3) in 29% and 0.2 mg/m(3) in 62%. Twenty-four-hour electrocardiographic (Holter) monitoring was used to determine the temporal variability of the heartrate (RR' interval) and the rates of change at low frequency (0.04-0.15Hz) and high frequency (0.15-0.40Hz). MMPI and MCMI personality assessment and shortterm memory, figure copy, controlled oral word association, and symbol digit tests were used. The five frog shop workers had abnormal sympathovagal balance with decreased high frequency variability (increased In LF/ln HF). Seven of the eight workers had symptoms of autonomic dysfunction and significantly decreased heart rate variability (rMSSD) but these did not distinguish the relative exposure. Mood or affect was disturbed in all with associated changes in short-term memory and attention in four of the subjects. There were no significant correlations with serum or urine manganese. Power spectrum analysis of 24-h ambulatory ECG indicating a decrease in parasympathetic high frequency activation of heart rate variability may provide a sensitive index of central autonomic dysfunction reflecting increased exposure to manganese, although the contribution of exposures to solvents and other metals cannot be excluded. Neurotoxicity due to the gouging, melding, and grinding of mild steel and high manganese alloys (11-25%) merits air manganese and neuropsychologic surveillance including autonomic function by Holter monitoring of cardiovagal activation. (C) 1998 Academic Press.

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6. Beuter A, Edwards R, De Geoffroy A, Mergler D, Hudnell K. (1999) Quantification of neuromotor function for detection of the effects of manganese. Neurotoxicology (Little Rock) 20(2-3):355-366.
BIOSIS COPYRIGHT: BIOL ABS. The effect of low level exposure to manganese (Mn) was examined in 297 subjects from southwest Quebec. Blood manganese (MnB) levels as well as other possibly relevant variables were obtained. We tested equipment and analysis procedures that we have developed to quantify aspects of motor function thought to be affected by exposure to toxins, in particular, rapid alternating movements, rapid and precise pointing movements, and tremor. (1) The eurythmokinesimeter measures timing and precision of co kinesimeter accurately measures rapid rotation of the forearms (pronation/supination). Characteristics quantifying the range, speed, period, shape and regularity of the oscillatory movements were calculated, as well as the smoothness of the movement on a fine scale and the coordination between the two hands. (3) Postural tremor of the arm and hand was measured using the accelerometry-based "TREMOR" system of Danish Product Development. We used the amplitude and frequency characte

7. Bocca B, Alimonti A, Bomboi G, Giubilei F, Forte G. (2006) Alterations in the level of trace metals in Alzheimer's disease. Trace Elements and Electrolytes 23(4):270-276.

In the present study, serum and blood trace elements and oxidative status in Alzheimer's disease patients and healthy individuals were compared in order to identify possible biomarkers of the disease. A Sector Field Inductively Coupled Plasma Mass Spectrometry (SF-ICP-MS) method was developed for the determination of Al, Ba, Be, Bi, Cd, Co, Cr, Hg, Li, Mn, Mo, Ni, Pb, Sb, Sn, Sr, Tl, V, W and Zr. Pre-treatment procedures based on high sample throughput, procedural simplicity and low contamination risk were utilized. The following significant imbalances in Alzheimer's disease were found: increment of Hg and Sri in serum ($p <= 0.01$), higher levels of Co, Li, Mn and Sri and lower levels of Mo in blood ($p < 0.01$), increased formation of serum oxidant species (SOS) and decreased antioxidant capacity (SAC) ($p < 0.001$).

8. Bouchard M, Mergler D, Baldwin M. (2005) Manganese exposure and age: neurobehavioral performance among alloy production workers. Environmental Toxicology and Pharmacology 19(3):687-694.
Manganese (Mn) is associated with neurotoxic effects under certain conditions of exposure. A recent study on environmental Mn exposure showed an Mn x age interaction for several neurobehavioral functions. The objective of the present study was to examine the neurobehavioral test results in relation to age and Mn exposure, using an existing data set on 74 workers from an Mn alloy production plant and referents pair-matched for age (&PLUSMN; 3 years), educational level (&PLUSMN; 2 years), number of children, and smoking status. The pair differences between Mn-exposed workers and referents increased significantly with age for scores on Delayed Word Recall, Trail Making B, Cancellation H, Nine-Hole Hand Steadiness Test, and Vibratometer. These results suggest that for certain neurobehavioral functions, and in particular for information processing, Mn-related deficits increase with age. This outcome could not be explained by higher cumulative Mn exposure. © 2005 Elsevier B.V. All rights reserved.

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BIOSIS COPYRIGHT: BIOL ABS. Postural stability was investigated by static posturography in 32 manganese exposed workers with exposure duration of 6.6 (range 1.1-15.7) years and 53 referent subjects. The mean current urine manganese concentration for the exposed was 6.0 mug/g creatinine (range 0.6 to 53.3). There was no significant differences between both groups for the postural sway parameters obtained during eyes open condition. However, significant differences were observed for L - length of sway path and Vel - mean velocity of the center of pressure along its path. The Romberg Ratios (the relationship between eyes closed/open conditions) for the exposed's Vel, L, and Ao were also significantly different from the referent. The study showed that manganese exposed workers had significantly poorer postural stability compared to a referent group. We postulate that this could be a subclinical effect of manganese on the basal ganglia (pallidus) resulting in the postural instability when the visual in

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BIOSIS COPYRIGHT: BIOL ABS. In 1983, Roels et al. (1987a,b) collected blood and urine samples and conducted neurological testing of workers at a manganese oxide and salt producing plant in Belgium, and at a nearby chemical plant. Workers from the manganese plant performed

significantly worse than workers from the chemical plant on tests of short-term memory capacity, eye-hand coordination, hand steadiness, and visual reaction time. Between 1985 and 1996, workers at the manganese plant were tested routinely using the same b osed longer. Large year-to-year differences were observed in some neurological test outcomes that could not be explained by age or Mn exposure. Older age was significantly associated with poorer performance on tests of short-term memory and eye-hand coordination. After controlling for age and year of testing, reduced hand steadiness was significantly associated with blood Mn and (marginally) urine Mn, and both reaction time and one measure of hand steadiness were significantly as

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Manganese intoxication is an unusual, severe form of intoxication. This report deals with a patient now 80 years old who accidentally ingested a solution of potassium permanganate for a period of at least 4 weeks 14 years ago. Since then, the patient suffers from a mild parkinsonian syndrome and distally accentuated polyneuropathies. Psychiatric disorders, especially demential or depressive symptoms, were not observed. Manganese analysis of his hair still shows a clear increase in manganese concentration. The MRI of his brain showed no pathological changes, in particular none of those often described with symmetric signal elevation in T-1 in the area of the basal ganglia. In this study, we present clinical, laboratory, and neuroradiological findings. Unusual in this case with a short exposition is the long duration and clinical improvement without I-dopa treatment.

12. Ericson JE, Crinella FM, Clarke-Stewart KA, Allhusen VD, Chan T, Robertson RT. (2007) Prenatal manganese levels linked to childhood behavioral disinhibition. Neurotoxicology and Teratology 29(2):181-187.
Although manganese (Mn) is an essential mineral, high concentrations of the metal can result in a neurotoxic syndrome affecting dopamine balance and behavior control. We report an exploratory study showing an association between Mn deposits in tooth enamel, dating to the 20th and 62-64th gestational weeks, and childhood behavioral outcomes. In a sample of 27 children, 20th week Mn level was significantly and positively correlated with measures of behavioral disinhibition, specifically, play with a forbidden toy (36 months), impulsive errors on a continuous performance and a children's Stroop test (54 months), parents' and teachers' ratings of externalizing and attention problems on the Child Behavior Checklist (1st and 3rd grades), and, teacher ratings on the Disruptive Behavior Disorders Scale (3rd grade). By way of contrast, Mn level in tooth enamel formed at the 62-64th gestational week was correlated only with teachers' reports of externalizing behavior in 1st and 3rd grades. Although the source(s) of Mn exposure in this sample are unknown, one hypothesis, overabsorption of Mn secondary to gestational iron-deficiency anemia, is discussed.

13. Forte G, Bocca B, Senofonte O, Petrucci F, Brusa L, Stanzione P, Zannino S, Violante N, Alimonti A, Sancesario G. (2004) Trace and major elements in whole blood, serum, cerebrospinal fluid and urine of patients with Parkinson's disease. Journal of Neural Transmission 111(8):1031-1040.

Quantifications of Al, Ca, Cu, Fe, Mg, Mn, Si and Zn were performed in urine, serum, blood and cerebrospinal fluid (CSF) of 26 patients affected by Parkinson's disease (PD) and 13 age-matched controls to ascertain the potential role of biological fluids as markers for this pathology. Analyses were performed by Inductively Coupled Plasma Atomic Emission Spectrometry and Sector Field Inductively Coupled Plasma Mass Spectrometry. The serum oxidant status (SOS) and anti-oxidant capacity (SAC) were also determined. Results showed a decreasing trend for Al in all the fluids of PD patients, with the strongest evidence in serum. Calcium levels in urine, serum and blood of PD patients were significantly higher than in controls. Copper and Mg concentrations were significantly lower in serum of PD patients. Levels of Fe in urine, blood and CSF of patients and controls were dissimilar, with an increase in the first two matrices and a decrease in CSF. No significant difference was found in levels of Mn between patients and controls. Urinary excretion of Si was significantly higher in PD subjects than in controls. No clear difference between Zn levels in the two groups was found for serum, urine or CSF, but an increase in Zn levels in the blood of PD patients was observed. The SOS level in PD was significantly higher while the corresponding SAC was found to be lower in patients than in controls, in line with the hypothesis that oxidative damage is a key factor in the pathogenesis of PD. The results on the whole indicate the involvement of Fe and Zn (increased concentration in blood) as well as of Cu (decreased serum level) in PD. The augmented levels of Ca and Mg in the fluids and of Si in urine of patients may suggest an involuntary intake of these elements during therapy.

14. Fortoul TI, Mendoza ML, Avila MD, Torres AQ, Osorio LS, Espejel GM, Fernandez GO. (2001) Manganese in lung tissue: Study of Mexico City residents' autopsy records from the 1960s and 1990s. Archives of Environmental Health 56(2):187-190.
During the conduct of autopsies performed on residents of Mexico City during the 1960s (20 males, 19 females) and 1990s (30 males and 18 females), concentrations of manganese in lung were studied with atomic absorption spectrometry. Concentrations of manganese were not significantly greater in the samples obtained in the 1990s (1.87 +/- 0.8 mug/gm [mean +/- standard deviation]) than in samples from the 1960s (1.72 +/- 1.2 mug/gm). Concentrations were not correlated with gender, smoking habit, age, or cause of death; however, there was a correlation with occupation. The findings suggest that manganese exposure via air does not represent a health hazard to residents of Mexico City, given that lung concentrations of manganese remained stable during the 30-y period studied. Investigators should monitor concentrations of manganese in suspended particles to follow-up on these findings.

15. Fredstrom S, Rogosheske J, Gupta P, Burns LJ. (1995) Extrapyramidal Symptoms in a Bmt Recipient with Hyperintense Basal Ganglia and Elevated Manganese. Bone Marrow Transplantation 15(6):989-992.
Neurologic syndromes attributed to conditioning or medications have been reported in BMT recipients. A patient is presented who developed extrapyramidal symptoms on day +56 after allogeneic BMT. Brain magnetic resonance images of this patient demonstrated hyperintense basal ganglia, which has been associated with manganese (Mn) toxicity. The patient had received total parenteral nutrition (TPN) with standard trace element supplementation and had been cholestatic. Serum Mn was elevated, and continued to be so 5 months after BMT, long after discontinuation of TPN. Cholestatic patients and those on long-term TPN have been found to have high blood or serum levels of Mn, but generally are asymptomatic, When other cholestatic

BMT patients were reviewed, all had elevated serum Mn. Manganese supplementation in TPN requires evaluation for BMT recipients.

16. Goldman SM, Quinlan PJ, Smith AR, Langston J, Tanner CM. (2004) Manganese exposure and risk of Parkinson's disease in twins. Movement Disorders 19:S162-S162.

17. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, Richardson RJ. (1997) Occupational exposures to metals as risk factors for Parkinson's disease. Neurology 48(3):650-658.
In a population-based case-control study, we investigated the potential role of occupational exposure to iron, copper, manganese, mercury, zinc, and lead as risk factors for Parkinson's disease (PD). Concurrently recruited, nondemented patients (n = 144) with idiopathic PD and controls (n = 464) consisting of men and women greater than or equal to 50 years of age, frequency-matched for age (within 5 years), race, and sex were enrolled. All had primary medical care at Henry Ford Health System in urban/suburban metropolitan Detroit. Subjects were given an extensive risk-factor questionnaire detailing actual worksite conditions of all jobs held for more than 6 months from age 18 onward. An industrial hygienist, blinded to the case-control status of subjects, rated occupational exposure to each of the metals of interest. When adjusted for sex, race, age, and smoking status, we found in those with more than 20 years' exposure a significantly increased association with PD for copper (OR = 2.49, 95% CI = 1.06, 5.89) and manganese (OR = 10.61, 95% CI = 1.06, 105.83). For more than 20 years' exposure to combinations of lead-copper (OR = 5.24, 95% CI = 1.59, 17.21), lead-iron (OR = 2.83, 95% CI = 1.07, 7.50), and iron-copper (OR = 3.69, 95% CI = 1.40, 9.71), there was a greater association with PD than with any of these metals alone. These findings suggest that chronic exposure to these metals is associated with PD, and that they may act alone or together over time to help produce the disease.

18. Gorell JM, Johnson CC, Rybicki BA, Peterson EL, Kortsha GX, Brown GG, Richardson RJ. (1999) Occupational exposure to manganese, copper, lead, iron, mercury and zinc and the risk of Parkinson's disease. Neurotoxicology 20(2-3):239-247.
A population-based case-control study was conducted in the Henry Ford Health System (HFHS) in metropolitan Detroit to assess occupational exposures to manganese, copper, lead, iron, mercury and zinc as risk factors for Parkinson's disease (PD). Non-demented men and women 50 years of age who were receiving primary medical care at HFHS were recruited, and concurrently enrolled cases (n = 744) and controls (n = 464) were frequency-matched for sex, race and age (+/- 5 years). A risk factor questionnaire, administered by trained interviewers, inquired about every job held by each subject for 6 months from age 18 onward, including a detailed assessment of actual job tasks, tools and environment. An experienced industrial hygienist, blinded to subjects' case-control status, used these data to rate every job as exposed or not exposed to one or more of the metals of interest. Adjusting for sex, race, age and smoking status, 20 years of occupational exposure to any metal was not associated with PD. However, more than 20 years exposure to manganese (Odds Ratio [OR] = 10.61, 95% Confidence Interval [CI] = 1.06, 105.83) or copper (OR = 2.49, 95% CI = 1.06,5.89) was associated with PD. Occupational exposure for > 20 years to combinations of lead-copper (OR = 5.24, 95% CI = 1.59,17.21), lead-iron (OR = 2.83, 95% CI = 1.07,7.50), and iron-copper (OR = 3.69, 95% CI = 7.40, 9.71) was also associated with the disease. No association of occupational exposure to iron, mercury or zinc

with PD was found. A lack of statistical power precluded analyses of metal combinations for chose with a low prevalence of exposure (i.e., manganese, mercury and zinc). Our findings suggest that chronic occupational exposure to manganese or copper, individually, or to dual combinations of lead iron and copper, is associated with PD. (C) 1999 Infer Press, Inc.

19. Gorell JM, Rybicki BA, Johnson CC, Peterson EL. (1999) Occupational metal exposures and the risk of Parkinson's disease. Neuroepidemiology 18(6):303-308.
Occupational exposure to specific metals (manganese, copper, lead, iron, mercury, zinc, aluminum and others) appears to be a risk factor for Parkinson's disease (PD) in some, but not all, case-control studies. These epidemiological studies are reviewed. Several methodological issues that may account for the lack of unanimity of findings are discussed, and suggestions for improved case-control methodology are offered. The study of the neurological disease outcome of workers who have had long-term, well-defined occupational exposure to one or more metals is also urged, with collaborative work including industrial hygienists, occupational toxicologists, neurologists, epidemiologists and biostatisticians. Such efforts, employing state-of-the-art case and control ascertainment and enrollment from suitable population bases, neurological diagnostic rigor and exposure assessment, will help to further define the potentially important roles played by metals in PD and other neurodegenerative disorders.

20. Greiffenstein MF, Lees-Haley PR. (2007) Neuropsychological correlates of manganese exposure: A meta-analysis. Journal of Clinical and Experimental Neuropsychology 29(2):113-126.
The hypothesized effect of recurrent low-dose manganese (Mn) exposure on neuropsychological function is controversial because of inconsistent findings across three decades of research. We conducted a meta-analysis on 41 variables from nineteen neuropsychological studies of Mn-exposed workers. The results showed: Large effect size (ES) for biological markers of Mn and lead levels; thirteen of 26 neurocognitive measures showing a small average ES; only one of 26 tasks showed a moderate ES; and small to medium ES for confounding/competing variables such as education and aptitude. Tasks with the highest ES included clerical substitution tasks, digit span, tapping endurance, and Swedish Performance Evaluation System "Additions" reaction time, but none exceeded the ES for education or aptitude. The mean ES of dose-response relationships was zero. The data did not support a theory of preclinical ("early") neuromotor or cognitive dysfunction. Overall, the pooled data are more consistent with covariate effect than toxic effect, insofar as the pooled exposure group showed demographics less favorable to neuropsychological performance than the pooled referent groups. Future consideration of demographic and biological covariates is necessary before inferring subtle toxin-induced brain damage because neuropsychological tests are nonspecific.

21. Ha@l/atek T, Sinczuk-Walczak H, Szymczak M, Rydzynski K. (2005) Neurological and respiratory symptoms in shipyard welders exposed to manganese. International Journal of Occupational Medicine and Environmental Health 3rd quarter 2005, Vol. 18, No. 3, p. 265-274. Illus. 51 ref.
This case-control study was performed to assess the use of neurophysiological tests for the detection of early effects of exposure to low manganese concentrations and to examine the use of Clara cell protein (CC16) as an early pulmonary biomarker of exposure to welding fumes. The study involved 59 shipyard welders and 23 controls, matched by age and smoking habits.

Subjective neurological symptoms, visual evoked potentials and electroencephalography were examined. Relationships between manganese concentrations in the air, blood and urine as well as between cumulative exposure indices were investigated. CC16 as an early pulmonary biomarker in welding exposure was examined by immunoassay. Findings are discussed. It was confirmed that these sensitive tests could be used for the detection of early effect of exposure to low manganese concentrations.

22. Hernandez EH, Discalzi G, Dassi P, Jarre L, Pira E. (2003) Manganese intoxication: The cause of an inexplicable epileptic syndrome in a 3 year old child. Neurotoxicology 24(4-5):633-639.
Excess manganese (Mn) can cause several neurotoxic effects, however only a few studies have reported epileptic syndromes related to manganese intoxication. We describe an epileptic syndrome due to manganese intoxication in a 3 year old male child. His blood manganese was elevated, but no other abnormal values or toxic substances were found in blood or urine. The electroencephalogram (EEG) showed a picture of progressive encephalopathy, while brain magnetic resonance was normal. The patient's conditions rapidly worsened to epileptic status despite the use of antiepileptic drugs. Chelating treatment with CaNa(2)EDTA was initiated to remove excess manganese and promptly succeeded in reverting epileptic symptoms. Concurrently, manganese blood levels and electroencephalogram progressively normalized. Thereafter it has been possible to discontinue antiepileptic treatment, and the patient remains in excellent conditions without any treatment.

23. Hobbesland A, Kjuus H, Thelle DS. (1999) Study of cancer incidence among 6363 male workers in four Norwegian ferromanganese and silicomanganese producing plants. Occupational and Environmental Medicine 56(9):618-624.
Objectives-Little has been known about the risk of cancer associated with occupational exposure to manganese. The objective of this study was therefore to examine the associations between duration of specific work and cancer incidence among employees in four Norwegian ferromanganese and silicomanganese producing plants. Methods-Among men first employed in 1933-91 and with at least 6 months in these plants, the incident cases of cancer during 1953-91 were obtained from The Cancer Registry of Norway. The numbers of various-cancers were compared with expected figures calculated from age and calendar time specific rates for Norwegian men during the same period. Internal comparisons of rates were performed urith Poisson regression analysis. The final cohort comprised 6363 men. Results-A total of 607 cases of cancer were observed against 596 cases expected (standardised incidence ratio (SIR) 1.02). Internal comparisons of rates showed a positive trend between the rate of all cancers and duration of furnace work, A slightly weaker trend was also found for duration of blue collar non-furnace work when lags of 25 or 30 years were applied in the annalyses. However, several results indicated that the incidence of all cancers among the non-furnace workers decreased during the period of active employment. Conclusions-Furnace and non-furnace workers may have exposures that increase the incidence of several cancers. The low incidence of cancer among non-furnace workers during the period of ongoing exposure cannot be explained. As this study cannot identify any causal factors, the role of exposure to manganese remains unclear.

24. Hossny E, Mokhtar G, El-Awady M, El-Wahab AA. (1998) Serum manganese deficiency in Egyptian children with bronchial asthma. Journal of Allergy and Clinical Immunology 101(1):S117-S117.

25. Hsieh CT, Liang JS, Peng SSF, Lee WT. (2007) Seizure associated with total parenteral nutrition-related hypermanganesemia. Pediatric Neurology 36(3):181-183.
The trace element manganese is usually supplied when total parenteral nutrition is used. However, long-term parenteral administration of manganese, which bypasses the normal. regulatory mechanism, may cause hypermanganesemia. Manganese poisoning presents clinically with parkinsonian-like symptoms and psychological changes. Seizures are a rare presentation of this disease. This report describes a 10-year-old female who had received total parenteral nutrition for 3 months because of short bowel syndrome, and presented with tonic-clonic seizure, decreased level of consciousness, and fever. The serum electrolytes, glucose and the cerebrospinal fluid examination were normal. The blood culture grew Pantoea agglomerans. The brain magnetic resonance imaging disclosed no evidence of central nervous system infection. However, symmetric high-intensity signal on T-1-weighted images was documented in the basal ganglia, especially in the globus pallidus. Her whole blood manganese level was 3.7 mu g/dL, which was significantly higher than the normal range (0.4-1.4 mu g/dL). Diagnosis of hypermanganesemia related to total parenteral nutrition was made. (c) 2007 by Elsevier Inc. All rights reserved.

26. Jimenezjimenez FJ, Molina JA, Aguilar MV, Arrieta FJ, Jorgesantamaria A, Cabreravaldivia F, Ayusoperalta L, Rabasa M, Vazquez A, Garciaalbea E and others. (1995) Serum and Urinary Manganese Levels in Patients with Parkinsons-Disease. Acta Neurologica Scandinavica 91(5):317-320.
To elucidate the possible role of manganese in the risk of developing Parkinson's disease (PD), we compared serum levels of manganese, and 24-h manganese excretion by urine in 29 PD patients and in 27 matched controls. We also measured chromium and cobalt in the same samples. All these values did not differ significantly between the groups, they were not influenced by antiparkinsonian drugs, and they did not correlate with age, age at onset and duration of the PD, scores of the Unified PD Rating Scale or the Hoehn and Yahr staging in the PD group. These results might suggest that serum levels and urinary excretion of manganese are apparently unrelated to the risk of developing PD.

27. Kenangil G, Ertan S, Sayilir I, Ozekmekci S. (2006) Progressive motor syndrome in a welder with pallidal T1 hyperintensity on MRI: A two-year follow-up. Movement Disorders 21(12):2197-2200.
Chronic exposure to manganese (Mn) fume during welding may lead to mainly extrapyramidal syndrome that is resistant to treatment. We present a 32-year-old patient who developed severe postural instability, Parkinsonism, dystonia, and pyramidal signs in the 10th year of welding. The neurological condition of the patient worsened markedly in the following 3 years, resulting in severe disability rendering him to be assisted in all his daily activities and he did not benefit from any dopaminergic agent. T1 sequences of the MRI of the brain showed pallidal hyperintensity symmetrically. Welders in our country often protect their eyes but ignore to use tools that protect them from inhalation of the fume. Since chronic Mn toxicity may cause serious disability and irreversible neurological disturbances, we strongly believe that it is necessary to

inform welders and their employers about this potential hazard. (C) 2006 Movement Disorder Society.

28. Kessler KR, Wunderlich G, Hefter H, Seitz RJ. (2003) Secondary progressive chronic manganism associated with markedly decreased striatal D2 receptor density. Movement Disorders 18(2):216-218.
We describe a patient with chronic manganism due to intoxication 40 years ago. Whereas previous reports on acute or subacute intoxication have shown no or only small reductions in striatal D2 receptor density, we found markedly decreased D2 receptor density using F-18-methylspiperone PET in this very late stage of chronic manganism, supporting the hypothesis that manganese intoxication may trigger a neuro-degenerative disease process. (C) 2002 Movement Disorder Society.

29. Kilic E, Saraymen R, Demiroglu A, Ok E. (2004) Chromium and manganese levels in the scalp hair of normals and patients with breast cancer. Biological Trace Element Research 102(1-3):19-25.
The adverse health effects linked with chromium and manganese and the diverse cellular and molecular effects of chromium and manganese make the study of chromium and manganese carcinogenesis and toxicology very interesting and complex. Quantitative elemental analysis of scalp hair of breast cancer patients (stage III) (n = 26) and controls (n = 27) were used to study to find correlation and possible changes between breast cancer and healthy controls. The graphite furnace atomic absorption analysis of quantitative method was used for the determination of chromium and manganese element levels. Comparison of mean elemental contents of the breast cancer patients with controls shows a significant enhancement of chromium ($p < 0.05$) but declining trends for manganase ($p < 0.05$) in breast cancer patients. Changes in element content in hair can serve as a guide to opening up new vistas in the treatment of breast cancer on the basis of an overall analysis of symptoms and signs.

30. Kim JW, Kim Y, Cheong HK, Ito K. (1998) Manganese induced Parkinsonism: A case report. Journal of Korean Medical Science 13(4):437-439.
BIOSIS COPYRIGHT: BIOL ABS. Manganese (Mn) intoxication is known to induce parkinsonism. Mn-induced parkinsonism preferentially affect the globus pallidus in contrast to idiopathic parkinsonism where degeneration predominantly involves the nigral pars compacta. We describe a 51-year-old man who had been occupationally exposed to Mn. He had parkinsonian features including masked face, resting tremor, and bradykinesia. He also had a cock walk and a particular propensity to fall in a backward gait. There was no sustained therapeutic response to levodopa. A fluorodopa PET scan was normal. This case indicates that Mn-induced parkinsonism can be differentiated from idiopathic parkinsonism in that the former has unique clinical features and a normal fluorodopa PET scan.

31. Kim Y, Kim JM, Kim JW, Yoo CI, Lee CR, Lee JH, Kim HK, Yang SO, Chung HK, Lee DS and others. (2002) Dopamine transporter density is decreased in parkinsonian patients with a history of manganese exposure: What does it mean? Movement Disorders 17(3):568-575.
Manganese (Mn) exposure can cause parkinsonism. Pathological changes Occur mostly in the pallidum and striatum. Two patients with a long history of occupational Mn exposure presented with Mn-induced parkinsonism. In I patient, magnetic resonance imaging (MRI) showed

findings consistent with Mn exposure, and Mn concentration was increased in the blood and urine. However, this patient's clinical features were typical of idiopathic Parkinson disease (PD). Previous pathological and positron emission tomography Studies indicate that striatal dopamine transporter density is normal in Mn-induced parkinsonism, whereas it is decreased in PD. Therefore, we performed [I-123]-(1e)-2beta-carboxymethoxy-3beta-(4([I-123]-beta-CIT) single-photon emission iodophenyl)tropane computed tomography. Severe reduction of striatal beta-CIT bindin,, was indicated, which is consistent with PD. We propose three interpretations: (1) the patients have PD, and Mn exposure is incidentals (2) Mn induces selective degeneration of presynaptic dopaminergic nerve terminals, thereby causing parkinsonism or (3) Mn exposure acts as a risk of PD in these patients. Our results and careful review of previous studies indicate that the axiom that Mn Causes parkinsonism by pallidal lesion may be over-simplified Mn exposure and parkinsonism may be more complex than previously thought. Further studies are required to elucidate the relationship between Mn and various forms of parkinsonism. (C) 2002 Movement Disorder Society.

32. Kim YH, Kim JW, Ito KG, Lim HS, Cheong HK, Kim JY, Shin YC, Kim KS, Moon YH. (1999) Idiopathic parkinsonism with superimposed manganese exposure: Utility of positron emission tomography. Neurotoxicology 20(2-3):249-252.
It is difficult to distinguish manganism from idiopathic parkinsonism by clinical signs only. Case history and examination: A 48-year-old welder for over 10 years complained of masked lace right side (arm and leg) resting tremor, and bradykinesia for over one year. Magnetic resonance imaging (MRI) findings showed symmetrical high signal intensities in the globus pallidus on T1 weighted image. These intensities disappeared almost completely six months after cessation of exposure. F-18-6-fluorodopa (F-18-dopa) positron emission tomography (PET) findings showed reduced F-18-dopa uptake in the left putamen, findings which appear in idiopathic parkinsonism. A PET study is necessary to distinguish manganism from idiopathic parkinsonism, especially in a working environment with elevated Mn concentrations, such as welding. (C) 1999 Intox Press, Inc.

33. Kocyigit A, Zeyrek D, Keles H, Koylu A. (2004) Relationship among manganese, arginase, and nitric oxide in childhood asthma. Biological Trace Element Research 102(1-3):11-18.
It has been demonstrated that the lowest intakes of manganese (Mn) were associated with more than a fivefold increased risk of bronchial reactivity. It was also known that nitric oxide (NO) production was found to be significantly higher in asthmatics. There is a reciprocal pathway between arginase and nitric oxide synthase (NOS) for NO production, and Mn is required for arginase activity and stability. We investigated plasma NO, arginase, and its cofactor Mn levels to evaluate this reciprocal pathway in patients with childhood asthma. Arginase activities and Mn and NO levels were measured in plasma from 31 patients with childhood asthma and 22 healthy control subjects. Plasma arginase activities and Mn concentrations were found to be significantly lower and NO levels were significantly higher in patients with childhood asthma as compared to the control subjects. There was a significantly positive correlation between plasma Mn and arginase and negative correlations between arginase and NO values and Mn and NO values in patients with childhood asthma. These data indicate that the lower concentration of Mn could cause lower arginase activity and this could also upregulate NO production by increasing L-arginine content in patients with childhood asthma.

34. Komaki H, Maisawa S, Sugai K, Kobayashi Y, Hashimoto T. (1999) Tremor and seizures associated with chronic manganese intoxication. Brain & Development 21(2):122-124.
Tremor and seizures developed in a 2-year-old girl receiving total parenteral nutrition. T1-weighted images on MRI revealed areas of hyperintensity in the basal ganglia, brainstem and cerebellum. Blood manganese was elevated. The symptoms and MRT abnormalities disappeared after withdrawal of manganese administration. The recommendation of daily parenteral manganese intake was discussed. (C) 1999 Elsevier Science B.V. All rights reserved.

35. Kondoh H, Iwase K, Higaki J, Tanaka Y, Yoshikawa M, Hori S, Osuga K, Kamiike W. (1999) Manganese deposition in the brain following parenteral manganese administration in association with radical operation for esophageal cencer: Report of a case. Surgery Today-the Japanese Journal of Surgery 29(8):773-776.
We report herein the case of a patient in whom manganese (Mn) deposition in the basal ganglia was detected by magnetic resonance imaging (MRI) subsequent to thoracic esophagectomy, performed following perioperative parenteral nutrition. A multi-trace-element supplement solution which included 20 mu mol of Mn per day had been parenterally administered for 7 days preoperatively and 21 days postoperatively. The serum level of total bilirubin reached a maximum value of 5.1mg/dl postoperatively. The T1-weighted MRI on the 32nd postoperative day demonstrated bilateral and symmetrical hyperintense lesions in the globus pallidus and the whole-blood Mn level on the 34th postoperative day was 4.9 mu g/l, the normal range being 0.8-2.5 mu g/l. This hyperintensity on T1-weighted MRI was gradually improved following normalization of the blood Mn level. This case report serves to demonstrate that even short-term perioperative parenteral nutrition may result in Mn deposition in the brain following radical surgery for esophageal cancer, especially in patients with hyperbilirubinemia.

36. Lucchini R, Bergamaschi E, Smargiassi A, Festa D, Apostoli P. (1997) Motor function, olfactory threshold, and hematological indices in manganese-exposed ferroalloy workers. Environmental Research 73(1-2):175-180.
BIOSIS COPYRIGHT: BIOL ABS. A cross-sectional study was conducted in 35 male subjects randomly selected from workers of a ferroalloy production plant and exposed to manganese (Mn) oxides; the objective was to detect early signs of neurologic impairment. The subjects' mean age was 39.4 years (SD, 8.4); the average exposure duration was 14.5 years (range, 5-29 years). A control group of industrial workers not exposed to neurotoxic chemicals and comparable in age and confounding factors was recruited. The intensity of Mn exposure was moderate, as reflected by airborne Mn concentrations in total dust averaging 93 mug/m3. Mn levels in blood (MnB) and urine (MnU) were significantly higher in the Mn-exposed workers than in control workers. A relationship (not found with MnU) was found between MnB and a cumulative exposure index calculated on the basis of air concentration and exposure history for each subject (r = 0.52; r2 = 0.27; P = 0.002). Psychomotor function scores were lower among Mn-exposed subjec MH - CHEMISTRY, CLINICAL

37. Masumoto K, Suita S, Taguchi T, Yamanouchi T, Nagano M, Ogita K, Nakamura M, Mihara F. (2001) Manganese intoxication during intermittent parenteral nutrition: Report of two cases. Journal of Parenteral and Enteral Nutrition 25(2):95-99.
Background and Methods: The administration of trace elements is thought to be needed in patients receiving long-term parenteral nutrition. Recently, manganese intoxication or deposition

was documented in such patients. We report two cases of manganese intoxication during intermittent parenteral nutrition including manganese. Manganese had been administered for 4 years at a frequency of one or two times per week in one case and for 5 years at a frequency of one or two times per month in the other case. Both cases showed mild symptoms with headache and dizziness. One case had mild hepatic dysfunction and the other did not. The whole-blood manganese level increased in one case, but not in the other case. T1-weighted magnetic resonance images revealed symmetrical high-intensity areas in basal ganglia and thalamus in both cases. After the administration of manganese was stopped, these symptoms all disappeared and the magnetic resonance images abnormalities gradually improved in both patients. Mild long-term manganese intoxication is thus considered to occur regardless of the frequency of using a manganese supplement. Conclusions: Patients should be carefully monitored when receiving long-term parenteral nutrition including manganese, even when the manganese dose is small and the frequency of receiving a manganese supplement is low.

38. Mergler D, Baldwin M, Belanger S, Larribe F, Beuter A, Bowler R, Panisset M, Edwards R, de Geoffroy A, Sassine MP and others. (1999) Manganese neurotoxicity, a continuum of dysfunction: Results from a community based study. Neurotoxicology 20(2-3):327-342. Excessive manganese (Mn) has been associated with neurobehavioral deficits and neurological and/or neuropsychiatric illness, but the level at which this metal can cause adverse neurotoxic effects, particularly with long-term exposure, is still unknown. The objective of the present study was to assess nervous system functions in residents exposed to manganese from a variety of environmental sources. A random stratified sampling procedure was used to select participants; persons with a history of workplace exposure to Mn and other neurotoxic substances were excluded. A self-administered questionnaire provided data on socio-demographic variables. Blood samples were analyzed for total manganese (MnB) lead, mercury and serum iron. Nervous system assessment included computer and hand-administered neurobehavioral tests, computerized neuromotor tests, sensory evaluation and a neurological examination. The present analyses include 273 persons (151 women and 122 men); MnB range: 2.5 mu g/L - 15.9 mu g/L (median: 7.3 mu g/L). Multivariate analyses were used and neuro-outcomes were examined with respect to MnB, laking into account potential confounders and covariables. Results were grouped according to neurofunctional areas and MANOVA analyses revealed that higher MnB (7.5 mu g/L) was significantly associated with changes in coordinated upper limb movements (Wilks' lambda = 0.92; p = 0.04) and poorer learning and recall (men: Wilks' lambda = 0.77; p = 0.002; women: Wilks' lambda = 0.86; p = 0.04). Further analyses revealed that with increasing log MnB (Simple regression : $p<0.05$) performance on a pointing task was poorer, frequency dispersion of hand-arm tremor decreased, while harmonic index increased, and the velocity of a pronation/supination arm movement was slower. An Mn-age interaction was observed for certain motor tasks, with the poorest performance observed among chose _50 y and in the higher MnB category. Differences between genders suggest that men may be at greater risk than women, although effects were also observed in women. These findings are consistent with the hypothesis that Mn neurotoxicity can be viewed on a continuum of dysfunction, with early, subtle changes at lower exposure levels. (C) 1999 Inter Press, Inc.

39. Molina JA, Jimenez-Jimenez FJ, Aguilar MV, Meseguer I, Mateos-Vega CJ, Gonzalez-Munoz MJ, de Bustos F, Porta J, Orti-Pareja M, Zurdo M and others. (1998) Cerebrospinal fluid

levels of transition metals in patients with Alzheimer's disease. Journal of Neural Transmission 105(4-5):479-488.
We compared CSF and serum levels of iron, copper, manganese, and zinc, measured by atomic absorption spectrophotometry, in 26 patients patients with Alzheimer's disease (AD) without major clinical signs of undernutrition, and 28 matched controls. CSF zinc levels were significantly decreased in AD patients as compared with controls ($p < 0.05$). The serum levels of zinc, and the CSF and serum levels of iron, copper, and manganese, did not differ significantly between AD-patient and control groups. These values were not correlated with age, age at onset, duration of the disease, and scores of the MiniMental State Examination in the AD group. Weight and body mass index were significantly lower in AD patients than in controls. Because serum zinc levels were normal, the possibility that low CSF zinc levels were due to a deficiency of dietary intake seems unlikely. However, it is possible that they might be related to the interaction of beta-amyloid and/or amyloid precursor protein with zinc, that could result in a depletion of zinc levels.

40. Muhtaseb MS, O'Reilly D, McKee R, Anderson J, Finlay IG. (2004) Patients who have had ileal-anal pouch surgery are at risk of manganese and vitamin B toxicity. British Journal of Surgery 91:5-5.

41. Myers JE, teWaterNaude J, Fourie M, Zogoe HBA, Naik I, Theodorou P, Tassel H, Daya A, Thompson ML. (2003) Nervous system effects of occupational manganese exposure on South African manganese mineworkers. Neurotoxicology 24(4-5):649-656.
Occupational exposure to airborne manganese dust has been shown to produce adverse effects on the central nervous system. Four hundred and eighty-nine blue and white collar manganese mineworkers from South Africa were studied cross-sectionally to investigate the nervous system effects of medium to low occupational manganese exposures. The different facilities included underground mines, surface processing plants, and office locations. A job exposure matrix was constructed using routine occupational hygiene data. Exposure variables included years of service, a cumulative exposure index (CEI) and average intensity of exposure (AINT) across all jobs, and blood manganese. Endpoints included items from the Q16, WHO-NCTB, SPES, and Luria-Nebraska test batteries, and a brief clinical examination. Potential confounders and effect modifiers included age, level of education, past medical history including previous head injury, previous neurotoxic job exposures, tobacco use, alcohol use and home language. Associations were evaluated by multiple linear and logistic regression modeling. Average exposure intensity across all jobs was 0.21 mg/m(3) manganese dust. Multivariate analyses showed that none of the symptom nor test results were associated with any measure of exposure including blood manganese, after adjustment for confounders. This relatively large null study indicates that manganese miners exposed on average across all jobs to MnO2 at levels near the American Conference of Governmental Industrial Hygienists Threshold Limit Value (ACGIH TLV) are unlikely to have a subclinical neurotoxicity problem.

42. Park J, Yoo CI, Sim CS, Kim HK, Kim JW, Jeon BS, Kim KR, Bang OY, Lee WY, Yi Y and others. (2005) Occupations and Parkinson's disease: A multi-center case-control study in South Korea. Neurotoxicology 26(1):99-105.

Objective: We performed a hospital based case-control study in South Korea (1) to clarify the role of occupational exposure, and especially manganese (Mn) exposure in the etiology of Parkinson's disease (PD) and (2) to discover the association between any occupations and PD. Methods: We selected two groups, PD patient group (NI) and controls (N-2). Three hundred sixty-seven consecutive outpatients with PD (177 men, 190 women) and 309 controls were interviewed about life style, past history, family history, education level, and occupational history etc. We employed a range of industrial categories as defined by section (the most broad category) and division (sub-category) of the Korea Standard Industry Code (KSIC) Manual. Along with KSIC, we also used the Korea Standard Classification of Occupations (KSCO) as proxies of occupational exposure. The odds ratios (ORs) and 95% confidence intervals (CA), adjusted for age, sex, smoking status, and education level are presented. Results: As regarding the exposure to hazardous materials, especially Mn, more subjects in the control group than the PD patient group 'have worked in the occupations with potential exposure to Mn ($P < 0.001$). Ever having worked in 'agriculture, hunting, and forestry' section of industry was positively associated with PD (OR 1.88), and 'agriculture production crops (OR 1.96)'division of industry was positively associated with PD. On the other hand, ever having worked in the 'manufacturing (OR 0.56)', 'transportation (OR 0.28)' section of industry, and 'transporting (OR 0.20)' division of industry were negatively associated with PD. 'Drivers (OR 0.13)'division of occupation also was negatively associated with PD. Conclusions: To our knowledge, this is the first case-control studies to find an inverse relationship between 'transporting' or 'technicians like machinery engineers' as his/her longest job and PD risk. Because of this unexpected finding, our work should be replicated in various populations.

43. Park J, Yoo CI, Sim CS, Kim JW, Yi Y, Shin YC, Kim DH, Kim Y. (2006) A retrospective cohort study of Parkinson's disease in Korean shipbuilders. Neurotoxicology 27(3):445-449. Objective: We performed a retrospective cohort study in South Korea to clarify the role of occupational exposure. especially to welding, in the etiology of Parkinson's disease (PD). Methods: We constructed a database of subjects classified into an exposure group (blue-collar workers) and a non-exposure group (white-collar workers) in two shipbuilding companies. Jobs of blue-collar workers were categorized into the first group of welding, the second group of fitting, grinding and finishing, cutting, and the other group. To determine new cases of PD during the follow-up period (1992-2003), we used the physician billing claims database of the National Health Insurance Corporation. For the detected PD patients in the physician billing claims database, a neurologist in our research team confirmed the appropriateness of each diagnosis by reviewing medical charts. Based on the review. we confirmed the numbers of new cases of PD and calculated the relative risk (RR) and the 95% confidence intervals (CI) by Cox regression analysis. Results: In a backward selection procedure, 'age' was a significant independent variable but exposure was not. Furthermore, the RR in welders (high exposure group) was also insignificant and less than that in others (very low exposure group). Conclusion: This longitudinal study of shipbuilding workers supports our previous case-control studies suggesting that exposure to manganese does not increase the risk of PD.

44. Ransom-Schwaeber MM. (2007) Manganese toxicity due to oral ingestion as an acne treatment. Neurology 68(12):A327-A327.

45. Rodriguez-Agudelo Y, Riojas-Rodriguez H, Rios C, Rosas I, Pedraza ES, Miranda J, Siebe C, Texcalac JL, Santos-Burgoa C. (2006) Motor alterations associated with exposure to manganese in the environment in Mexico. Science of the Total Environment 368(2-3):542-556.
Overexposure to manganese (Mn) causes neurotoxicity (a Parkinson-like syndrome) or psychiatric damage ("manganese madness"). Several studies have shown alterations to motor and neural behavior associated with exposure to Mn in the workplace. However, there are few studies on the effects of environmental exposure of whole populations. We studied the risk of motor alterations in people living in a mining district in Mexico. We studied 288 individual people (168 women and 120 men) from eight communities at various distances from manganese extraction or processing facilities in the district of Molango. We measured manganese concentrations in airborne particles, water, soil and crops and evaluated the possible routes of Mn exposure. We also took samples of people's blood and determined their concentrations of Mn and lead (Pb). We used "Esquema de Diagnostico Neuropsicologico" Ardila and Ostrosky-Solis's neuropsychological battery to evaluate motor functions. Concentrations of Mn in drinking water and maize grain were less than detection limits at most sampling sites. Manganese extractable by DTPA in soils ranged between 6 and 280 mg kg(-1) and means were largest close to Mn extraction or processing facilities. Air Mn concentration ranged between 0.003 and 5.86 mu g/m(3); the mean value was 0.42 mu g/m(3) and median was 0.10 mu g/m(3), the average value (geometric mean) resulted to be 0.13 mu g/m(3). Mean blood manganese concentration was 10.16 mu g/l, and geometric mean 9.44 mu g/l, ranged between 5.0 and 31.0 mu g/l. We found no association between concentrations of Mn in blood and motor tests. There was a statistically significant association between Mn concentrations in air and motor tests that assessed the coordination of two movements (OR 3.69; 95% Cl 0.9, 15.13) and position changes in hand movements (OR 3.09; CI 95% 1.07, 8.92). An association with tests evaluating conflictive reactions (task that explores verbal regulations of movements) was also found (OR 2.30; Cl 95% 1.00, 5.28). It seems from our results that people living close to the manganese mines and processing plants suffer from an incipient motor deficit, as a result of their inhaling manganese-rich dust.

46. Ross C, O'Reilly DS, McKee R. (2006) Potentially clinically toxic concentrations of whole blood manganese in a patient fed enterally with a high tea consumption. Annals of Clinical Biochemistry 43:226-228.
This report describes a 37-year-old female patient who after seven years on intermittent overnight enteral feeding supplementation was noted to have an increased whole blood manganese concentration. Manganese toxicity is well documented after pathological absorption through inhalation via the lungs, or after intravenous administration to patients on long-term total parenteral nutrition. A dietary history revealed high tea consumption. The association between high blood manganese concentrations and enteral/oral nutrition does not appear to have previously been described.

47. Sadek AH, Rauch R, Schulz PE. (2003) Parkinsonism due to Manganism in a Welder. International Journal of Toxicology 22(5):393-401.
A 33-year-old right-handed male presented complaining of a 2-year history of progressive cognitive slowing, rigidity, tremors, slowing of movements, and gait instability leading to falls. On examination, he had a Mini-Mental Status Examination (MMSE) score of 29, slowed saccadic eye pursuit, hypomimia, cogwheel rigidity, a 3- to 4-Hz tremor, and a "cock-walk" gait.

His symptoms and signs were similar to idiopathic Parkinson's disease; however, he was young, inattention and forgetfulness occurred early in the course of the disorder, levodopa was unhelpful, and his gait was atypical. His work up for secondary causes of parkinsonism was negative, except for increased signal intensity on T1-weighted magnetic resonance image (MRI) in the bilateral basal ganglia. Typical etiologies for that finding were ruled-out, which led to further inquiries into the patient's lifestyle. He was a welder, and discussion with his employer revealed that he used a steel-manganese alloy, he often worked in a confined ship's hold, and he did not use a respiratory mask. Because manganese toxicity can produce increased T1-weighted signal intensities in the basal ganglia, the authors tested his serum and urine manganese, and both were elevated. This patient emphasizes the importance of a careful occupational history in persons presenting with atypical manifestations of a neurodegenerative disorder. It also lends support to the hypothesis that welding can produce enough exposure to manganese to produce neurologic impairment.

48. Sassine MP, Mergler D, Bowler R, Hudnell HK. (2002) Manganese accentuates adverse mental health effects associated with alcohol use disorders. Biological Psychiatry 51(11):909-921.
Background: A population-based study, on earl, v neurotoxic effects of environmental exposure to manganese (Mn) enabled its to investigate the relation between blood Mn levels (MnB), alcohol consumption, and risk for alcohol use disorders (AUD) on mental health. Methods: participants were selected using a random stratified sampling procedure. Self-administered questionnaires provided data on alcohol consumption, sociodemographics, medical history, and lifestyle. Mood states were assessed with the Brief Symptom Inventory (BSI), and risk for AUD was surveyed using a behavioral screening questionnaire and categorized into no, low, and high risk. Of 297 participants, 253 current drinkers who had responded to all questions on alcohol use were retained. Results: Psychologic distress increased with risk for AUD and alcohol consumption greater than or equal to 420 g/week. Higher MnB levels (greater than or equal to7.5 mug/L) intensified the relation between risk for AUD and BSI settle scores. The prevalence odd ratios for positive cases of psychologic distress with risk for AUD, 1.98 [1.13-3.46], differed Amen divided by MnB strata: lower MnB: 1.34 [0.64-2.85]; higher MnB: 4.22 [1.65-10.77]. Conclusions: These findings suggest that higher levels of blood manganese significantly increase neuropsychiatric symptoms associated with risk for alcohol use disorders. Biol Psychiatry 2002;51:909-921 (C) 2002 Society of Biological Psychiatry.

49. Shinotoh H, Snow BJ, Chu NS, Huang CC, Lu CS, Lee C, Takahashi H, Calne DB. (1997) Presynaptic and postsynaptic striatal dopaminergic function in patients with manganese intoxication: A positron emission tomography study. Neurology 48(4):1053-1056.
BIOSIS COPYRIGHT: BIOL ABS. We performed PET on four patients with chronic industrial Mn intoxication; presynaptic and postsynaptic dopaminergic function were measured with (18F)6-fluoro-L-dopa (6FD) and (11C)raclopride (RAC). All patients had a rigid-akinetic syndrome; they had no sustained benefit from L-dopa. Influx constants (Ki) of 6FD were normal in the caudate and putamen. RAC binding was mildly reduced in the caudate and normal in the putamen. We conclude that nigrostriatal dopaminergic dysfunction is not responsible for the parkinsonism caused by chronic Mn intoxication. The pathology is likely to be downstream of the dopaminergic projection.

50. Sjogren B, Iregren A, Frech W, Hagman M, Johansson L, Tesarz M, Wennberg A. (1996) Effects on the nervous system among welders exposed to aluminium and manganese. Occupational and Environmental Medicine 53(1):32-40.
Objectives-The purpose was to study the effects on the nervous system in welders exposed to aluminium and manganese. Methods-The investigation included questionnaires on symptoms, psychological methods (simple reaction time, finger tapping speed and endurance, digit span, vocabulary, tracking, symbol digit, cylinders, olfactory threshold, Luria-Nebraska motor scale), neurophysiological methods (electroencephalography, event related auditory evoked potential (P-300), brainstem auditory evoked potential, and diadochokinesometry) and assessments of blood and urine concentrations of metals (aluminium, lead, and manganese). Results-The welders exposed to aluminium (n = 38) reported more symptoms from the central nervous system than the control group (n = 39). They also had a decreased motor function in five tests. The effect was dose related in two of these five tests. The median exposure of aluminium welders was 7065 hours and they had about seven times higher concentrations of aluminium in urine than the controls. The welders exposed to manganese (n = 12) had a decreased motor function in five tests. An increased latency of event related auditory evoked potential was also found in this group. The median manganese exposure was 270 hours. These welders did not have higher concentrations of manganese in blood than the controls. Conclusions-The neurotoxic effects found in the groups of welders exposed to aluminium and manganese are probably caused by the aluminium and manganese exposure, respectively. These effects indicate a need for improvements in the work environments of these welders.

51. Staunton M, Phelan DM. (1995) Manganese Toxicity in a Patient with Cholestasis Receiving Total Parenteral-Nutrition. Anaesthesia 50(7):665-665.

52. Wardle CA, Forbes A, Roberts NB, Jawhari AV, Shenkin A. (1999) Hypermanganesemia in long-term intravenous nutrition and chronic liver disease. Journal of Parenteral and Enteral Nutrition 23(6):350-355.
Background: Hypermanganesemia and cholestatic liver disease are both recognized complications of long-term IV nutrition. Manganese is primarily excreted in bile, and recent studies have indicated that manganese toxicity may play a role in the pathogenesis of IV nutrition-associated cholestasis. Methods: Whole blood and plasma manganese concentrations were measured in patients receiving long-term home IV nutrition (HIN, n = 30). Whole blood manganese concentrations also were measured in patients with chronic liver disease (CLD, n = 10) and control subjects (n = 10). Results: Whole blood manganese concentrations of all. CLD patients were within the reference interval (73 to 210 nmol/L) and were not different from those of the control group (151 +/- 44 nmol/L, CLD vs 155 +/- 35 nmol/L, control; not significant), despite the presence of cholestasis. In contrast, whole blood manganese concentration was increased (>210 nmol/L) in 26 patients, and plasma manganese concentration increased (>23 nmol/L) in 23 of the patients receiving HIN. None of the patients exhibited neurologic signs of manganese toxicity. There was no correlation between whole blood manganese concentrations and markers of cholestasis, IV manganese intake, or duration of HIN. However, plasma manganese concentration correlated both with average weekly IV manganese intake (r = .44, p = .02) and with gamma-glutamyl transferase (r = .43, p = .02) and alkaline phosphatase activities (I = .55, p = .003). Conclusions: Cholestatic liver disease does not appear to contribute to increased whole blood manganese concentrations in patients not receiving HIN. Plasma manganese

concentrations in patients receiving HIN reflect recent manganese exposure and impaired excretion where cholestasis is present. The lack of relationship between plasma and whole blood manganese concentrations suggests that factors other than manganese intake and excretion affect intracellular concentrations.

53. Wasserman GA, Liu XH, Parvez F, Ahsan H, Levy D, Factor-Litvak P, Kline J, van Geen A, Slavkovich V, Lolacono NJ and others. (2006) Water manganese exposure and children's intellectual function in Araihazar, Bangladesh. Environmental Health Perspectives 114(1):124-129.
Exposure to manganese via inhalation has long been known to elicit neurotoxicity in adults, but little is known about possible consequences of exposure via drinking water. In this study, we report results of a cross-sectional investigation of intellectual function in 142 10-year-old children in Araihaza, Bangladesh, who had been consuming tube-well water with an average concentration of 793 mu g Mn/L and 3 mu g arsenic/L. Children and mothers came to our field clinic, where children received a medical examination in which weight, height, and head circumference were measured. Children's intellectual function was assessed on tests drawn from the Wechsler Intelligence Scale for Children, version III, by summing weighted items across domains to create Verbal, Performance, and Full-Scale raw scores. Children provided urine specimens for measuring urinary As and creatinine and were asked to provide blood samples for measuring blood lead, As, Mn, and hemoglobin concentrations. After adjustment for sociodemographic covariates, water Mn was associated with reduced Full-Scale, Performance, and Verbal raw scores, in a dose-response fashion; the low level of As in water had no effect. In the United States, roughly 6% of domestic household wells have Mn concentrations that exceed 300 mu g Mn/L, the current U.S. Environmental Protection Agency, lifetime health advisory level. We conclude that in both Bangladesh and the United States, some children are at risk for Mn-induced neurotoxicity.

54. Woolf A, Wright R, Amarasiriwardena C, Bellinger D. (2002) A child with chronic manganese exposure from drinking water. Environmental Health Perspectives 110(6):613-616.
The patient's family bought a home in a suburb, but the proximity of the house to wetlands and its distance from the town water main prohibited connecting the house to town water. The family had a well drilled and they drank the well water for 5 years, despite the fact that the water was turbid, had a metallic taste, and left an orange-brown residue on clothes, dishes, and appliances. When the water was tested after 5 years of residential use, the manganese concentration was elevated (1.21 ppm; U.S. Environmental Protection Agency reference, <0.05 ppm). The family's 10-year-old son had elevated manganese concentrations in whole blood, urine, and hair. The blood manganese level of his brother was normal, but his hair manganese level was elevated. The patient, the 10-year-old, was in the fifth grade and had no history of learning problems; however, teachers had noticed his inattentiveness and lack of focus in the classroom. Our results of cognitive testing were normal, but tests of memory revealed a markedly below-average performance: the patient's general memory index was at the 13th percentile, his verbal memory at the 19th percentile, his visual memory at the 14th percentile, and his learning index at the 19th percentile. The patient's free recall and cued recall tests were all 0.5-1.5 standard deviations (1 SD = 16th percentile) below normal. Psychometric testing scores showed normal IQ but unexpectedly poor verbal and visual memory. These findings are consistent with the known toxic effects of manganese, although a causal relationship cannot necessarily be inferred.

55. Yanik M, Kocyigit A, Tutkun H, Vural H, Herken H. (2004) Plasma manganese, selenium, zinc, copper, and iron concentrations in patients with schizophrenia. Biological Trace Element Research 98(2):109-117.
A number of essential trace elements play a major role in various metabolic pathways. Selenium (Se), manganese (Mn), copper (Cu), zinc (Zn), and iron (Fe) are essential trace elements that have been studied in many diseases, including autoimmune, neurological, and psychiatric disorders. However, the findings of previous research on the status of trace elements in patients with schizophrenia have been controversial. We studied these elements in patients with a DSM-IV diagnosis of schizophrenia and compared them with sex- and age-matched healthy controls. Plasma Cu concentrations were significantly higher ($p < 0.01$) and Mn and Fe concentrations were lower ($p < 0.05$ and $p < 0.05$, respectively) in schizophrenic patients than in controls. Se and Zn concentrations and protein levels did not differ between patients and healthy controls. These observations suggest that alterations in essential trace elements Mn, Cu, and Fe may play a role in the pathogenesis of schizophrenia. However, findings from trace element levels in schizophrenia show a variety of results that are difficult to interpret.

56. Yiin SJ, Lin TH, Shih TS. (1996) Lipid peroxidation in workers exposed to manganese. Scandinavian Journal of Work Environment & Health 22(5):381-386.
BIOSIS COPYRIGHT: BIOL ABS. Objectives: The following hypothesis was tested: plasma manganese concentration is associated positively with the product of lipid peroxidation, and lipid peroxidation is associated negatively with the activities of antioxidants in workers exposed to manganese. Methods: The plasma manganese concentration of 22 manganese-exposed workers and 45 referents was determined by graphite furnace atomic absorption spectrophotometry. Malondialdehyde, the product of lipid peroxidation, was determined by high-performance liquid chromatography, and the activities of protective enzymes were measured by ultraviolet-visible spectrophotometry. Results: The activities of superoxide dismutase, glutathione peroxidase, and catalase spread widely among the referents. The activity of superoxide dismutase and the concentrations of malondialdehyde and manganese were significantly higher in the manganese workers than in the referents. The concentration of malondialdehyde in the exposed workers wa

57. Yoshikawa K, Matsumoto M, Hamanaka M, Nakagawa M. (2003) A case of manganese induced parkinsonism in hereditary haemorrhagic telangiectasia. Journal of Neurology Neurosurgery and Psychiatry 74(9):1312-1314.
A 44 year old right handed woman complained of difficulty in moving. She and her relatives had skin telangiectasia or recurrent epistaxis. On neurological examination, she had a mask-like facies and bradykinesia in both extremities. Laboratory examinations showed iron deficiency anaemia and mild liver dysfunction with raised serum manganese. On T1 weighted cranial magnetic resonance imaging there were hyperintense areas in the globus pallidus bilaterally, suggesting manganese deposition. Abdominal angiography confirmed multiple portal-systemic shunts in the liver, and a needle biopsy of the liver showed diffuse dilatation of the sinusoids with fatty change. Levodopa did not improve the bradykinesia. This appears to be a case of hereditary haemorrhagic telangiectasia with manganese induced parkinsonism, which may be a new type of neurological disorder in such patients.

4.2 LESS-THAN-LIFETIME AND CHRONIC STUDIES AND CANCER BIOASSAYS IN ANIMALS—ORAL AND INHALATION

4.2.1 Less-than-lifetime and Chronic Studies

Key References (32)

1. Ahn SS, Lee KM. (1998) Neurotoxicity of chronic manganese exposure causing frontal lobe dysfunction. Journal of Neurochemistry 70:S29-S29.

2. Chen MT, Yiin SJ, Sheu JY, Huang YL. (2002) Brain lipid peroxidation and changes of trace metals in rats following chronic manganese chloride exposure. Journal of Toxicology and Environmental Health-Part A 65(3-4):305-316.
The aim of this study was to investigate the effects of chronic daily, 30-d administration of manganese chloride (MnCl2) to male Sprague-Dawley rats on lipid peroxidation and changes of trace elements (manganese, iron, copper, zinc) in various brain regions. Rats were intraperitoneally injected with MnC2 (20 mg/kg) once daily for 30 consecutive days. The Mn accumulated in frontal cortex, corpus callosum, hippocampus, striatum, hypothalamus, medulla, cerebellum, and spinal cord. Malondialdehyde, an end product of lipid peroxidation, was markedly decreased in frontal cortex and cerebellum. An increased level of Cu was observed in frontal cortex, medulla, and a cerebellum. A decreased Fe level was found only in cerebellum, and a decreased Zn level was observed in hippocampus and striatum. In a second group of animals, Mn (20 mg/kg/d) and glutathione (CSH, 75 mg/kg/d) were administered ip for 30 d. In CSH-Mn-treated rats, compared to Mn-treated rats, MDA concentrations were significantly reduced in frontal cortex, medulla and cerebellum. The changes of trace elements in rat brain were similar to the Mn-treated group. We suggest that Mn is an atypical antioxidant, as well as not involved in oxidative damage in rat brain. Fe and Cu may play roles in the protective effect of Mn against lipid peroxidation in rat brain.

3. Desole MS, Esposito G, Migheli R, Fresu L, Sircana S, Zangani D, Miele M, Miele E. (1995) Cellular Defense-Mechanisms in the Striatum of Young and Aged Rats Subchronically Exposed to Manganese. Neuropharmacology 34(3):289-295.
A deficiency of striatal dopamine (DA) is generally accepted as an expression of manganese (Mn) toxicity in experimental animals. Since compromised cellular defence mechanisms may be involved in Mn neurotoxicity, we investigated the response of the neuronal antioxidant system [ascorbic acid (AA) oxidation, glutathione (GSH) and uric acid levels] and neurochemical changes in the striatum in aged rats exposed to Mn. Levels of dopamine (DA), dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), 5-hydroxytryptamine (5-HT), 5-hydroxyindoleacetic acid (5-HIAA), AA, dehydroascorbic acid (DHAA), GSH and uric acid were determined after subchronic oral exposure to MnCl2 200 mg/kg (3-month-old rats) and 30-100-200 mg/kg (20-month-old rats). Aged rats had basal levels of striatal DA, DOPAC, HVA, 5-HT, 5-HIAA, GSH and AA lower than those of young rats. In the striatum of aged rats, Mn induced biphasic changes in the levels of DA, DOPAC, HVA (an increase at the lower dose and a decrease at the higher dose) and DHAA (opposite changes). Mn decreased GSH levels and increased uric acid levels both in the striatum and in synaptosomes in all groups of aged rats. All of these parameters were affected to a lesser extent in young rats. In conclusion, the response of

cellular defence mechanisms in aged rats is consistent with a Mn-induced increase in the formation of reactive oxygen species. An age-related impairment of the neuronal antioxidant system may play an enabling role in Mn neurotoxicity.

4. Dorman DC, McManus BE, Parkinson CU, Manuel CA, McElveen AM, Everitt JI. (2004) Nasal toxicity of manganese sulfate and manganese phosphate in young male rats following subchronic (13-week) inhalation exposure. Inhalation Toxicology 16(6-7):481-488.
Growing evidence suggests that nasal deposition and transport along the olfactory nerve represents a route by which inhaled manganese and certain other metals are delivered to the rodent brain. The toxicological significance of olfactory transport of manganese remains poorly defined. In rats, repeated intranasal instillation of manganese chloride results in injury to the olfactory epithelium and neurotoxicity as evidenced by increased glial fibrillary acidic protein (GFAP) concentrations in olfactory bulb astrocytes. The purpose of the present study was to further characterize the nasal toxicity of manganese sulfate (MnSO4) and manganese phosphate (as hureaulite) in young adult male rats following subchronic (90-day) exposure to air, MnSO4 (0.01, 0.1, and 0.5 mg Mn/m(3)), or hureaulite (0.1 mg Mn/m(3)). Nasal pathology, brain GFAP levels, and brain manganese concentrations were assessed immediately following the end of the 90-day exposure and 45 days thereafter. Elevated end-of-exposure olfactory bulb, striatum, and cerebellum manganese concentrations were observed following MnSO4 exposure to greater than or equal to0.01, greater than or equal to0.1, and 0.5 mg Mn/m(3), respectively. Exposure to MnSO4 or hureaulite did not affect olfactory bulb, cerebellar, or striatal GFAP concentrations. Exposure to MnSO4 (0.5 mg Mn/m(3)) was also associated with reversible inflammation within the nasal respiratory epithelium, while the olfactory epithelium was unaffected by manganese inhalation. These results confirm that high-dose manganese inhalation can result in nasal toxicity (irritation) and increased delivery of manganese to the brain; however, we could not confirm that manganese inhalation would result in altered brain GFAP concentrations.

5. Dorman DC, Struve MF, Gross EA, Wong BA, Howroyd PC. (2005) Sub-chronic inhalation of high concentrations of manganese sulfate induces lower airway pathology in rhesus monkeys. Respiratory Research 6.
Background: Neurotoxicity and pulmonary dysfunction are well-recognized problems associated with prolonged human exposure to high concentrations of airborne manganese. Surprisingly, histological characterization of pulmonary responses induced by manganese remains incomplete. The primary objective of this study was to characterize histologic changes in the monkey respiratory tract following manganese inhalation. Methods: Subchronic (6 hr/day, 5 days/week) inhalation exposure of young male rhesus monkeys to manganese sulfate was performed. One cohort of monkeys (n = 4-6 animals/exposure concentration) was exposed to air or manganese sulfate at 0.06, 0.3, or 1.5 mg Mn/m(3) for 65 exposure days. Another eight monkeys were exposed to manganese sulfate at 1.5 mg Mn/m(3) for 65 exposure days and held for 45 or 90 days before evaluation. A second cohort (n = 4 monkeys per time point) was exposed to manganese sulfate at 1.5 mg Mn/m(3) and evaluated after 15 or 33 exposure days. Evaluations included measurement of lung manganese concentrations and evaluation of respiratory histologic changes. Tissue manganese concentrations were compared for the exposure and control groups by tests for homogeneity of variance, analysis of variance, followed by Dunnett's multiple comparison. Histopathological findings were evaluated using a Pearson's Chi-Square test. Results: Animals exposed to manganese sulfate at = 0.3 mg Mn/m(3) for 65 days had increased

lung manganese concentrations. Exposure to manganese sulfate at 1.5 mg Mn/m(3) for = 15 exposure days resulted in increased lung manganese concentrations, mild subacute bronchiolitis, alveolar duct inflammation, and proliferation of bronchus-associated lymphoid tissue. Bronchiolitis and alveolar duct inflammatory changes were absent 45 days post-exposure, suggesting that these lesions are reversible upon cessation of subchronic high-dose manganese exposure. Conclusion: High-dose subchronic manganese sulfate inhalation is associated with increased lung manganese concentrations and small airway inflammatory changes in the absence of observable clinical signs. Subchronic exposure to manganese sulfate at exposure concentrations (<= 0.3 mg Mn/m(3)) similar to the current 8-hr occupational threshold limit value established for inhaled manganese was not associated with pulmonary pathology.

6. Dorman DC, Struve MF, Vitarella D, Byerly FL, Goetz J, Miller R. (2000) Neurotoxicity of manganese chloride in neonatal and adult CD rats following subchronic (21-day) high-dose oral exposure. Journal of Applied Toxicology 20(3):179-187.
The purpose of this study was to evaluate the relative sensitivity of neonatal and adult CD rats to manganese-induced neurotoxicity, Identical oral manganese chloride (MnCl2) doses (0, 25, or 50 mg kg(-1) body wt. day(-1)) were given to neonatal rats throughout lactation (i.e. from postnatal day (PND) 1 through 21) and to adult male rats for 21 consecutive days. The MnCl2 doses administered to neonates were ca, 100-fold higher than those resulting from the consumption of an equivalent volume of rat's milk. Rats were assessed using similar behavioral and neurochemical evaluations. Several statistically significant changes occurred in Mn-exposed rats relative to control animals. Neonates given the high dose of MnCl2 had reduced body weight gain. An increased pulse-elicited acoustic startle response amplitude was observed in neonates from both MnCl2 treatment groups on PND 21. Increased striatal, hippocampal, hindbrain and cortical Mn concentrations were observed in all Mn-exposed neonates on PND 21. Increased hypothalamic and cerebellar Mn concentrations were also observed on PND 21 in neonates from the high-dose group only. Increased striatal, cerebellar and brain residue Mn concentrations were observed in adult rats from the high-dose group. Increased striatal dopamine and 3,4-dihydroxyphenylacetic acid levels were observed only in PND 21 neonates from the high-dose group, No treatment-related changes were observed in clinical signs, motor activity (assessed in neonates on PND 13, 17, 21 +/- 1 and in adults), passive avoidance (assessed in neonates on PND 20 +/- 1 and in adults) or neuropathology (assessed in PND 21 neonates only). The results of our experiment suggest that neonates may be at greater risk for Mn-induced neurotoxicity when compared to adults receiving similar high oral levels of Mn. Copyright (C) 2000 John Wiley & Sons, Ltd.

7. Guilarte TR, Chen MK, McGlothan JL, Verina T, Wong DF, Zhou Y, Alexander M, Rohde CA, Syversen T, Decamp E and others. (2006) Nigrostriatal dopamine system dysfunction and subtle motor deficits in manganese-exposed non-human primates. Experimental Neurology 202(2):381-390.
We tested the hypothesis that movement abnormalities induced by chronic manganese (Mn) exposure are mediated by dysfunction of the nigrostriatal dopamine system in the non-human primate striatum. Motor function and general activity of animals was monitored in parallel with chronic exposure to Mn and Positron Emission Tomography (PET) studies of in vivo dopamine release, dopamine transporters and dopamine receptors in the striaturn. Analysis of metal concentrations in whole blood and brain was obtained and post-mortem, analysis of brain tissue

was used to confirm the in vivo PET findings. Chronic Mn exposure resulted in subtle motor function deficits that were associated with a marked decrease of in vivo dopamine release in the absence of a change in markers of dopamine (DA) terminal integrity or dopamine receptors in the striaturn. These alterations in nigrostriatal DA system function were observed at blood Mn concentrations within the upper range of environmental, medical and occupational exposures in humans. These findings show that Mn-exposed non-human primates that exhibit subtle motor function deficits have an apparently intact but dysfunctional nigrostriatal DA system and provide a novel mechanism of Mn effects on the dopaminergic system.

8. Guilarte TR, McGlothan JL, Degaonkar M, Chen MK, Barker PB, Syversen T, Schneider JS. (2006) Evidence for cortical dysfunction and widespread manganese accumulation in the nonhuman primate brain following chronic manganese exposure: A H-1-MRS and MRI study. Toxicological Sciences 94(2):351-358.
Exposure to high levels of manganese (Mn) is known to produce a complex neurological syndrome with psychiatric disturbances, cognitive impairment, and parkinsonian features. However, the neurobiological basis of chronic low-level Mn exposure is not well defined. We now provide evidence that exposure to levels of Mn that results in blood Mn concentrations in the upper range of environmental and occupational exposures and in certain medical conditions produces widespread Mn accumulation in the nonhuman primate brain as visualized by T-1-weighted magnetic resonance imaging. Analysis of regional brain Mn distribution using a "pallidal index equivalent" indicates that this approach is not sensitive to changing levels of brain Mn measured in postmortem tissue. Evaluation of longitudinal H-1-magnetic resonance spectroscopy data revealed a significant decrease ($p = 0.028$) in the N-acetylaspartate (NAA)/creatine (Cr) ratio in the parietal cortex and a near significant decrease ($p = 0.055$) in frontal white matter (WM) at the end of the Mn exposure period relative to baseline. Choline/Cr or myo-Inositol/Cr ratios did not change at any time during Mn exposure. This indicates that the changes in the NAA/Cr ratio in the parietal cortex are not due to changes in Cr but in NAA levels. In summary, these findings suggest that during chronic Mn exposure a significant amount of the metal accumulates not only in the basal ganglia but also in WM and in cortical structures where it is likely to produce toxic effects. This is supported by a significantly decreased, in the parietal cortex, NAA/Cr ratio suggestive of ongoing neuronal degeneration or dysfunction.

9. Gwiazda R, Kern C, Smith D. (2005) Progression Of Neurochemical Effects In Different Brain Regions As A Function Of The Magnitude And Duration Of Manganese Exposure. Toxicol Sci 84(1-S):122-123.
Manganese (Mn) is known to elicit symptoms resembling those of Parkinson’s disease (PD) at high exposure levels, but its effects at low levels of exposure are uncertain. Because of the similarity of behavioral deficits at elevated Mn exposure to PD symptoms, earlier Mn toxicity studies have proposed that striatal dopamine (DA) depletion, a hallmark of PD, is also produced by Mn, despite the observation in humans that Mn accumulates in the globus pallidus. To reconcile this, we have proposed the hypothesis that there is a progression of effects from the globus pallidus to striatum as a function of increasing magnitude of Mn dose and treatment duration (Gwiazda et al., NeuroToxicology, 95:1-8, 2002). To test this, we administered Mn ip 3 times/wk to Sprague-Dawley rats at nominal doses of 0, 1.2, 4.8 and 9.6 mg/Kg over 5 wks, and 0, 1.2, 4.8 mg/Kg over 15 wks. We conducted a battery of motor tests, spontaneous motor

activity (SMA) and rotorod measurements, evaluated brain, blood, and plasma Mn levels, and neurochemical levels in the striatum, globus pallidus, substantia nigra and motor regions of the thalamus. Mn treatment increased DA levels in the globus pallidus in animals receiving the highest Mn doses over both 5 and 15 wks, but had no effect on striatal or substantia nigra DA levels. Motor deficits measured as impairment in the balance beam and in hind limb hopping, and shorter latency to fall from the rotorod were observed at the highest dose at 5 weeks. No Mn effects were detected on SMA. Blood and brain Mn showed similar relative increases as a function of nominal dose at 5 and 15 wks, even though the cumulative Mn doses of 15 wks animals were three times higher than in animals exposed for 5 wks. These results suggest that 1) Across a wide range of Mn doses the globus pallidus is a more sensitive locus of Mn toxicity compared to the striatum, and 2) The magnitude of the Mn nominal dose is more important than exposure duration in bringing about an increase in Mn body burden and eliciting Mn toxicity.

10. Gwiazda R, Lucchini R, Smith D. (2007) Adequacy and consistency of animal studies to evaluate the neurotoxicity of chronic low-level manganese exposure in humans. Journal of Toxicology and Environmental Health-Part a-Current Issues 70(7):594-605.
The adequacy of existing animal studies to understand the effects of chronic low- level manganese exposures in humans is unclear. Here, a collection of subchronic to chronic rodent and nonhuman primate studies was evaluated to determine whether there is a consistent dose-response relationship among studies, whether there is a progression of effects with increasing dose, and whether these studies are adequate for evaluating the neurotoxicity of chronic low-level manganese exposures in humans. Neurochemical and behavioral effects were compared along the axis of estimated internal cumulative manganese dose, independent of the route of exposure. In rodents, motor effects emerged at cumulative doses below those where occupationally exposed humans start to show motor deficits. The main neurochemical effects in rodents were an increase in striatal gamma- aminobutyric acid (GABA) concentration throughout the internal cumulative dose range of 18 to 5300 mg Mn/ kg but a variable effect on striatal dopamine concentration emerging at internal cumulative doses above similar to 200 mg Mn/ kg. Monkey studies showed motor deficits and effects on the globus pallidus at relatively low doses and consistent harmful effects on both the globus pallidus and the caudate and putamen at higher doses (> 260 mg Mn/ kg). Internal cumulative manganese doses of animal studies extend more than two orders of magnitude (< 1 to 5300 mg Mn/ kg) above the doses at which occupationally exposed humans show neurological dysfunction (10 - 15 mg Mn/ kg). Since the animal data indicate that manganese neurotoxicity may be different at low compared to elevated exposures, most existing animal model studies might be of limited relevance for the risk assessment of chronic low- level manganese exposure to humans.

11. Gwiazda RH, Lee D, Sheridan J, Smith DR. (2002) Low cumulative manganese exposure affects striatal GABA but not dopamine. Neurotoxicology 23(1):69-76.
The introduction of the anti-knock methylcyclopentadienyl manganese (Mn) tricarbonyl (MMT) in gasoline has raised concerns about the potential for manganese neurotoxicity. Because subpopulations such as the elderly in the early stages of neurodegenerative disease may be at increased risk for manganese toxicity, a pre-Parkinsonism rat model was used to evaluate whether sub-chronic manganese exposure can aggravate the neurochemical and behavioral dysfunctions characteristic of Parkinsonism. Sub-threshold levels of dopamine depletion of 3.5, 53 and 68% were generated via intrastriatal unilateral 6-hydroxydopamine (6-OHDA) doses. A

sub-chronic dosing regimen of low cumulative manganese exposure (4.8 mg Mn/kg body weight, 3 i.p. injections per week x 5 weeks) was started 4 weeks after 6-OHDA treatments. Neurochemical and neuromotor (functional observational battery (FOB)) measures were evaluated. Manganese produced significant ($P < 0.05$) reductions of 30-60% in motor function. This effect was exacerbated in the presence of a pre-Parkinsonism condition [Neurotox. Teratol. 22 (2000) 851]. Manganese did not affect striatal dopamine, but resulted in significant increases in striatal γ-aminobutyric acid (GABA) of 16 and 22% ($P < 0.01$) in both striati and a borderline non-significant 4% increase in frontal cortex ($P = 0.076$). Manganese treatment produced increased aspartate ($P < 0.01$) in the manganese and 6-OHDA treated striatum. In light of previous studies predominantly showing dopamine depletion with elevated manganese exposures, the significant effects of manganese on striatal GABA but not on striatal dopamine at the low cumulative exposure administered here suggest a progression in manganese toxicity with increasing cumulative dose, whereby GABA levels are adversely affected before striatal dopamine levels. Because these neurochemical disruptions were accompanied by motor dysfunction that was exacerbated in the presence of a pre-Parkinsonism condition, an increased environmental burden of manganese may have deleterious effects on populations with sub-threshold neurodegeneration in the basal ganglia (e.g. pre-Parkinsonism).

12. Hussain S, Lipe GW, Slikker W, Ali SF. (1997) The effects of chronic exposure of manganese on antioxidant enzymes in different regions of rat brain. Neuroscience Research Communications 21(2):135-144.
The present study was designed to investigate if chronic exposure to manganese (Mn) produces an effect on antioxidant enzymes such as superoxide dismutase (SOD), glutathione peroxidase (GPx) activities and reduced glutathione (GSH) content in different regions of rat brain. Adult male Sprague-Dawley (CD) rats were dosed with 0, 2.5 or 5.0 mg MnCl2/kg, for 3 months (5 days/week). The activity of total superoxide dismutase did not vary significantly in any region of the brain with either 2.5 or 5.0 mg MnCl2/kg. A significant increase of Mn-superoxide dismutase (Mn-SOD) activity was attained in hippocampus, cerebellum and brain stem. The Cu,Zn-superoxide dismutase activity was reduced in all regions of the brain, however, reduction was not statistically significant. No significant effect of Mn on glutathione peroxidase activity was observed in any region of the brain. Glutathione content was significantly reduced in cerebellum, whereas, no change was observed in other brain regions. The results show that chronic exposure to manganese significantly increased the Mn-superoxide dismutase activity in selected brain regions. Therefore, increased Mn-SOD may enhance the antioxidant ability of the brain to reduce oxidative stress.

13. Komiskey H. (2005) Influence Of Subacute Manganese Sulfate On Dopamine And N-Methyl-D-Aspartate Receptors. Toxicol Sci 84(1-S):122.
The potential of manganese sulfate (MnSO4) to alter the dopamine (D2 + D3) and N-methyl-D-aspartate (NMDA) receptor after fourteen days of daily gavage was studied in rats. Sprague-Dawley male rats were randomly given, by gavage, one of six liquid mixtures (suspended in 40 ‰corn starch; 10 ‰sucrose, and 12 ‰dextrinized corn starch) of manganese sulfate (MnSO4), negative control (40 ‰corn starch, 10 ‰sucrose, and 12 ‰dextrinized corn starch), or the positive control (6 mg/kg midazolam). The doses of the MnSO4 were given to provide: 1.0, 10, 30, or 100 milligrams manganese/kg. Binding studies of the (D2 + D3) receptor with raclopride

were preformed in the basal ganglia. Binding studies of the NMDA receptor with CGP-39653 were preformed in the cerebellum, cerebral cortex, globus pallidus, and hippocampus. The receptor binding studies indicate that fourteen of daily gavage with 1 to 100 mg/kg MnSO4 did not alter the affinity of the NMDA receptor or the maximum number of binding sites in the three of the brain areas examined (cerebellum, cerebral cortex, and globus pallidus). Only the affinity of the NMDA receptor in the hippocampus was altered by the 14-day oral exposure to 10 mg/kg MnSO4. In contrast, the affinity of (D2 + D3) binding sites was not altered by any of the liquid mixtures containing manganese relative to the negative control given for fourteen days. The liquid mixtures containing the highest concentrations of manganese altered the maximum number of (D2 + D3) binding sites. The receptor binding studies indicate that two weeks of daily gavage with 10 mg/kg MnSO4 altered the affinity of the NMDA receptor in only one of the four brain regions examined, while higher oral concentrations of MnSO4 altered the maximum number of (D2 + D3) binding sites in the basal ganglia.

14. Lipe GW, Duhart H, Newport GD, Slikker W, Ali SF. (1999) Effect of manganese on the concentration of amino acids in different regions of the rat brain. Journal of Environmental Science and Health Part B-Pesticides Food Contaminants and Agricultural Wastes 34(1):119-132.
The present study was designed to determine if chronic exposure of weanlings and adult rats to Mn produces significant alterations in amino acid concentrations in different regions of the rat brain. Weanling (30 day old) and adult (90 day old) male rats were exposed to 10 and 20 mg Mn/kg body weight per day, by gavage, for 30 days. Forty-eight hours after the last dose, animals were sacrificed by decapitation and brains were dissected into different regions to determine the concentration of amino acids by HPLC/EC. A dose dependent decrease in body weight gain was found in the adult, but not in the weanling rats. Significant increases occurred in concentrations of aspartate, glutamate, glutamine, taurine and gamma-aminobutyric acid (GABA) in the cerebellum of the adult rats dosed with 20 mg/kg per day, Mn. A significant decrease in the concentration of glutamine was observed in caudate nucleus and hippocampus of weanling rats dosed with 10 mg/kg, Mn. These data suggest that chronic Mn exposure can produce a decrease in body weight gain in adult rats and alterations in amino acids in different regions of weanling and adult rat brains.

15. Newland MC. (1999) Animal models of manganese's neurotoxicity. Neurotoxicology 20(2-3):415-432.
Manganese's neurotoxicity continues to present a puzzling array of differences across individuals and across published reports in the profile of effects seen in humans and nonhuman species, but some of the sources of individual variability are becoming clear from studies of animals. The kinetics of manganese is a critical component of any assessment of risk associated with exposure. After inhalation, the uptake of manganese into and elimination from the central nervous system are slow and same manganese remains in the nervous system a year after inhalation. Comparison with other parenteral routes suggests that manganese depots in lung prolongs exposure even after environmental exposure has ended. Manganese's neurotoxicity is associated with its appearance in basal ganglia structures, especially the globus pallidus. Manganese a Iso appears in the pituitary gland but the functional consequences of this are not well understood. Other critical components in characterizing manganese's neurotoxicity appear to be the behavioral endpoints used, the species studied, and the exposure rate. Overt

neurological signs and excitability are associated with high exposure rates and the appearance of manganese throughout basal ganglia and basal forebrain regions. More focused behavioral endpoints are required to detect the subtle signs associated with slow exposure rates low exposure levels, but when such designs are used the effect is unequivocal. At lower exposure levels, doses of 5 mg/kg and greater, deficits in a task in which a monkey executed a rowing type motion against a spring approximating its body weight were clearly related to manganese exposure while other traditional measures of response patterns under schedules of reinforcement remained intact. Excitability and other signs of emotionality have not been reported at low exposure rates. In rodents, manganese accumulation and alterations in the function or concentration of neurotransmitters have been reported. Investigations of behavioral effects in these species, which usually involved locomotor activity, have resulted in less consistent results. Manganese produces a constellation of neurotoxic signs whose appearance and detection are influenced by dose and exposure rate. Despite investigations of manganese's neurotoxicity in animals over a wide range of exposure levels, a NOAEL has not been identified. (C) 1998 Inter Press, Inc.

16. Normandin L, Beaupre LA, Salehi F, St-Pierre A, Kennedy G, Mergler D, Butterworth RE, Philippe S, Zayed J. (2004) Manganese distribution in the brain and neurobehavioral changes following inhalation exposure of rats to three chemical forms of manganese. Neurotoxicology 25(3):433-441.
The central nervous system is an important target for manganese (Mn) intoxication in humans; it may cause neurological symptoms similar to Parkinson's disease. Manganese compounds emitted from the tailpipe of vehicles using methylcyclopentadienyl manganese tricarbonyl (MMT) are primarily Mn phosphate, Mn sulfate, and Mn phosphate/ sulfate mixture. The purpose of this study is to compare the patterns of Mn distribution in various brain regions (olfactory bulb, frontal parietal cortex, globus pallidus, striatum and cerebellum) and other tissues (lung, liver kidney, testis) and the neurobehavioral damage following inhalation exposure of rats to three Mn species. Rats (n = 15 rats per Mn species) were exposed 6 h per day, 5 days per week for 13 consecutive weeks to metallic Mn, Mn phosphate or Mn phosphate/ sulfate mixture at about 3000 mug m(-3) and compared to controls. At the end of the exposure period, spontaneous motor activity was measured for 36 h using a computerized autotrack system. Mn in tissues was determined by instrumental neutron activation analysis (INAA). The Mn concentrations in the brain were significantly higher in rats exposed to Mn phosphate and Mn phosphate/sulfate mixture than in control rats or rats exposed to metallic Mn. Exposure to Mn phosphate/sulfate mixture caused a decrease in the total ambulatory count related to locomotor activity. Our results confirm that Mn species and solubility have an influence on the brain distribution of Mn in rats. (C) 2003 Elsevier Inc. All rights reserved.

17. Normandin L, Carrier G, Gardiner PF, Kennedy G, Hazell AS, Mergler D, Butterworth RF, Philippe S, Zayed J. (2002) Assessment of bioaccumulation, neuropathology, and neurobehavior following subchronic (90 days) inhalation in Sprague-Dawley rats exposed to manganese phosphate. Toxicology and Applied Pharmacology 183(2):135-145.
Methylcyclopentadienyl manganese tricarbonyl (MMT) is an organic manganese (Mn) compound added to unleaded gasoline. It has been suggested that the combustion products of MMT containing Mn, such as manganese phosphate, could cause neurological symptoms similar to Parkinson's disease in humans. The aim of this work was to investigate the exposure-response

relationship of bioaccumulation, neuropathology, and neurobehavior following a subchronic inhalation exposure to manganese phosphate in Sprague-Dawley male rats. Rats were exposed 6 h/day, 5 days/week for 13 consecutive weeks at 30, 300, or 3000 mug/m(3) Mn phosphate and compared to controls. Some rats were implanted with chronic EMG electrodes in the gastrocnemius muscle of the hind limb to assess tremor at the end of Mn exposure. Spontaneous motor activity was measured for 36 h using a computerized auto-track system. Rats were then sacrificed by exsanguination and Mn level in different brain tissues and other organs was determined by instrumental neutron activation analysis. Neuronal cell counts were obtained by assessing the sum of five grid areas for the caudate/putamen and the sum of two adjacent areas for the globus pallidus. Increased manganese concentrations were observed in all tissues of the brain and was dose-dependent in olfactory bulb and caudate/putamen. In fact, beginning with the highest level of exposure (3000 mug/m) and ending with the control group, Mn concentrations in the olfactory bulb were 2.47 vs 1.28 vs 0.77 vs 0.64 ppm ($P < 0.05$) while for the caudate/putamen, Mn concentrations were 1.06 vs 0.73 vs 0.62 vs 0.47 ppm ($P < 0.05$). The Mn concentrations in lung were also dose-dependent (10.30 vs 1.40 vs 0.42 vs 0.17 ppm; $P < 0.05$). No statistical difference was observed for loss of neurons in caudate/putamen and globus pallidus. Locomotor activity assessment and tremor assessment did not reveal in neurobehavioral changes between the groups. Our results reinforce the hypothesis that the olfactory bulb and caudate/putamen are the main brain tissues for Mn accumulation after subchronic inhalation exposure. (C) 2002 Elsevier Science (USA).

18. Ponnapakkam T, Iszard M, Henry-Sam G. (2003) Effects of oral administration of manganese on the kidneys and urinary bladder of Sprague-Dawley rats. International Journal of Toxicology 22(3):227-232.
The purpose of this study was to investigate the effect of oral administration of manganese acetate on the kidneys and urinary bladder of Sprague-Dawley (SD) rats. Male and female SD rats (150 to 175 g), 6 weeks old, were administered varying doses of manganese acetate for 63 days by oral gavage. At the end of 63 days, 50% of the animals were sacrificed and kidney tissue was isolated and fixed for histopathological studies (study A). The remaining 50% were cross-mated and dosing ceased. Animals were sacrificed after 2 weeks (study B). Male treated animals were noted to have viscous, gritty urine in the urinary bladder, and the high-dose groups had urinary bladder stones (uroliths). Histopathologically, the most striking lesions were observed in the kidneys and prostate glands of male animals. Mild-to-moderate tubulointerstitial nephritis with tubular proteineous and glomerulosclerosis was observed in animals of all treatment groups. Urolithiasis in the urinary bladder was confirmed in 33% to 66% of treated animals. Female animals did not show a significant difference above controls in renal tissues. Results of this study suggest that male rats are more sensitive to the effects of high levels of manganese given orally than female rats and that the genitourinary structures represent target organs of toxicity.

19. Reaney SH, Bench G, Smith DR. (2006) Brain accumulation and toxicity of Mn(II) and Mn(III) exposures. Toxicological Sciences 93(1):114-124.
Concern over the neurotoxic effects of chronic moderate exposures to manganese has arisen due to increased awareness of occupational exposures and to the use of methylcyclopentadienyl manganese tricarbonyl, a manganese-containing gasoline antiknock additive. Little data exist on how the oxidation state of manganese exposure affects toxicity. The objective of this study was to better understand how the oxidation state of manganese exposure affects accumulation and

subsequent toxicity of manganese. This study utilized a rat model of manganese neurotoxicity to investigate how ip exposure to Mn(II)-chloride or Mn(III)pyrophosphate at total cumulative doses of 0, 30, or 90 mg Mn/kg body weight affected the brain region distribution and neurotoxicity of manganese. Results indicate that Mn(III) exposures produced significantly higher blood manganese levels than equimolar exposures to Mn(II). Brain manganese concentrations increased in a dose-dependent manner, with Mn(III) exposures producing significantly higher (> 25%) levels than exposures to Mn(II) but with no measurable differences in the accumulation of manganese across different brain regions. Gamma amino butyric acid concentrations were increased in the globus pallidus (GP) with manganese exposure. Dopamine (DA) levels were altered in the GP, with the highest Mn(II) and Mn(III) exposures producing significantly different DA levels. In addition, transferrin receptor and H-ferritin protein expression increased in the GP with manganese exposure. These data substantiate the heightened susceptibility of the GP to manganese, and they indicate that the oxidation state of manganese exposure may be an important determinant of tissue toxico-dynamics and subsequent neurotoxicity.

20. Salehi F, Carrier G, Normandin L, Kennedy G, Butterworth RF, Hazell A, Therrien G, Mergler D, Philippe S, Zayed J. (2001) Assessment of bioaccumulation and neurotoxicity in rats with portacaval anastomosis and exposed to manganese phosphate: A pilot study. Inhalation Toxicology 13(12):1151-1163.
The use of the additive methylcyclopentadienyl manganese tricarbonyl in unleaded gasoline has resulted in increased attention to the potential toxic effects of manganese (Mn). Hypothetically, people with chronic liver disease may be more sensitive to the adverse neurotoxic effects of Mn. In this work, bioaccumulation of Mn, as well as histopathology and neurobehavioral damage, in end-to-side portacaval anastomosis (PCA) rats exposed to Mn phosphate via inhalation was investigated. During the week before the PCA operation, 4 wk after the PCA operation, and at the end of exposure, the rats were subjected to a locomotor evaluation (day-night activities) using a computerized autotrack system. Then a group of 6 PCA rats (EXP) was exposed to 3050 mug m(-3) (Mn phosphate) for 8 h/day, 5 days/wk for 4 consecutive weeks and compared to a control group (CON), 7 PCA rats exposed to 0.03 mug m(-3). After exposure, the rats were euthanized and Mn content in tissues and organs was determined by neutron activation analysis. The manganese concentrations in blood (0.05 mug/g vs. 0.02 mug/g), lung (1.32 mug/g vs. 0.24 mug/g), cerebellum (0.85 mug/g vs. 0.64 mug/g), frontal cortex (0.87 mug/g vs. 0.61 mug/g), and globus pallidus (3.56 mug/g vs. 1.33 mug/g) were significantly higher in the exposed group compared to the control group ($p < .05$). No difference was observed in liver, kidney, testes, and caudate putamen between the two groups. Neuronal cell loss was assessed by neuronal cell counts. The loss of cells in globus pallidus and caudate putamen as well as in frontal cortex was significantly higher ($p < .05$) for the EXP group. Assessment of the locomotor activities did not reveal any significant difference. This study constitutes a first step toward our understanding of the potential adverse effects of Mn in sensitive populations.

21. Salehi F, Krewski D, Mergler D, Normandin L, Kennedy G, Philippe S, Zayed J. (2003) Bioaccumulation and locomotor effects of manganese phosphate/sulfate mixture in Sprague-Dawley rats following subchronic (90 days) inhalation exposure. Toxicology and Applied Pharmacology 191(3):264-271.

Methylcyclopentadienyl manganese tricarbonyl (NEWT) is an organic manganese (Mn) compound added to unleaded gasoline in Canada. The primary combustion products of MMT are Mn phosphate, Mn sulfate, and a Mn phosphate/Mn sulfate mixture. Concerns have been raised that the combustion products of MMT containing Mn could be neurotoxic, even at low levels of exposure. The objective of this study is to investigate exposure-response relationships for bioaccumulation and locomotor effects following subchronic inhalation exposure to a mixture of manganese phosphates/sulfate mixture. A control group and three groups of 30 male Sprague-Dawley rats were exposed in inhalation chambers for a period of 13 weeks, 5 days per week, 6 h a day. Exposure concentrations were 3000, 300, and 30 mug/m(3). At the end of the exposure period, locomotor activity and resting time tests were conducted for 36 h using a computerized autotrack system. Rats were then euthanized by exsanguination and Mn concentrations in different tissues (liver, lung, testis, and kidney) and blood and brain (caudate putamen, globus pallidus, olfactory bulb, frontal cortex, and cerebellum) were determined by neutron activation analysis. Increased manganese concentrations were observed in blood, kidney, lung, testis, and in all brain sections in the highest exposure group. Mn in the lung and in the olfactory bulb were dose dependent. Our data indicate that the olfactory bulb accumulated more Mn than other brain regions following inhalation exposure. Locomotor activity was increased at 3000 mug/m(3), but no difference was observed in resting time among the exposed groups. At the end of the experiment, rats exposed to 300 and 3000 mug/m(3) exhibited significantly decreased body weight in comparison with the control group. Biochemical profiles also revealed some significant differences in certain parameters, specifically alkaline phospatase, urea, and chlorate.

22. Salehi F, Normandin L, Krewski D, Kennedy G, Philippe S, Zayed J. (2006) Neuropathology, tremor and electromyogram in rats exposed to manganese phosphate/sulfate mixture. Journal of Applied Toxicology 26(5):419-426.
In Canada, Methylcyclopentadienyl manganese tricarbonyl (MMT) replaced tetraethyl lead in gasoline as an antiknock agent from 1976 until 2003. The combustion of MMT leads to increased manganese (Mn) concentrations in the atmosphere, and represents one of the main sources of human exposure to Mn. The nervous system is the major target of the toxicity of Mn and Mn compounds. The purpose of this study was to investigate exposure-response relationships for neuropathology and tremor, and the associated electromyogram (EMG), following subchronic inhalation exposure of rats to a mixture of Mn phosphate/sulfate particles. Rats were exposed 6 h per day, 5 days per week for 13 consecutive weeks at 30, 300 or 3000 mu g m(-3) Mn phosphate/sulfate mixture and compared with controls. Half of the rats had EMG electrodes implanted in the gastrocnemius muscle of the hind limb to assess tremor at the end of Mn exposure. Two days after the end of Mn exposure, rats were killed by exsanguination and Mn concentrations in the brain (caudate putamen, globus pallidus and frontal cortex) were determined by neutron activation analysis while neuropathology was assessed by counting neuronal cells in 2.5 mm X 2.5 nun grid areas. Increased Mn concentrations were observed in all brain sections at the highest level of exposure. The neuronal cell loss was significantly different in the globus pallidus and the caudate putamen at the highest level of exposure (3000 mu g m(-3)). No sign of tremor was observed among the rats. In conclusion, exposure to a high level of Mn phosphate/sulfate mixture brought on neuropathological changes in a specific area of the brain; however, no sign of tremor was observed.

23. Schneider JS, Decamp E, Koser AJ, Fritz S, Gonczi H, Syversen T, Guilarte TR. (2006) Effects of chronic manganese exposure on cognitive and motor functioning in non-human primates. Brain Research 1118:222-231.
Acute exposure to manganese is associated with complex behavioral/psychiatric signs that may include Parkinsonian motor features. However, little is known about the behavioral consequences of chronic manganese exposures. In this study, cynomolgus macaque monkeys were exposed to manganese sulfate (10-15 mg/kg/week) over an exposure period lasting 272 +/- 17 days. Prior to manganese exposure, animals were trained to perform tests of cognitive and motor functioning and overall behavior was assessed by ratings and by videotaped analyses. By the end of the manganese exposure period, animals developed subtle deficits in spatial working memory and had modest decreases in spontaneous activity and manual dexterity. In addition, stereotypic or compulsive-like behaviors such as compulsive grooming increased in frequency by the end of the manganese exposure period. Blood manganese levels measured at the end of the manganese exposure period ranged from 29.4 to 73.7 mu g/l (mean = 55.7 +/- 10.8 (compared to levels of 5.1-14.2 mu g/l at baseline (mean = 9.2 +/- 2.7)), placing them within the upper range of levels reported for human environmental, medical or occupational exposures. These results suggest that chronic exposure to levels of manganese achieved in this study may have detrimental effects on behavior, cognition and motor functioning. (c) 2006 Elsevier B.V. All rights reserved.

24. Shinotoh H, Snow BJ, Hewitt KA, Pate BD, Doudet D, Nugent R, Perl DP, Olanow W, Calne DB. (1995) MRI and PET studies of manganese-intoxicated monkeys. Neurology 45(6):1199-1204.
BIOSIS COPYRIGHT: BIOL ABS. Using MRI and PET, we investigated the consequences of manganese intoxication in a primate model of parkinsonism and dystonia. Three rhesus monkeys were injected intravenously with doses of 10 to 14 mg/kg of MnCl2 on seven occasions, each a week apart. Two animals became hypoactive with abnormal extended posturing in the hind limbs. These motor disturbances did not improve with administration of levodopa. In all three monkeys, T1-weighted MRI demonstrated high signal intensities in the regions of the striatum, globus pallidus, and substantia nigra. No significant changes were found on (18F)6-fluoro-L-dopa, (11C)raclopride, or (18F)fluorodeoxyglucose PET. These results are consistent with the pathologic findings, which were primarily confined to the globus pallidus, and indicate that manganese intoxication is associated with preservation of the nigrostriatal dopaminergic pathway, despite clinical evidence of parkinsonian deficits. Chronic manganese intoxication may caus

25. Spadoni F, Stefani A, Morello M, Lavaroni F, Giacomini P, Sancesario G. (2000) Selective vulnerability of pallidal neurons in the early phases of manganese intoxication. Experimental Brain Research 135(4):544-551.
Prolonged exposure to manganese in mammals may cause an extrapyramidal disorder characterized by dystonia and rigidity. Gliosis in the pallidal segments underlies the well-established phase of the intoxication. The early phase of the intoxication may be characterized by psychic, nonmotor signs, and its morphological and electrophysiological correlates are less defined. In a rat model of manganese intoxication (20 mg/ml in drinking water for 3 months), neither neuronal loss nor gliosis was detected in globus pallidus (GP). However, a striking vulnerability of manganese-treated GP neurons emerged. The majority of GP neurons isolated

from manganese-treated rats died following brief incubation in standard dissociation media. In addition, patch-clamp recordings in the whole-cell configuration were not tolerated by surviving GP neurons. Neither coeval but untreated GP neurons nor striatal ones manifested analogous susceptibility. Using the perforated-patch mode of recording we attempted at identifying the functional hallmarks of GP vulnerability: in particular, voltage-gated calcium currents and glutamate-induced currents were examined. Manganese-treated GP neurons exhibited calcium currents similar to control cells aside from a slight reduction in the dihydropyridine-sensitive current facilitation. Strikingly, manganese-treated GP cells - but not striatal ones - manifested peculiar responses to glutamate, since repeated applications of the excitatory amino acid, at concentrations which commonly promote desensitizing responses, produced instead an irreversible cell damage. Possible mechanisms are discussed.

26. St-Pierre A, Normandin L, Carrier G, Kennedy G, Butterworth R, Zayed J. (2001) Bioaccumulation and locomotor effect of manganese dust in rats. Inhalation Toxicology 13(7):623-632.
The primary goal of this study is to determine the effects of Mn exposure via inhalation. The bioaccumulation of Mn in different organs and tissues, the alteration of biochemical parameters, and the locomotor activity were assessed. A group of 26 male Sprague-Dawley rats (E) were exposed to 3750 mug/m(3) of Mn dust for 6 h/day, 5 days/wk for 13 consecutive weeks and compared to a control group of 12 rats (C) exposed to 4 mug/m(3). After exposure, neurological evaluation was carried out for 36 h (a night-day-night cycle) using a computerized autotrack system. Rats were then sacrificed by exsanguination, and Mn content in organs and tissues was determined by neutron activation analysis. Mn concentrations in lung, putamen, and cerebellum were significantly higher in E than in C (0.30 vs. 0.17, 0.89 vs. 0.44, 0.63 vs. 0.48 ppm; $p < .01$), as well as in the kidney, frontal cortex, and globus pallidus (1.15 vs. 0.96, 0.84 vs. 0.47, 1.28 vs. 0.55 ppm; $p < .05$). Potassium concentration was significantly lower in E than in C (5.11 vs. 5.79 mmol/L; $p < .05$), as was alkaline phosphatase (106.9 vs. 129.6 U/L; $p < .01$). Locomotor activity indicated higher distance covered in the first 12-h period for E (45 383 vs. 36 098 cm; $p < .05$) and lower resting time in the last 12-h period for E (36 326 vs. 37 393 s; $p < .05$). This study is the first of several ongoing studies in our laboratory that address health concerns associated with inhalation exposure to different Mn species and to different levels of exposure.

27. Tapin D, Kennedy G, Lambert J, Zayed J. (2006) Bioaccumulation and locomotor effects of manganese sulfate in Sprague-Dawley rats following subchronic (90 days) inhalation exposure. Toxicology and Applied Pharmacology 211(2):166-174.
Methylcyclopentadienyl manganese tricarbonyl (MMT) is an organic compound that was introduced as an antiknock additive to replace lead in unleaded fuel. The combustion of MMT results in the emission of fine Mn particulates mainly in the form of manganese sulfate and manganese phosphate. The objective of this study is to determine the effects of subchronic exposure to Mn sulfate in different tissues, on locomotor activity, on neuropathology, and on blood serum biochemical parameters. A control group and three groups of 30 male SpragueDawley rats were exposed 6-h/day, 5 days/week for 13 consecutive weeks at 30, 300. or 3000 mu g/m(3) Mn Sulfate. Locomotor activity was measured during 36 h using an Auto-Track System. Blood and the following tissues were collected and analyzed for manganese content by neutron activation analysis: olfactory bulb, globus pallidus, caudate/putamen, cerebellum, frontal cortex, liver, lung, testis, and kidney. Neuronal cell counts were obtained for the

caudate/putamen and the globus pallidus and clinical biochemistry was assessed. Manganese concentrations were increased in blood, kidney, lung, and testis and in all brain regions in the 3000 mu g/m(3) exposure group. Significant differences were also noted in the 300 mu g/m(3) exposure group, Neuronal cell counts for the globus pallidus were significantly different between the two highest exposed groups and the controls. Locomotor activity for all exposure concentrations and resting time for the middle and highest concentrations for the two night resting periods were significantly increased. Total ambulatory count was decreased significantly for all exposure concentrations. Biochemical profiles also presented significant differences. No body weight loss was observed between all groups. These results suggest that neurotoxicity could occur at low exposure levels of Mn sulfate, one of the main combustion products of MMT.

28. Taylor MD, Erikson KM, Dobson AW, Fitsanakis VA, Dorman DC, Aschner M. (2006) Effects of inhaled manganese on biomarkers of oxidative stress in the rat brain. Neurotoxicology 27(5):788-797.
Manganese (Mn) is a ubiquitous and essential element that can be toxic at high doses. In individuals exposed to high levels of this metal, Mn can accumulate in various brain regions, leading to neurotoxicity. In particular, Mn accumulation in the mid-brain structures, such as the globus pallidus and striatum, can lead to a Parkinson's-like movement disorder known as manganism. While the mechanism of this toxicity is currently unknown, it has been postulated that Mn may be involved in the generation of reactive oxygen species (ROS) through interaction with intracellular molecules, such as superoxide and hydrogen peroxide, produced within mitochondria. Conversely, Mn is a required component of an important antioxidant enzyme, Mn superoxide dismutase (MnSOD), while glutamine synthetase (GS), a Mn-containing astrocyte-specific enzyme, is exquisitely sensitive to oxidative stress. To investigate the possible role of oxidative stress in Mn-induced neurotoxicity, a series of inhalation studies was performed in neonatal and adult male and female rats as well as senescent male rats exposed to various levels of airborne-Mn for periods of time ranging from 14 to 90 days. Oxidative stress was then indirectly assessed by measuring glutathione (GSH), metallothionein (MT), and GS levels in several brain regions. MT and GS mRNA levels and regional brain Mn concentrations were also determined. The collective results of these studies argue against extensive involvement of ROS in Mn neurotoxicity in rats of differing genders and ages. There are, however, instances of changes in individual endpoints consistent with oxidative stress in certain brain tissues.

29. Torrente M, Colomina MT, Domingo JL. (2005) Behavioral effects of adult rats concurrently exposed to high doses of oral manganese and restraint stress. Toxicology 211(1-2):59-69.
The behavioral effects Of concurrent exposure of high doses of manganese (Mn) and restraint stress were assessed in adult rats. Male Sprague-Dawley rats (250-300 g) received 0, 275 and 550 mg/kg/day of Mn in the drinking water for 19 weeks. Each group was divided into two subgroups. Animals in one subgroup were restrained for 2 h/day. During the treatment period, food and water intake, and body weight were weekly recorded. At the end of the treatment period, activity levels were monitored in an open-field. Learning was evaluated by a water-maze task during five consecutive days. A trial probe was also conducted to assess the time spent in the platform quadrant. Body weight and food consumption were significantly reduced in the

group receiving 550 mg/kg/day of Mn. A two-way analysis of variance (ANOVA) revealed an overall effect of Mn on the total distance traveled. Differences on spatial learning were observed in the acquisition period, in which rats given 550 mg/kg/day of Mn (alone or restrained) were impaired in comparison with the control and the restrained only groups. In the probe trial, there was an impaired retention in the group treated with Mn at 550 mg/kg/day. The results of this investigation in the open-field and water maze suggest that it would be plausible that restraint stress and a high exposure to Mn interact at common neurotransmitter levels but inducing opposite effects. (c) 2005 Elsevier Ireland Ltd. All rights reserved.

30. Vezer T, Papp A, Hoyk Z, Varga C, Naray M, Nagymajtenyi L. (2005) Behavioral and neurotoxicological effects of subchronic manganese exposure in rats. Environmental Toxicology and Pharmacology 19(3):797-810.
In male Wistar rats, behavioral and electrophysiological investigations, and blood and brain manganese level determinations, were performed; during 10 weeks treatment with low-dose manganese chloride and a 12 weeks post-treatment period. Three groups of 16 animals each received daily doses of 14.84 and 59.36 mg/kg b.w. MnCl2 (control: distilled water) via gavage. During treatment period, Mn accumulation was seen first in the blood, then in the brain samples of the high-dose animals. Short- and long-term spatial memory performance of the treated animals decreased, spontaneous open field activity (OF) was reduced. The number of acoustic startle responses (ASR), and the pre-pulse inhibition (PPI) of these, diminished. In the cortical and hippocampal spontaneous activity, power spectrum was shifted to higher frequencies. The latency of the sensory evoked potentials increased, and their duration, decreased. By the end of the post-treatment period, Mn levels returned to the control in all samples. The impairment of long-term spatial memory remained, as did the number of acoustic startle responses. Pre-pulse inhibition, however, returned to the pre-treatment levels. The changes of the open field activity disappeared but a residual effect could be revealed by administration Of D-amphetamine. The electrophysiological effects were partially reversed. By applying a complex set of methods, it was possible to obtain new data for a better-based relationship between the known effects of Mn at neuronal level and the behavioral and electrophysiological outcomes of Mn exposure. © 2005 Elsevier B.V. All rights reserved.

31. Witholt R, Gwiazda RH, Smith DR. (2000) The neurobehavioral effects of subchronic manganese exposure in the presence and absence of pre-parkinsonism. Neurotoxicology and Teratology 22(6):851-861.
Recent studies have implicated chronic elevated exposures to environmental agents, such as metals (e.g., manganese, Mn) and pesticides, as contributors to neurological disease. In particular, there is a concern that sensitive subpopulations such as the aged may be at increased risk for the onset of neurologic disorders because elevated exposures to Mn is associated with increased incidence of parkinsonism. Here, we utilized a rat model of pre-parkinsonism to investigate the effects of Mn exposure on neurotoxicity and the exacerbation of parkinsonism. A pre-parkinsonism state was induced using a unilateral intrastriatal injection of 6-hydroxydopamine (6-OHDA), followed 4 weeks later by Mn exposure (4.8 mg Mn/kg x 3 intraperitoneal injections/week) for 5 weeks. Female Sprague-Dawley rats (n = 44) were divided among the following treatments: (A) control, saline/vehicle; (B) Mn only; (C) 6-OHDA only; and (D) 6-OHDA + Mn. Brain Mn levels were measured by ICP MS. Neurobehavioral function was assessed following Mn exposure using a functional observational battery (FOB) consisting

of 10 neurobehavioral tests. Unilateral O-OHDA lesions produced significant ipsilateral vs, contralateral striatal dopamine depletions (60-70%), but no measurable impairment of neurobehavioral function, thereby substantiating this pre-parkinsonism (i.e., subthreshold) model. In contrast, Mn exposure resulted in significant impairment of neurobehavioral function for eight of the 10 FOE tests. No effects of Mn exposure on striatal dopamine depletion were detected, despite the 3.4-fold increase in brain Mn levels over controls. Notably, Mn exposure in the presence of a pre-parkinsonism state significantly exacerbated the neurobehavioral impairment in the reactivity to handling ($P < .049$) and hopping contralateral rear limb ($P < .033$) FOE tests. While the persistence and Mn dose - response relationship of these neurobehavioral effects were not evaluated here, these results nonetheless suggest that chronic Mn exposure may increase the risk of neurobehavioral impairment in subpopulations that are in a pre-parkinsonism state.

32. Yang PY, Klimis-Tavantzis DJ. (1998) Manganese deficiency alters arterial glycosaminoglycan structure in the Sprague-Dawley rat. Journal of Nutritional Biochemistry 9(6):324-331.
This study was designed to investigate the effect of dietary manganese on rat arterial glycosaminoglycan structure. Weanling male Sprague-Dawley rats were randomly assigned to two groups and were fed either a manganese-deficient or a manganese-sufficient diet. After 15 weeks, proteoglycans and glycosaminoglycans were extracted from the aorta and isolated by DEAE-Sephacel chromatography. The disaccharide composition of glycosaminoglycans was determined by high performance liquid chromatography following chondroitinase ABC digestion. Manganese deficiency significantly (P less than or equal to 0.01) reduced the total amount of arterial proteoglycans. The molecular size of chrondroitin sulfate in both the manganese-deficient and the manganese-sufficient group ranged between 3 X 10⁴ and 6 X 10⁴. The size of chondroitin sulfate of the manganese-deficient groups was slightly small than that of the manganese-sufficient group as analyzed for Sepharose CL-6B column chromatography. Results on the disaccharide composition of glycosaminoglycans showed that Delta Di-OS, Delta Di-4S, and Delta Di-6S accounted for 90% of the disaccharides. There was a significant increase in the ratio of Delta Di-6S to Delta Di-4S disaccharides in chondroitin sulfate in the manganese-deficient group (Delta Di-6S:Delta Di-4S, 2.0) compared with the manganese-sufficient group (1.2). Our results demonstrate for the first time that dietary manganese deficiency not only reduced the total proteoglycan content of the aorta, but also alters the molecular weight and sulfation pattern of chrondroitin sulfate in that tissue. This alteration may change the composition of the extracellular matrix and consequently affect the structural properties of the vascular wall. (J. Nutr. Biochem. 9:324-331, 1998)

Supporting References (3)

1. Chen MT, Sheu JY, Lin TH. (2000) Protective effects of manganese against lipid peroxidation. Journal of Toxicology and Environmental Health-Part A 61(7):569-577.
The aim of this study was to investigate the effects of chronic, daily, 30-d administration of manganese chloride (MnCl2) to male Sprague-Dawley rats on lipid peroxidation in various tissues. Rats were intraperitoneally injected with MnCl2 (20 mg/kg) once daily for 30 consecutive days. The Mn accumulated in liver, spleen, adrenal glands, heart, kidneys, lung, and

testes. This was associated with decreased lipid peroxidation in liver, spleen, and adrenal glands and a decrease in the levels of Fe in these tissues. In a second group of animals, Mn (20 mg/kg/d) and glutathione (GSH, 15 mg/kg/d) were administered ip for 30 d. GSH counteracted the Mn-induced protective fall in lipid peroxidation, but Fe levels remained lower in liver and spleen. Mn decreases lipid peroxidation in certain tissues, which may involve lowering Fe content, but interaction with Fe is not the sole mechanism.

2. Desole MS, Serra PA, Esposito G, Delogu MR, Migheli R, Fresu L, Rocchitta G, Miele M. (2000) Glutathione deficiency potentiates manganese-induced increases in compounds associated with high-energy phosphate degradation in discrete brain areas of young and aged rats. Aging Clinical and Experimental Research 12(6):470-477.
Aging is a factor known to increase neuronal vulnerability to oxidative stress, which is widely accepted as a mechanism of manganese-induced neuronal damage. We previously showed that subchronic exposure to manganese induced greater energy impairment (as revealed by increases in hypoxanthine, xanthine and uric acid levels) in the striatum and brainstem of aged rats vs young rats. This study shows that inhibition of glutathione (GSH) synthesis, by means of buthionine (SR) sulfoximine, decreased GSH levels and increased the ascorbic acid oxidation status in the striatum and limbic forebrain of both young and aged rats. In addition, inhibition of GSH synthesis greatly potentiated the manganese-induced increase in inosine, hypoxanthine, xanthine and uric acid levels in both regions of aged rats; moreover, inhibition of GSH synthesis significantly increased inosine, hypoxanthine, xanthine and uric acid levels in both regions of young rats, compared with the manganese-treated group. These results suggest that an impairment in the neuronal antioxidant system renders young rats susceptible to manganese-induced energetic impairment, and further support the hypothesis that an impairment in this system plays a permissive role in the increase of neuronal vulnerability that occurs with aging.

3. Husain M, Khanna VK, Roy A, Tandon R, Pradeep S, Seth PK. (2001) Platelet dopamine receptors and oxidative stress parameters as markers of manganese toxicity. Human & Experimental Toxicology 20(12):631-636.
The present study has been undertaken to investigate whether neurotoxic effects of manganese (Mn) are reflected in platelets in rats to monitor the usefulness of platelet as peripheral model. Exposure of rats to Mn (10 or 15 mg/kg bw, i.p.) for 45 days caused a significant increase in membrane fluidity as evidenced by decrease in fluorescence polarisation in platelets (11% and 14%) and striatum (9% and 13%). These rats exhibited a significant increase in superoxide dismutase activity both in platelets (24% and 37%) and striatum (31% and 42%), respectively, in comparison to controls. Exposure of rats to Mn for 45 days (15 mg/kg bw, i.p.) caused a significant decrease in reduced glutathione content (platelets 20%, striatum 24%) and catalase activity (platelets 35%, striatum 44%) compared to control rats. Rats exposed to Mn (10 or 15 mg/kg bw, i.p.) for 15 days exhibited a significant increase in dopamine receptors both in platelets (55% and 40%) and striatum (38% and 31%). The results suggest that exposure to Mn may alter the membrane functions and impair the anti-oxidant defense mechanism both in platelets and brain. The study also suggests that dopaminergic mechanisms are impaired following Mn exposure and such changes are reflected in platelets. Interestingly, parallel changes both in striatum and platelets, as observed in the present study, strengthen the usefulness of platelets as a peripheral neuronal model.

4.2.2 Cancer bioassays

Key References (0)

There were no key references identified for this section.

Supporting References (0)

There were no supporting references identified for this section.

4.3 REPRODUCTIVE AND DEVELOPMENTAL STUDIES—ORAL AND INHALATION

Key References (12)

1. Colomina MT, Domingo JL, Llobet JM, Corbella J. (1996) Effect of day of exposure on the developmental toxicity of manganese in mice. Veterinary and Human Toxicology 38(1):7-9.
Manganese is embryotoxic and fetotoxic in mammals. The aim of this study was to determine whether the day of exposure would modify the developmental toxicity of manganese (II). Pregnant Swiss mice were given single sc doses of 50 mg manganese chloride tetrahydrate/kg on day 9, 10, ii or 12 of gestation. No maternal deaths, abortions or early deliveries were observed. Dams were killed on gestational day 18 and the uterine contents examined. Embryotoxicity, evidenced by significant increases in number of late resorptions and in percentage of postimplantation loss, was especially relevant in groups dosed on gestational days 9 or 10. Fetotoxicity (reduced fetal body weight and increased incidence of skeletal defects) was also especially remarkable from doses on days 9 or 10 of gestation. However, no teratogenic effects were noted in any group. Although mouse conceptus are adversely affected by sc exposure to manganese on any of the gestational days 9-12, days 9 and 10 of gestation are the most sensitive for manganese-induced embryo/fetal toxicity in mice.

2. Eder K, Kralik A, Kirchgessner M. (1996) The effect of manganese supply on thyroid hormone metabolism in the offspring of manganese-depleted dams. Biological Trace Element Research 55(1-2):137-145.
The present study was performed to investigate the effect of manganese (Mn) supply on metabolism of thyroid hormones in the rat. A study with rats was carried out over two generations. Female rats were raised with a Mn-deficient diet (0.1 mg Mn/kg), and mated to produce a second generation. The male rats of the second generation were used as subjects for the investigation They were divided into five groups and fed diets with Mn concentrations of 0.1, 0.5, 2.2, 10, and 46 mg/kg for 40 d. For assessment of thyroid hormone metabolism, concentrations of thyroid hormones in serum and activity of hepatic type I 5'deiodinase (5'D-I) were measured. Feeding diets with 0.1 mg Mn/kg impaired growth and food conversion, influenced parameters of thyroid hormone metabolism, and changed some clinical-chemical parameters, such as concentrations of total protein, albumin, calcium (Ca) and magnesium (Mg) as well as activity of alkaline phosphatase in serum. Regarding the thyroid hormone metabolism,

rats fed the diet with a Mn level of 0.1 mg/kg had a higher 5'D-I activity in liver, and consequently a higher concentration of triiodothyronine in serum than the rats fed the other diets. Ln contrast, the concentrations of total and free thyroxine were not influenced by the Mn intake. Growth, clinical-chemical parameters, concentrations of thyroid hormones in serum, and activity of hepatic 5'D-I were similar in the rats fed diets with Mn concentrations between 0.5 and 46 mg/kg. The present study shows that feeding a diet with a very low Mn concentration affects growth and thyroid hormone metabolism and that a dietary level of 0.5 mg Mn/kg is adequate for growth and thyroid hormone metabolism in the offspring of Mn-depleted dams.

3. Garcia SJ, Syversen T, Gellein K, Aschner M. (2005) Iron Deficient And Manganese Enhanced Diets Alter Metals And Transporters In The Developing Rat Brain. Toxicol Sci 84(1-S):122.
Fe-deficiency is a prevalent nutritional disorder, affecting ~2 billion people, mostly pregnant and lactating women and children. Fe and Mn share similar transport mechanisms, competing for transport. In adults Mn toxicity leads to neurological disturbances, but little is known about developmental Mn toxicity. To study the interactions of Fe and Mn during brain development, pregnant Sprague-Dawley rats were fed one of four semi-purified diets from gestational day 7 until postnatal day (PN)21: control (35 Fe:10 Mn mg/kg diet), low Fe (ID; 3 Fe:10 Mn), high Mn (Mn; 35 Fe:100 Mn), or low Fe with high Mn (IDMn; 3 Fe:100 Mn). Control neonates were cross-fostered to experimental or control dams on PN4 and exposed to the diets via lactation until PN21. Hematological measurements confirmed Fedeficiency (decreased Fe, hemoglobin; increased transferrin (Tf), total Fe binding capacity) in dams and pups fed “ID” or “IDMn” diets, while those fed “Mn” had some trends toward similar hematological changes. Western blot analysis revealed that both “ID” and “IDMn” increased expression of the metal transporters, Tf receptor and divalent metal transporter 1 (DMT1). Inductively coupled plasma mass spectrometry (ICP-MS) showed that all three experimental diets decreased brain Fe levels, while both Mn enhanced diets increased brain Mn levels. In addition, “ID” increased copper (Cu); “Mn” increased chromium (Cr); and “IDMn” increased Cr, Cu, cobalt (Co), zinc (Zn), and vanadium (V). Upregulated DMT1, a non-specific transporter, may be a route for increased metals in the brain following dietary manipulations. Because each of the metals affected by low Fe and/or high Mn are esessential metals for normal development and function, homeostatic disturbances may contribute to later consequences.

4. Pappas BA, Zhang D, Davidson CM, Crowder T, Park GA, Fortin T. (1997) Perinatal manganese exposure: Behavioral, neurochemical, and histopathological effects in the rat. Neurotoxicology and Teratology 19(1):17-25.
BIOSIS COPYRIGHT: BIOL ABS. Manganese chloride (Mn) was dissolved in the drinking water (0, 2, or 10 mg/ml) of dams and their litters from conception until postnatal day (PND) 30. Parturition was uneventful in the Mn-exposed rats and no physical abnormalities were observed. The rats exposed to 10 mg/ml Mn showed a 2.5-fold increase in cortical Mn levels. Their weight gain was attenuated from PND 9-24 and they were hyperactive at PND 17. Neither the 2 nor the 10 mg/ml Mn-exposed groups differed from the controls on the elevated plus apparatus or on the Morris water maze and the radial arm maze. Brain monoamine levels and choline acetyltransferase activity were unaffected. Tyrosine hydroxylase immunohistochemistry showed that dopamine cells of the substantia nigra were intact. Glial fibrillary acidic protein immunoreactivity was not increased in cortex, caudate, and hippocampus. However, both the

low- and high-dose Mn-exposed groups showing thinning of the cerebral cortex. This could have resulted f

5. Ponnapakkam TP, Bailey KS, Graves KA, Iszard MB. (2003) Assessment of male reproductive system in the CD-1 mice following oral manganese exposure. Reproductive Toxicology 17(5):547-551.
Manganese has wide industrial applications and exposure to manganese can result in serious health conditions. The purpose of this study was to determine the reproductive effect of oral manganese exposure in male mice. Manganese acetate was tested at three dose levels (7.5, 15.0, and 30.0 mg/kg/day) for 43 days. The control group (0 mg/kg/day) received distilled water. Control negative group did not receive anything. Reproductive organ weights were recorded. Histopathology was performed on right testis, epididymis, seminal vesicle, and the accessory glands. Cauda epididymal, testicular sperm counts, and sperm motility was evaluated on the organ from the left side. The results of this study suggest that exposure to manganese caused a statistically significant ($P < 0.001$) decrease in sperm motility and sperm counts at 15.0 and 30.0 mg/kg/day. There were no alterations in the fertility or pathology of the testicular tissue in the manganese-treated mice when compared with the controls.

6. Ponnapakkam TP, Henry-Sam GA, Iszard MB. (2001) A comparative study of the reproductive toxicity of manganese in rats and mice. Faseb Journal 15(4):A585-A585.

7. Torrente M, Albina ML, Colomina MT, Corbella J, Domingo JL. (2000) Interactions in developmental toxicology: effects of combined administration of manganese and hydrocortisone. Trace Elements and Electrolytes 17(4):173-179.
Objective: The maternal and embryo/fetal toxicity of concurrent administration of hydrocortisone (HC), as a substitute of a potential "stressor", and manganese (Mn) were assessed in pregnant mice. Methods: Animals were divided into four groups and received subcutaneous injections of MnCl(2)x4H(2)O at 0, 1, 2 and 4 mg/kg/day on gestation days 6 - 18. Each group was subdivided into two subgroups. Mice in each subgroup received 0 or 5 mg/kg/day of HC (s.c.) from days 6 to 18 of gestation. Cesarean sections were performed on day 18 of gestation and all live fetuses were examined for malformations and variations. Results: In the groups treated with MnCl2 at 4 mg/kg/day, either alone or combined with HC, maternal toxicity was evidenced by significant decreases in body weight gain during treatment, body weight at termination, and gravid uterine weight. In turn, the most notable reproductive finding was the dramatic number of resorptions found in the group concurrently exposed to 4 mg/kg/day of MnCl2 and 5 mg/kg/day of HC. No live fetuses were found in this group. A delayed ossification in a number of bones was also observed at 4 mg/kg/day of MnCl2 only. Conclusion: The enhancement of Mn-induced maternal and embryo/fetal adverse effects by concurrent administration of HC was only evident at the doses of Mn which are also toxic by themselves.

8. Torrente M, Colomina MT, Domingo JL. (2002) Effects of prenatal exposure to manganese on postnatal development and behavior in mice: Influence of maternal restraint. Neurotoxicology and Teratology 24(2):219-225.
Manganese (Mn) is an essential trace element whose deficiency and excess have been reported to cause central nervous system (CNS) disturbances, On the other hand, during pregnancy,

maternal stress has been shown to enhance the developmental toxicity of a number of metals. In this study, the maternal toxicity and developmental effects of a concurrent exposure to Mn and restraint stress were evaluated in mice. Pregnant animals were divided into three groups and received subcutaneous injections of manganese chloride tetrahydrate (MnCl2.4H(2)O) at 0.1 and 2 mg/kg/day on Gestation Days 6-18. Each group was divided into two subgroups. Mice in one subgroup were subjected to restraint for 2 h/day on Days 6-18 of gestation. Pregnant mice were allowed to deliver, and pups were evaluated for physical and neuromotor maturation. Subsequently, adult mice were also evaluated for activity and learning. A significant increase in perinatal mortality was observed at 2 mg/kg/day Mn. A delay in some developmental landmarks (eye opening, testes descent) due to Mn exposure (2 mg/kg/day) was also seen in both restrained and unrestrained animals. No differences in motor resistance and coordination, or in learning at the passive avoidance test, were noted in adult mice. At the current Mn doses, combined exposure to Mn and stress during the prenatal period did not produce long-lasting effects on adult mice.

9. Tran TT, Chowanadisai W, Crinella FM, Chicz-DeMet A, Lonnerdal B. (2002) Effect of high dietary manganese intake of neonatal rats on tissue mineral accumulation, striatal dopamine levels, and neurodevelopmental status. Neurotoxicology 23(4-5):635-643.
Mn is an essential element, but may become neurotoxic at high levels. Recent reports of high Mn levels in hair of children with neurodevelopmental deficits suggest that these deficits could be due to Mn-induced neurotoxic effects on brain dopamine (DA) systems, although the mechanism is not well understood. Infant formulas contain considerably higher concentrations of Mn than human milk. Thus, formula-fed infants are exposed to high levels of Mn at a time when Mn homeostasis is incompletely developed. We studied the effects of dietary Mn supplementation of rat pups on tissue Mn accumulation, brain dopamine levels, infant neurodevelopmental status, and behavior at maturity. Newborn rats were supplemented daily with 0, 50, 250, or 500 mug Mn given orally from day I to day 20. Mineral analysis of small intestine and brain at day 14 showed a significant increase of tissue Mn in supplemented rats. Neurodevelopmental tests conducted at various ages showed significant delays as a function of Mn supplementation. At day 32, there was a significant positive relationship between passive avoidance errors and Mn supplementation levels. Brains of animals killed on day 40 showed a significant inverse relationship between Mn supplementation level and striatal dopamine concentration. These observations suggest that dietary exposure to high levels of Mn during infancy can be neurotoxic to rat pups and result in developmental deficits.

10. Tran TT, Kelleher SL, Lonnerdal B. (2002) Effect of high manganese intake and iron deficiency in infant rats on DMT-1 expression and tissue mineral accumulation. Faseb Journal 16(4):A617-A617.

11. Weber S, Dorman DC, Lash LH, Erikson K, Vrana KE, Aschner M. (2002) Effects of manganese (Mn) on the developing rat brain: Oxidative-stress related endpoints. Neurotoxicology 23(2):169-175.
lie evaluated biochemical endpoints related to oxidative stress in brains of neonatal rats exposed to manganese (Mn). Oral Mn chloride (MnCl2) (0, 25, or 50 mg Mn chloride kg(-1) body weight per day) was given daily to neonatal rats throughout lactation (i.e. front postnatal day (PND) 1 to

21). As previously reported by (J. Appl. Toxicol. 20 (2000) 179), this treatment paradigm results in increased cerebral cortex (CTX) Mn concentrations in PND 21 rats front both Mn treatment groups. High dose Mn exposure also results in increased cerebellar Mn concentrations. This preliminary study determined whether this exposure paradigm also affects cerebrocortical or cerebellar metallothionein (MT) mRNA levels, glutamine synthetase (GS) activity, GS protein levels, as well as total glutathione (GSH) levels. High dose Mn exposure significantly increased ($P < 0.05$) total cerebrocortical GSH without accompanying changes in any of the other measured parameters. Therefore, it is unlikely that high dose Mn exposure is associated with oxidative stress in this experimental paradigm.

12. Zhang BY, Chen S, Ye FL, Zhu CC, Zhang HX, Wang RB, Xiao CF, Wu TC, Zhang GG. (2002) Effect of manganese on heat stress protein synthesis of new-born rats. World Journal of Gastroenterology 8(1):114-118.

AIM: To study the effect of manganese (Mn) on heat stress protein 70 (HSP70) synthesis in the brain and liver of newborn rats whose mother-rats were exposed to Mn. METHODS: 32 female rats were randomly divided into four groups. One group was administrated with physiological saline only as control group, the other three groups were administrated with 7.5, 15 and 30 mg . kg(-1) manganese chloride (MnCl2.) by intraperitioneal injection every two days for two weeks. After delivery, the mother-rats received MnCl2 unceasingly for a week with the same method. Then the contents of Mn, Zn, Cu and Fe in the livers of the newborn rats were determined by atomic absorption spectroscopy; The level of HSP70 in the brains and the livers of the new-born rats as detected by Western-dot-blotting, and the SOD activities were measured simultaneously. RESULTS: The contents of Mn in the livers of new-born rats of the experimental groups (respective 1.38 +/- 0.18, 2.73 +/- 0.65, 3.44 +/- 0.89 mug . g(-1)) were significantly increased compared with the control group (0.88 +/- 0.18mug . g(-1); $P < 0.01$); The contents of Fe in the livers of new-born rats of 15 and 30 mg . kg(-1) experimental groups (426 +/- 125, 572 +/- 175μg . g(-1) respectively) were significantly increased compared with the control group (286 +/- μg . g(-1); $P < 0.05$), the levels of Zn in the livers of the new-born rats of three experimental groups(254 +/- 49, 263 +/- 47, 213 +/- 28mug . g(-1), respectively) were lower than those of the control group (335 +/- 50mug.g(-1); respective $P < 0.05$, $P < 0.01$); and the levels of Cu showed no significant difference among the four groups (three experimental groups: 75 +/- 21, 68 +/- 241 and 78 +/- 18mug . g(-1); control group: 83 +/- 9mug . g(-1); $P > 0.05$). There was a significant increase in the levels of HSP70 in the brains of new-born rats of the 30 mg . kg(-1) group (19.5 x 10(3) +/- 1.3 x 10(3) A; control group: 14.3 x 10(3) +/- 1.4 x 10(3)A; $P < 0.01$), and the levels of HSP70 in the livers of new-born rats of three experimental groups (respective 19.6 x 10(3) +/- 3.9 x 10(3)A, 18.5 x 10(3) +/- 3.8 x 10(3)A, 22.4 x 10(3) +/- 1.9 x 10(3) A) also increased than control group(13.3 x 10(3) +/- 1.0 x 10(3)A; $P < 0.01$), but the SOD activities showed no significant difference among brains of the four groups (experimental groups: 5.04 +/- 0.43, 4.83 +/- 0.48, 4.60 +/- 0.84 ku . g(-1); control group: 4.91 +/- 0.37 ku . g(-1) $P > 0.05$). The SOD activities in the livers of 15 mg . kg(-1) group(5.41 +/- 0.44 ku . g(-1)) was lower than the control group(5.95 +/- 0.36 ku . g(-1); $P < 0.05$). CONCLUSION: While mother-rats were exposed to manganese, the metabolisms of Mn,Zn and Fe of new-born rats in the livers were Influenced and were situated in a stress status, thus HSP70 syntheses Is induced in the brains and livers of new-born rats, but the mechanism of this effect in the developmental toxicity of Mn remains to be further studied.

Supporting References (93)

1. Agte V, Jahagirdar M, Chiplonkar S. (2005) Apparent absorption of eight micronutrients and phytic acid from vegetarian meals in ileostomized human volunteers. Nutrition 21(6):678-685.
Objectives: Apparent absorption of eight micronutrients and degradation of phytic acid were studied in human subjects who underwent ileostomy. The prominent factors affecting micronutrient absorption from vegetarian Indian meals (n = 11) were identified. Methods: Levels of β-carotene, ascorbic acid, riboflavin, and thiamine in food and ileostomy contents were estimated by spectrophotometry and spectrofluorometry. Contents of zinc iron, copper, and manganese were estimated by atomic absorption spectrometry and that of phytic acid by gradient elution ion exchange chromatography. Statistical analyses were done with SPSS 10.0. Results: Absorption of β-carotene,. ascorbic acid, riboflavin, and thiamine was 63% to 75.6%. There was a negative non-significant trend in values of β-carotene absorption with increased intake of 0-carotene (r = -0.51, P > 0.1) and iron (r = -0.67, P = 0.1) but a positive significant trend with riboflavin intakes (r = 0.84, P = 0.018). Percentage of absorption of ascorbic acid showed weak positive associations with intakes of riboflavin (r = 0.71) and ascorbic acid (r = 0.5). Percentage of absorption of ascorbic acid was positively correlated. with percentage of absorption of β-carotene (r = 0.80, P < 0.05), iron, and riboflavin (r = 0.64, P = 0.086), indicating some common influencing factors. Percentages of absorption for zinc (20.2), iron (9.9), and copper (17.6) was comparable with those reported for soy. protein-based, high phytate diets. Pattern of phytic acid in the meals and output indicated partial degradation and absorption (34%). Conclusions: For vegetarian Indian meals, apparent absorptions of β-carotene and ascorbic acid were 76% and 73.5% and of riboflavin and thiamine was 63%. Zinc, copper, and iron showed a lower absorption (10% to 20%). © 2005 Elsevier Inc. All rights reserved.

2. Anastassopoulou J, Theophanides T. (2002) Magnesium-DNA interactions and the possible relation of magnesium to carcinogenesis. Irradiation and free radicals. Critical Reviews in Oncology Hematology 42(1):79-91.
Magnesium deficiency causes renal complications. The appearance of several diseases is related to its depletion in the human body. In radiotherapy, as well as in chemotherapy, especially in treatment of cancers with cis-platinum, hypomagnesaemia is observed. The site effects of chemotherapy that are due to hypomagnesaemia are decreased using Mg supplements. The role of magnesium in DNA stabilization is concentration dependent. At high concentrations there is an accumulation of Mg binding, which induces conformational changes leading to Z-DNA, while at low concentration there is deficiency and destabilization of DNA. The biological and clinical consequences of abnormal concentrations are DNA cleavage leading to diseases and cancer. Carcinogenesis and cell growth are also magnesium-ion concentration dependent. Several reports point out that the interaction of magnesium in the presence of other metal ions showed that there is synergism with Li and Mn, but there is magnesium antagonism in DNA binding with the essential metal ions in the order: Zn > Mg > Ca. In the case of toxic metals such as Cd, Ga and Ni there is also antagonism for DNA binding. It was found from radiolysis of deaerated aqueous solutions of the nucleoside 5'-guanosine monophosphate (5'-GMP) in the presence as well as in the absence of magnesium ions that, although the addition of hydroxyl radicals ((OH)-O-.) has been increased by 2-fold, the opening of the imidazole ring of the

guanine base was prevented. This effect was due to the binding of Mg2+ ions to N7 site of the molecule by stabilizing the five-member ring imitating cis-platinum. It was also observed using Fourier Transform Infrared spectroscopy, Raman spectroscopy and Fast Atom Bombardment mass spectrometry that (OH)-O-. radicals subtract H atoms from the C1', C4' and C5' sites of the nucleotide. Irradiation of 5'-GMP in the presence of oxygen (2.5 x 10(-4) M) shows that magnesium is released from the complex. There is spectroscopic evidence that superoxide anions (O-2(-.)) react with magnesium ions leading to magnesium release from the complex. From radiolysis data it was suggested that magnesium ions can act as radiosensitizers in the absence of oxygen, while in the presence of oxygen they act as protectors and stabilizers of DNA. (C) 2002 Elsevier Science Ireland Ltd. All rights reserved.

3. Anderson JG, Cooney PT, Erikson KM. (2007) Brain manganese accumulation is inversely related to gamma-amino butyric acid uptake in male and female rats. Toxicological Sciences 95(1):188-195.
Iron (Fe) is an essential trace metal involved in numerous cellular processes. Iron deficiency (ID) is reported as the most prevalent nutritional problem worldwide. Increasing evidence suggests that ID is associated with altered neurotransmitter metabolism and a risk factor for manganese (Mn) neurotoxicity. Though recent studies have established differences in which the female brain responds to ID-related neurochemical alterations versus the male brain, little is known about the interactions of dietary ID, Mn exposure, and sex on gamma-amino butyric acid (GABA). Male and female Sprague-Dawley rats were randomly divided into four dietary treatment groups: control (CN), control/ Mn supplemented, ID, and ID/Mn supplemented. After 6 weeks of treatment, both ID diets caused a highly significant decrease in Fe concentrations across all brain regions compared to CN in both sexes. Both ID and Mn supplementation led to significant accumulation of Mn across all brain regions in both sexes. There was no main effect of sex on Fe or Mn accumulation. Striatal synaptosomes were utilized to examine the effect of dietary intervention on H-3-GABA uptake. At 4 weeks, there was a significant correlation between Fe concentration and H-3-GABA uptake in male rats ($p < 0.05$). At 6 weeks, there was a significant inverse correlation between Mn concentration and 3H-GABA uptake in male and female rats and a postitive correlation between Fe concentration and H-3-GABA uptake in female rats ($p < 0.05$). In conclusion, ID-associated Mn accumulation is similar in both sexes, with Mn levels affecting GABA uptake in both sexes in a comparable fashion.

4. Anderson JG, Cooney PT, Erikson KM. (2007) Inhibition of DAT function attenuates manganese accumulation in the globus pallidus. Environmental Toxicology and Pharmacology 23(2):179-184.
Manganese (Mn) is an essential nutrient, though exposure to high concentrations may result in neurotoxicity characterized by alterations in dopamine neurobiology. To date, it remains elusive how and why Mn targets dopaminergic neurons although recently the role of the dopamine transporter has been suggested. Our primary goal of this study was to examine the potential roles of the monoamine transporters, dopamine transporter (DAT), serotonin transporter (SERT), and norepinephrine transporter (NET), in neuronal Mn transport. Using striatal synaptosomes, we found that only inhibition of DAT significantly decreased Mn accumulation. Furthermore, weanling rats chronically exposed to Mn significantly accumulated Mn in several brain regions. However, rats receiving the specific DAT inhibitor GBR 12909 (1 mg/kg bw, three times/week; 4 weeks) had significantly lower Mn levels only in the globus pallidus compared to saline-

treated rats ($p < 0.05$). Our data show that inhibition of DAT exclusively inhibits Mn accumulation in the globus pallidus during chronic exposure. (c) 2006 Elsevier B.V. All rights reserved.

5. Antonini JM, Santaimaria AB, Jenkins NT, Albini E, Lucchini R. (2006) Fate of manganese associated with the inhalation of welding fumes: Potential neurological effects. Neurotoxicology 27(3):304-310.
Welding fumes are a complex mixture composed of different metals. Most welding fumes contain a small percentage of manganese. There is an emerging concern among occupational health officials about the potential neurological effects associated with the exposure to manganese in welding fumes. Little is known about the fate of manganese that is complexed with other metals in the welding particles after inhalation. Depending on the welding process and the composition of the welding electrode, manganese may be present in different oxidation states and have different solubility properties. These differences may affect the biological responses to manganese after the inhalation of welding fumes. Manganese intoxication and the associated neurological symptoms have been reported in individual cases of welders who have been exposed to high concentrations of manganese-containing welding fumes due to work in poorly ventilated areas. However, the question remains as to whether welders who are exposed to low levels of welding fumes over long periods of time are at risk for the development of neurological diseases. For the most part, questions remain unanswered. There is still paucity of adequate scientific reports on welders who suffered significant neurotoxicity, hence there is a need for well-designed epidemiology studies that combine complete information on the occupational exposure of welders with both behavioral and biochemical endpoints of neurotoxicity. Published by Elsevier Inc.

6. Aschner M. (2000) Manganese: Brain transport and emerging research needs. Environmental Health Perspectives 108:429-432.
Idiopathic Parkinson's disease (IPD) represents a common neurodegenerative disorder. An estimated 2% of the U.S. population, age 65 and older, develops IPD. The number of IPD patients will certainly increase over the next several decades as the baby-boomers gradually step into this high-risk age group, concomitant with the increase in the average life expectancy. While many studies have suggested that industrial chemicals and pesticides may underlie [PD, its etiology remains elusive. Among the toxic metals, the relationship between manganese intoxication and IPD has long been recognized. The neurological signs of manganism have received close attention because they resemble several clinical disorders collectively described as extrapyramidal motor system dysfunction, and in particular, IPD and dystonia. However, distinct dissimilarities between IPD and manganism are well established, and it remains to be determined whether Mn plays an etiologic role in IPD. It is particularly noteworthy that as a result of a recent court decision, methylcyclopentadienyl Mn tricarbonyl (MMT) is presently available in the United States and Canada for use in fuel, replacing lead as an antiknock additive. The impact of potential long-term exposure to low levels of MMT combustion products that may be present in emissions from automobiles has yet to be fully evaluated. Nevertheless, it should be pointed out that recent studies with Various environmental modeling approaches in the Montreal metropolitan (where MMT has been used for more than 10 years) suggest that airborne Mn revels were quite similar to those in areas where MMT was not used. These studies also show that Mn is emitted from the tail pipe of motor vehicles primarily as a mixture of manganese

phosphate and manganese sulfate. This brief review characterizes the Mn speciation in the blood and the transport kinetics of Mn into the central nervous system, a critical step in the accumulation of Mn within the brain, outlines the potential susceptibility of selected populations (e.g., iron-deficient) to Mn exposure, and addresses future research needs for Mn.

7. Aschner M, Lukey B, Tremblay A. (2006) The manganese health research program (MHRP): Status report and future research needs and directions. Neurotoxicology 27(5):733-736.
The manganese (Mn) research health program (MHRP) symposium was a full day session at the 22nd International Neurotoxicology Conference. Mn is a critical metal in many defense and defense-related private sector applications including steel making and fabrication, improved fuel efficiency, and welding, and a vital and large component in portable power sources (batteries). At the current time, there is much debate concerning the potential adverse health effects of the use of manganese in these and other applications. Due to the significant use of manganese by the Department of Defense, its contractors and its suppliers, the Manganese Health Research Program (MHRP) seeks to use the resources of the federal government, in tandem with manganese researchers, as well as those industries that are involved with manganese, to determine the exact health effects of manganese, as well as to devise proper safeguard measures for both public and private sector workers. Humans require manganese as an essential element; however, exposure to high levels of this metal is sometimes associated with adverse health effects, most notably within the central nervous system. Exposure scenarios vary extensively in relation to geographical location, urban versus rural environment, lifestyles, diet, and occupational setting. Furthermore, exposure may be brief or chronic, it may be to different types of manganese compounds (aerosols or salts of manganese with different physical and/or chemical properties), and it may occur at different life-stages (e.g., in utero, neonatal life, puberty, adult life, or senescence). These factors along with diverse genetic composition that imposes both a background and disease occurrence likely reflect on differential sensitivity of individuals to manganese exposure. Unraveling these complexities requires a multipronged research approach to address multiple questions about the role of manganese as an essential metal as well as its modulation of disease processes and dysfunction. A symposium on the Health Effects of Manganese (Mn) was held on Wednesday, September 14, 1005, to discuss advances in the understanding on role of Mn both in health and disease. The symposium was sponsored by the Manganese Health Research Program (MHRP). This summary provides background on the MHRP, identifies the speakers and topics discussed at the symposium, and identifies research needs and anticipated progress in understanding Mn health- and disease-related issues. (C)2005 Elsevier Inc. All rights reserved.

8. Aschner M, Vrana KE, Zheng W. (1999) Manganese uptake and distribution in the central nervous system (CNS). Neurotoxicology 20(2-3):173-180.
Information about the nature of manganese (Mn)-binding ligands in plasma and serum, and its transport mechanism across the blood-brain barrier (BBB) is sparse. Most studies to date have focused on distribution, excretion, and accumulation of intravenous and intraperitoneal solutions of soluble divalent salts of Mn. Mn is transported in the blood primarily in the divalent oxidation state (Mn2+) and crosses the BBB via specific carriers ata rate far slower than in other tissues. Mn transport across the BBB occurs both in the 2+ and 3+ oxidation state. Within the CNS, Mn accumulates primarily within astrocytes, presumably because the astrocyte-specific enzyme, glutamine synthetase (GS) represents an important regulatory target of Mn. Compared to Mn2+,

Mn3+ has a slower elimination rate and therefore, may have a greater tendency to accumulate in tissues. Furthermore, in view of the dependence of Mn accumulation within the CNS on iron (Fe) homeostasis, the oxidation state of Mn may represent a key determinant in the differential distribution, accumulation and secretion profiles of Mn, a fact that has received little attention in experimental biology toxicology. Accordingly, the distribution and membrane transport of Mn emphasizes the importance of: 1) the oxidation state of Mn, as it governs the affinity of Mn to endogenous ligands, and 2) the reaction of Mn3+ with transferrin, the plasma iron-carrying protein. This review will focus on transport kinetics of Mn across the BBB (both in the 2+ and 3+ oxidation state), the putative role of transferrin in the transport of Mn across the BBB, the transport of Mn by astrocytes, as well as the physiological significance of Mn to the function GS. (C) 1999 Inter Press, Inc.

9. Azin F, Raie RM, Mahmoudi MM. (1998) Correlation between the levels of certain carcinogenic and anticarcinogenic trace elements and esophageal cancer in northern Iran. Ecotoxicology and Environmental Safety 39(3):179-184.
Levels of four carcinogenic (Ni, Fe, Cu, Pb) and four anticarcinogenic (Zn, Se, Mn, Mg) trace elements were measured in hair samples from esophageal cancer patients, their unaffected family members, and members of families with no history of cancer. Measurements were also made in non-esophageal cancer patients, using atomic absorption spectroscopy, inductively coupled plasma-emission spectroscopy, and neutron activation analysis. The results showed that Ni and Cu concentrations were significantly higher and Mg and Mn concentrations were significantly lower in all cancer cases. Levels of Zn, Fe, Se, and Pb were not significantly different in the above-mentioned groups. In addition, the serum albumin fraction, which is reported to have antioxidant activity, was found to be significantly lower among esophageal cancer patients. (C) 1998 Academic Press.

10. Barrington WW, Angle CR, Willcockson NK, Padula MA, Korn T. (1998) Autonomic function in manganese alloy workers. Environmental Research 78(1):50-58.
The observation of orthostatic hypotension in an index case of manganese toxicity lead to this prospective attempt to evaluate cardiovascular autonomic function and cognitive and emotional neurotoxicity in eight manganese alloy welders and machinists. The subjects consisted of a convenience sample consisting of an index case of manganese dementia, his four co-workers in a "frog shop" for gouging, welding, and grinding repair of high manganese railway track and a convenience sample of three mild steel welders with lesser manganese exposure also referred because of cognitive or autonomic symptoms. Frog shop air manganese samples 9.6-10 years before and 1.2-3.4 years after the diagnosis of the index case exceeded 1.0 mg/m(3) in 29% and 0.2 mg/m(3) in 62%. Twenty-four-hour electrocardiographic (Holter) monitoring was used to determine the temporal variability of the heartrate (RR' interval) and the rates of change at low frequency (0.04-0.15Hz) and high frequency (0.15-0.40Hz). MMPI and MCMI personality assessment and shortterm memory, figure copy, controlled oral word association, and symbol digit tests were used. The five frog shop workers had abnormal sympathovagal balance with decreased high frequency variability (increased In LF/ln HF). Seven of the eight workers had symptoms of autonomic dysfunction and significantly decreased heart rate variability (rMSSD) but these did not distinguish the relative exposure. Mood or affect was disturbed in all with associated changes in short-term memory and attention in four of the subjects. There were no significant correlations with serum or urine manganese. Power spectrum analysis of 24-h

ambulatory ECG indicating a decrease in parasympathetic high frequency activation of heart rate variability may provide a sensitive index of central autonomic dysfunction reflecting increased exposure to manganese, although the contribution of exposures to solvents and other metals cannot be excluded. Neurotoxicity due to the gouging, melding, and grinding of mild steel and high manganese alloys (11-25%) merits air manganese and neuropsychologic surveillance including autonomic function by Holter monitoring of cardiovagal activation. (C) 1998 Academic Press.

11. Bizarro P, Sanchez I, Lopez I, Pasos F, Delgado V, Gonzalez-Villalva A, Colin-Barenque L, Acevedo S, Nino-Cabrera G, Mussali-Galante P and others. (2004) Morphological Changes In Testes. After Manganese Inhalation. Study In Mice. Toxicologist 78(1-S):157.
Manganese (Mn) has been used as an antiknocking agent in gasoline. Its increase in the atmosphere enhances the risk of its inhalation and the induction of systemic damage. Some reports mention that oral administration of MnCl2 induces reproductive delay in male mice. Prostatic cancer has been identified among exposed workers. The objective of this study was to identify in a murine inhalation model in CD-1 male mice. Animals inhaled MnCl2 0.02M, 1h, twice a week, for 4 weeks, sacrificed once a week and processed for light and electron microscopy. Light changes evidenced necrosis of stem cells, binucleated spermatocytes and dense nuclear structures. Ultrastructural changes in Leydig cells consisted in hyperplastic endoplasmic reticulum forming whorl-like structures. As a consequence of these modifications the function of the testes might be altered, as well as its endocrine function.

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Mangafodipir trisodium injection (MnDPDP) is an intravenously administered manganese chelate undergoing clinical evaluation for magnetic resonance imaging contrast enhancement of the hepatobiliary system. The anticipated single clinical dose for adults is 5 mu mol/kg body wt. MnDPDP, as well as the inorganic salt, MnCl2, was previously shown to induce a specific syndrome of skeletal abnormalities in rats. The syndrome malformations included angulated or irregularly shaped clavicle, femur, fibula, humerus, ilium, radius, scapula, tibia, and/or ulna. The objective of the present study was to assess the developmental toxicity of MnDPDP in a second mammalian species, the New Zealand White rabbit. MnDPDP was intravenously administered daily to groups of rabbits (22 per group) on Days 6 through 18 of pregnancy at doses of 0 (saline), 5, 20, 40, and 60 mu mol/kg MnDPDP. Fetuses were examined on Day 29 of pregnancy for external, visceral, and skeletal abnormalities. Treatment with MnDPDP did not result in overt symptoms of maternal toxicity, and there were no significant effects on maternal body weight gains or feed consumption. The maternal no-observed-adverse-effect level (NOAEL), therefore, was 60 mu mol/kg MnDPDP. Treatment with MnDPDP resulted in a significant increase in postimplantation loss at 60 mu mol/kg, but there was no significant increase in external, visceral,

or skeletal abnormalities at any dose. The developmental NOAEL for MnDPDP, therefore, was 40 mu mol/kg. These results indicate that the developmental toxicity profile of MnDPDP differs considerably in the rat and rabbit. In the rat, this compound induces specific skeletal abnormalities, whereas in the rabbit, embryo/fetal toxicity is the most sensitive developmental endpoint with no evidence for the induction of specific skeletal abnormalities. (C) 1996 Society of Toxicology

14. Bouchard M, Mergler D, Baldwin M, Sassine MP, Bowler R, MacGibbon B. (2003) Blood manganese and alcohol consumption interact on mood states among manganese alloy production workers. Neurotoxicology 24(4-5):641-647.
Long-term exposure to manganese (Mn) can induce neurotoxic effects including neuromotor, neurocognitive and neuropsychiatric effects, but there is a great interpersonal variability in the occurrence of these effects. It has recently been suggested that blood Mn (MnB) may interact with alcohol use disorders, accentuating neuropsychiatric symptoms. The objective of the present study was to explore a possible interaction between alcohol consumption and MnB on mood states, using an existing data set on Mn exposed workers. Respirable Mn exposure in the plant averaged 0.23 mg/m(3) and was correlated with MnB. All participants for whom all data on MnB concentration and mood (assessed with the Profile of Mood States (POMS)) were available and who reported currently drinking alcohol were included in the analyses (n = 74). Workers were grouped according to their MnB concentration (<10 and greater than or equal to10 mug/l) and alcohol consumption (<400 and greater than or equal to400 g per week). Two-way ANOVAs were performed on each POMS scale and Mann-Whitney tests were used to assess group differences. Workers in the higher alcohol consumption group had higher scores on three POMS scales: tension, anger and fatigue. There was no difference for POMS scale scores between MnB subgroups. Dividing the group with respect to alcohol consumption and MnB showed that the group with high alcohol consumption and high MnB displayed the highest scores. In the lower MnB category, those in the higher alcohol consumption group did not have higher scores than the others. The interaction term for alcohol consumption and MnB concentration was statistically significant ($P < 0.05$) for the depression, anger fatigue and confusion POMS scales. There was a tendency for tension ($P < 0.06$), and it was not significant for vigor. This study shows the first evidence of an interaction between MnB and alcohol consumption on mood states among Mn exposed workers and supports the results from a previous population-based study.

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Adverse mood effects of overexposure to Manganese (Mn) have been described in 15 studies which frequently report an association of Mn exposure with adverse effects in six dimensions of mood: 1) anxiety, nervousness, irritability; 2) psychotic experiences; 3) emotional disturbance; 4) fatigue lack of vigor, sleep disturbance; 5) impulsive/compulsive behavior; 6) aggression hostility. Only 1.15 studies used a standardized psychological measure of mood, while the current study of environmental Mn exposure used two standardized mood scales in evaluating low levels of Mn exposure and mood sequelae. The Profile of Moods State (POMS) and Brief Symptom Inventory (BSI) were used, and results indicate that men who are older and have higher Mn levels show significant disturbances on four of the six mood dimensions. Increased scores were seen in the anxiety, nervousness, irritability; emotional disturbance; and aggression,

hostility dimensions relative to those who had lower levels of Mn. The BSI and POMS are useful adjuncts in the assessment of mood/Mn effects. (C) 1999 Inter Press, Inc.

16. Bredow S, Falgout MM, Divine KK. (2005) A Potential Mechanism For Pulmonary Manganese-Toxicity: Manganese Induces Pulmonary VEGF Expression In Vitro. Toxicol Sci 84(1-S):234.
The respiratory tract constitutes a major route of entry and absorption for airborne Manganese (Mn) dust and fume particles. Although chronic Mn-exposure causes toxic responses in lung, little is known about the underlying mechanisms that mediate these effects. In non-pulmonary cell lines Mn induces cellular expression of Vascular Endothelial Growth Factor (VEGF) in vitro. VEGF is perhaps the most important positive regulator of angiogenesis, the sprouting and growth of new blood vessels from the existing vasculature. Angiogenic activity, which is usually low under normal physiological conditions, contributes to the pathogenesis of many diseases, and elevated VEGF levels frequently correlate with poor prognosis and disease outcome. Here we demonstrate that Mn increases VEGF expression in vitro in several human pulmonary epithelial cell lines (A549, Calu-3, NCI-H292). Cells were transiently transfected with a reporter plasmid containing the gene for firefly luciferase under the control of the VEGF wild type-promoter. Twenty-eight hours later, MnCl2 was directly added to the medium in concentrations ranging from 50 to 1000 µM. The cells were incubated for another 20 hours and then lyzed. Analysis of the cell lysates for firefly activity revealed cell- and dose-dependent increases in promoter activity between 1.5 and 3.5-fold. Interestingly in comparison to non-treated controls, exposure to 0.25 mM MnCl2 for 20 hours increases promoter activity 2-fold for up to 24 hours after Mn is removed. Further, growing the cells in the presence of 0.25 mM MnCl2 for 2 weeks did not affect their viability. These data suggest that Mn might promote changes in pulmonary angiogenic growth factor expression, which, over time, could affect lung vasculature morphology, leading to enhanced susceptibility to disease. Further studies may provide an insight into the pathogenesis of, and therapeutic targets for, lung diseases such as asthma and other chronic inflammatory airway diseases.

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The aim of study was to assess acute effects oi the divalent manganese ion (Mn2+) in an intact bur isolated heart preparation. Rat hearts were perfused in the Langendorff mode at constant flow rate. Left ventricular (LV) developed pressure (LVDP), LV pressure first derivatives (LVdp/dt max and min), heart rate (HR) and aortic pressure (AoP) were recorded. Ventricular contents of high energy phosphate compounds (HEP) and Mn metal were measured at the end of experiment. Infusion of MnCl2 for 5 min with perfusate concentrations 1-3000 mu M induced an immediate depression of contractile function at and above 33 mu M and negative chronotropy at and above 300 mu M. These EC(50) values were found (mu M): LVDP 250: LVdp/dt max 160. LVdp/dp min 120, HR 1000; and increase in AoP 80. Recovery of function during a 14 min washout period was rapid and extensive. except for Mn2+ 300 mu M. Somewhat unexpected, Mn2+ 30-1000 mu M raised coronary vascular resistance up to about twice the control level, whereas the vasoconstrictory response was overcome at 3000 mu M. Mn2+ 3000 mu M reduced tissue HEP. Ventricular Mn content rose stepwise for perfusate Mn2+ above 1 mu M UP to about 55 times the control level for perfusate Mn2+ 3000 mu M, it is concluded that: acute

effects of Mn2+ like depression of contractility and rate is rapidly reversible: and rat hearts accumulate and buffer large amounts of Mn2+ without affecting cardiac function or energy metabolism in the acute stage.

18. Buchman AL, Neely M, Grossie VB, Truong L, Lykissa E, Ahn C. (2001) Organ heavy-metal accumulation during parenteral nutrition is associated with pathologic abnormalities in rats. Nutrition 17(7-8):600-606.
OBJECTIVES: Metabolic bone disease, hepatic abnormalities, splenic insufficiency, and nephropathy have been associated with long-term total parenteral nutrition (TPN). We determined the heavy-metal contamination in TPN solutions and investigated whether it was associated with organ deposition and pathologic organ damage. METHODS: Five representative TPN solutions (two adult standard solutions, one renal solution, and one standard pediatric solution to reflect clinical practice) and 28 TPN components were analyzed with inductively coupled plasma mass spectrometry. Twenty-six male Fisher 344 rats were assigned to two groups (chow/NaCl = 8 and TPN = 18). TPN or NaCl was infused gt a rate of 50 mL/d. After 14 d, serum, femurs, spine, liver, kidneys, brain, spleen, and testes were analyzed for heavy-metal deposition by using inductively coupled plasma mass spectrometry. Tissues were fixed in formalin, sectioned, and stained with hematoxylin and eosin, periodic acid Schiff, and Masson's trichrome stain. Kidneys were fixed in gluteraldehyde for ultrastructural examination with scanning electron microscopy. RESULTS: The predominant sources of contaminants in TPN were amino acids (Al, As, Cr, Ge, Pb, Sn), dextrose (As, Ba, Cr, Sn), Ca gluconate (Al), K(2)PO4 (Al), lipid emulsion (As, Sn), and vitamins (As). Significant variations in the level of contamination depended on TPN formulation and brand of constituents. In the kidney, Pb, Cr, and Mn concentrations were greater than in controls, although there was no correlation with serum creatinine. Hepatic Cr and Pb concentrations were greater in TPN rats, although there was no correlation with serum aspartate aminotransferase or total bilirubin. Splenic Ba, Cr, Ge, Pb, Mn, and Sn concentrations were greater in TPN rats. Only serum Cr concentration was significantly correlated with splenic concentration ($r = 0.46$, $P = 0.04$). Brain and serum Ba concentrations were significantly correlated ($r = 0.60$, $P = 0.007$). No significant correlations were observed between any other metal in serum and that metal's respective organ concentration. No increase in heavy-metal accumulation was seen in the femur, spine, or testis. There were no significant depositions of As, Cd, Hg, St, or V in any of the organs examined. Serum Al and Cr concentrations were significantly increased in TPN rats, although there was no correlation with tissue concentrations. No significant increases in heavy-metal concentrations in tissue or plasma were observed for any of the other metals measurable by inductively coupled plasma mass spectrometry. Histologically in the TPN group, 50% of the rats had mild to moderate hepatic steatosis and 33% to 50% developed renal morphologic abnormalties; brains and spleens remained histologically normal. CONCLUSIONS: We found significant heavy-metal contamination of TPN solutions, and this contamination can lead to organ deposition and subsequent histologic abnormalities. (C) Elsevier Science Inc. 2001.

19. Cardozo-Pelaez F, Cox DP, Bolin C. (2005) Lack of the DNA repair enzyme OGG1 sensitizes dopamine neurons to manganese toxicity during development. Gene Expression 12(4-6):315-323.
Onset of Parkinson's disease (PD) and Parkinson-like syndromes has been associated with exposure to diverse environmental stimuli. Epidemiological studies have demonstrated that

exposure to elevated levels of manganese produces neuropathological changes localized to the basal ganglia, including neuronal loss and depletions in striatal dopamine content. However, understanding the mechanisms associated with manganese neurotoxicity has been hampered by the lack of a good rodent model. Elevated levels of 8-hydroxy-2'-deoxyguanosine (oxo(8)dG) have been found in brain areas affected in PD. Whether increased DNA damage is responsible for neuronal degeneration or is a mere epiphenomena of neuronal loss remains to be elucidated. Thus, by using mice deficient in the ability to remove oxo(8)dG we aimed to determine if dysregulation of DNA repair coupled to manganese exposure would be detrimental to dopaminergic neurons. Wild-type and OGG1 knockout mice were exposed to manganese from conception to postnatal day 30; in both groups, exposure to manganese led to alterations in the neurochemistry of the nigrostriatal system. After exposure, dopamine levels were elevated in the caudate of wild-type mice. Dopamine was reduced in the caudate of OGG1 knockout mice, a loss that was paralleled by an increase in the dopamine index of turnover. In addition, the reduction of dopamine in caudate putamen correlated with the accumulation of oxo(8)dG in midbrain. We conclude that OGG1 function is essential in maintaining neuronal stability during development and identify DNA damage as a common pathway in neuronal loss after a toxicological challenge.

20. Chaki H, Furuta S, Matsuda A, Yamauchi K, Yamamoto K, Kokuba Y, Fujibayashi Y. (2000) Magnetic resonance image and blood manganese concentration as indices for manganese content in the brain of rats. Biological Trace Element Research 74(3):245-257.
Neurological disorders similar to parkinsonian syndrome and signal hyperintensity in brain on TI-weighted magnetic resonance (MR) images have been reported in patients receiving long-term total parenteral nutrition (TPN). These symptoms have been associated with manganese (Mn) depositions in brain. Although alterations of signal intensity on T-1-weighted MR images in brain and of Mn concentration in blood are theoretically considered good indices for estimating Mn deposition in brain, precise correlations between these parameters have not been demonstrated as yet. Male Sprague-Dawley rats received TPN with 10-fold the clinical dose of the trace element preparation (TE-5) for 7 d. At 0, 2, 4, 6, and 8 wk post-TPN, the cortex, striatum, midbrain, and cerebellum were evaluated by MR images, and Mn concentration in blood and Mn content in these brain sites were measured by atomic absorption spectrometry. Immediately after TPN termination, signal hyperintensity in brain sites and elevated Mn content in blood and brain sites were observed. These values recovered at 4 wk post-TPN. A positive correlation was observed between either the signal intensity in certain brain sites or Mn content in blood and the relevant brain sites.

21. Chang JY, Liu LZ. (1999) Manganese potentiates nitric oxide production by microglia. Molecular Brain Research 68(1-2):22-28.
Manganese toxicity has been associated with clinical symptoms of neurotoxicity which are similar to the symptoms observed in Parkinson's disease. Earlier reports indicated that reactive microglia was present in the substantia nigra of patients with Parkinson's disease. Using N9 microglial cells, the current study was designed to determine whether high levels of manganese were associated with microglial activation. Results indicated that manganese significantly increased the bacterial lipopolysaccharide-induced nitric oxide production. This potent activity of manganese was not shared by other transition metals tested, including iron, cobalt, nickel, copper and zinc. Immunohistochemical staining and Western blot analysis indicated that

manganese increased the cellular production of inducible nitric oxide synthase. Northern blot analysis indicated that manganese Likely increased iNOS gene transcription since this agent increased the mRNA level of the inducible nitric oxide synthase. In contrast to other transition metals tested, manganese did not appear to be cytotoxic to microglial cells. These results suggested that manganese could induce sustained production of neurotoxic nitric oxide by activated microglial cells, which might cause detrimental consequences to surrounding neurons. (C) 1999 Elsevier Science B.V. All rights reserved.

22. Chen CJ, Ou YC, Lin SY, Liao SL, Chen SY, Chen JH. (2006) Manganese modulates pro-inflammatory gene expression in activated glia. Neurochemistry International 49(1):62-71.
Redox-active metals are of paramount importance for biological functions. Their impact and cellular activities participate in the physiological and pathophysiological processes of the central nervous system (CNS), including inflammatory responses. Manganese is an essential trace element and it is required for normal biological activities and ubiquitous enzymatic reactions. However, excessive chronic exposure to manganese results in neurobehavioral deficits. Recent evidence suggests that manganese neurotoxicity involves activation of microglia or astrocytes, representative CNS immune cells. In this study, we assessed the molecular basis of the effects of manganese on the modulation of pro-inflammatory cytokines and nitric oxide (NO) production in primary rat cortical glial cells. Cultured glial cells consisted of 85% of astrocytes and 15% of microglia. Within the assayed concentrations, manganese was unable to induce tumor necrosis factor alpha (TNF-alpha) and inducible nitric oxide synthase (iNOS) expression, whereas it potentiated iNOS and TNF-alpha gene expression by lipopol gamma-saccharide/interferon-gamma-activated glial cells. The enhancement was accompanied by elevation of free manganese, generation of oxidative stress, activation of mitogen-activated protein kinases, and increased NF-KB and AP-1 binding activities. The potentiated degradation of inhibitory molecule IKB-alpha was one of underlying mechanisms for the increased activation of NF-KB by manganese. However, manganese decreased iNOS enzymatic activity possibly through the depletion of cofactor since exogenous tetrahydrobiopterin reversed manganese's action. These data indicate that manganese could modulate glial inflammation through variable strategies. (c) 2006 Elsevier Ltd. All rights reserved.

23. Cheng J, Fu JL, Zhou ZC. (2003) The inhibitory effects of manganese on steroidogenesis in rat primary Leydig cells by disrupting steroidogenic acute regulatory (StAR) protein expression. Toxicology 187(2-3):139-148.
Manganese is known to impede the male reproductive function, however, the mechanisms through which the adverse effects are mediated are not clearly elucidated. In order to get insight into those mechanisms, the effects of manganese on the biosynthesis of testosterone by primary rat Leydig cells were examined. Primary Leydig cells were exposed to various concentrations of manganese chloride for different periods of time. Dose and time-dependent reductions of human chorionic gonadotropin (hCG)-stimulated testosterone level were observed in the culture medium. The expression of Steroidogenic Acute Regulatory (StAR) protein and the activities of P450 side-chain cleavage (P450scc) and 3beta-hydroxysteroid dehydrogenase (3beta-HSD) enzymes were also detected. The expression of StAR protein stimulated by hCG was suppressed by manganese chloride at all concentrations (0.01, 0.1, 1.0 mM) and time points (2, 4, 24, 48 h) tested. Progesterone productions treated with 22R-hydroxycholesterol or pregnenolone were reduced after treated by manganese chloride for 24 or 48 h, respectively. The manganese

exposure effect on cell viability was significant at 1.0 and 1.5 mM at 24 h, while at 48 It it was significant at every concentration tested. The decreasing effect of manganese on mitochondrial membrane potential was significant at every concentration measured and every time point tested. These data suggest that manganese exposure for 2 and 4 h inhibited rat primary Leydig cell steroidogenesis by decreasing StAR protein expression while 24 and 48 h exposure of manganese chloride caused adverse effects on both StAR protein and P450scc and 3beta-HSD enzyme activity to reduce steroidogenesis. Manganese may also disrupt StAR expression and/or function secondary to mitochondrial dysfunction.

24. Chua ACG, Stonell LM, Savigni DL, Morgan EH. (1996) Mechanisms of manganese transport in rabbit erythroid cells. Journal of Physiology-London 493(1):99-112.
1. The mechanisms of manganese transport into erythroid cells were investigated using rabbit reticulocytes and mature erythrocytes and Mn-54-labelled MnCl2 and Mn-2-transferrin. In some experiments iron uptake was also studied. 2. Three saturable manganese transport mechanisms were identified, two for Mn2+ (high and low affinity processes) and one for transferrin-bound manganese (Mn-Tf). 3. High affinity Mn2+ transport occurred in reticulocytes but not erythrocytes, was active only in low ionic strength media such as isotonic sucrose and had a K-m of 0.4 mu M. It was inhibited by metabolic inhibitors and several metal ions. 4. Low affinity Mn2+ transport occurred in erythrocytes as well as in reticulocytes and had K-m values of approximately 20 and 50 mu M for the two types of cells, respectively. The rate of Mn2+ transport was maximal in isotonic KCl, RbCl or CsCl, and was inhibited by NaCl and by amiloride, valinomycin, diethylstilboestrol and other ion transport inhibitors. The direction of Mn2+ transport was reversible, resulting in Mn2+ efflux from the cells. 5. The uptake of transferrin-bound manganese occurred only with reticulocytes and depended on receptor-mediated endocytosis of Mn-Tf. 6. The characteristics of the three saturable manganese transport mechanisms were similar to corresponding mechanisms of iron uptake by erythroid cells, suggesting that the two metals are transported by the same mechanisms. 7. It is proposed that high affinity manganese transport is a surface representation of the process responsible for the transport of manganese across the endosomal membrane after its release from transferrin. Low affinity transport probably occurs by the previously described Na+ - Mg2+ antiport, and may function in the regulation of intracellular manganese concentration by exporting manganese from the cells.

25. Cox D, Bolin C, Cardozo-Pelaez F. (2003) Assessment of dopaminergic neurons, DNA damage, DNA repair, and antioxidants in a model for manganese (MN) neurotoxicity. Free Radical Biology and Medicine 35:S156-S156.

26. Crossgrove J, Zheng W. (2004) Manganese toxicity upon overexposure. Nmr in Biomedicine 17(8):544-553.
Manganese (Mn) is a required element and a metabolic byproduct of the contrast agent mangafodipir trisodium (MnDPDP). The Mn released from MnDPDP is initially sequestered by the liver for first-pass elimination. which allows an enhanced contrast for diagnostic imaging. The administration of intravenous Mn impacts its homeostatic balance in the human body and can lead to toxicity. Human Mn deficiency has been reported in patients oil parenteral nutrition and in micronutrient studies. Mn toxicity has been reported through occupational (e.g. welder)

and dietary overexposure and is evidenced primarily in the central nervous system, although lung. cardiac, liver. reproductive and fetal toxicity have been noted. Mn neurotoxicity results from all accumulation of the metal in brain tissue and results in a progressive disorder of the extrapyramidal system which is similar to Parkinson's disease. In order for Mn to distribute from blood into brain tissue, it must cross either the blood-brain barrier (BBB) or the blood-cerebrospinal fluid barrier (BCB). Brain import, with no evidence of export, would lead to brain Mn accumulation and neurotoxicity. The mechanism for the neuro-degenerative damage specific to select brain regions is not clearly understood. Disturbances in iron homeostasis and the valence state of Mn have been implicated as key factors in contributing to Mn toxicity. Chelation therapy with EDTA and supplementation with levodopa are the current treatment options, which are mildly and transiently efficacious. In conclusion. repeated administration of Mn Or compounds that readily release Mn. may increase the risk of Mn-induced toxicity. Copyright (C) 2004 John Wiley Soils. Ltd.

27. Davis CD, Schafer DM, Finley JW. (1998) Effect of biliary ligation on manganese accumulation in rat brain. Biological Trace Element Research 64(1-3):61-74.
Neurologic and radiologic disorders have been reported to occur in miners inhaling manganese (Mn)-laden dust and in humans receiving long-term parenteral nutrition. These abnormalities have been attributed to Mn intoxication because of elevated serum Mn concentrations. Because the liver, by way of the bile, is the major route of Mn excretion, it is possible that anything that decreases biliary excretion could increase accumulation of Mn in the brain. The purpose of this study was to determine whether biliary ligation would increase Mn accumulation in the brain of rats that were exposed to deficient or adequate amounts of dietary manganese. The first experiment had a 2 x 3 factorial design, two levels of Mn (0 or 45 mu g/g diet) and three surgical treatments (control, sham, or bile-ligation). Animals were sacrificed 10 d after being fed Mn-54. In experiment 2, animals that had a sham operation or bile-ligation were sacrificed at 8 time points after being injected intraportally with 54Mn complexed to albumin. The biliary-ligated animals had a significantly ($p < 0.001$) smaller percentage of the 54Mn in their brains (when expressed as a percentage of whole animal 54Mn) than the sham-operated animals. Mn deficiency had a similar effect. However, we did observe an increased accumulation of the radioisotope in the brain over time. Therefore, in short-term studies, biliary-ligated rats do not appear to be a good model for Mn accumulation in the brains of people with cholestatic liver disease.

28. Degner D, Bleich S, Riegel A, Sprung R, Poser W, Ruther E. (2000) A follow-up study in enteral manganese intoxication: clinical, laboratory, and neuroradiological aspects. Nervenarzt 71(5):416-419.
Manganese intoxication is an unusual, severe form of intoxication. This report deals with a patient now 80 years old who accidentally ingested a solution of potassium permanganate for a period of at least 4 weeks 14 years ago. Since then, the patient suffers from a mild parkinsonian syndrome and distally accentuated polyneuropathies. Psychiatric disorders, especially demential or depressive symptoms, were not observed. Manganese analysis of his hair still shows a clear increase in manganese concentration. The MRI of his brain showed no pathological changes, in particular none of those often described with symmetric signal elevation in T-1 in the area of the basal ganglia. In this study, we present clinical, laboratory, and neuroradiological findings.

Unusual in this case with a short exposition is the long duration and clinical improvement without I-dopa treatment.

29. Desoize B. (2003) Metals and metal compounds in carcinogenesis. In Vivo 17(6):529-539.
Several metals and metal containing compounds are potent mutagens and carcinogens. The most often blamed are chromium, arsenic, nickel, vanadium, iron, copper and manganese. Although each of them has its own mechanism of action, it is believed that most of their mechanisms of action involve reactive oxygen species (ROS). Furthermore, nickel modulates gene expression by induction of DNA methylation and/or suppression of histone acetylation. Arsenic activity on cell metabolism is multiple; it seems that cell transformation is induced by long-term exposure to a low level of arsenic. The paradox of arsenic is that it has also a valuable therapeutic efficacy in cancer treatment. Manganese is known to cause DNA damage, although it does not represent a significant carcinogenic risk. Magnesium deficiency and iron excess,are not exactly carcinogenetic, but certain concentrations of these metal ions are needed to prevent cancer.

30. Desole MS, Sciola L, Delogu MR, Sircana S, Migheli R. (1996) Manganese and 1-methyl-4-(2'-ethylphenyl)-1,2,3,6-tetrahydropyridine induce apoptosis in PC12 cells. Neuroscience Letters 209(3):193-196.
Oxidative stress is thought to play a key role both in the neurotoxin MPTP- and manganese (Mn)-induced neurotoxicity and in apoptotic cell death. In the present study, we report that Mn and the MPTP analogue 1-methyl-4-(2'-ethylphenyl)-1,2,3,6-tetrahydropyridine (2'Et-MPTP), which is metabolized by MAO-A to 1-methyl-4-(2'-ethylphenyl)-pyridinium ion (at concentrations of 0.5 and 1.0 mM), induced apoptosis in PC12 cells. Apoptosis was tested by terminal deoxynucleotidyl transferase-mediated 2'-deoxyuridine-5'-triphosphate nick end labelling (TUNEL) technique, flow cytometry and fluorescence microscopy. Both Mn and 2'Et-MPTP induced also a time-dependent decrease in cell viability, as determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Only Mn-induced apoptosis and decrease in cell viability were inhibited by the antioxidant ascorbic acid. We conclude that apoptosis may be an important mechanism of cell death in MPTP- and Mn-induced parkinsonism. However, an oxidative stress mechanism may be recognized only in the Mn-induced apoptosis.

31. DiLorenzo D, Ferrari F, Agrati P, deVos H, Apostoli P, Alessio L, Albertini A, Maggi A. (1996) Manganese effects on the human neuroblastoma cell line SK-ER3. Toxicology and Applied Pharmacology 140(1):51-57.
SK-ER3 cells were recently demonstrated to represent a valuable model for the study of estrogen-inducible differentiation of neural cells in culture. This system may constitute an important tool also for the analysis of the effects of neurotoxic drugs. The present study demonstrates that short term exposure to Mn causes increased proliferation rate of SK-ER3 cells regardless of their differentiation. Long term treatment causes cell death in undifferentiated cells at concentrations of the metal as low as 100 nM. When the cells are differentiated with estrogens, death is observed only with a Mn concentration two orders of magnitude higher. Measurement of neurite extension and quantitation of tyrosine hydroxylase content after long-term exposure to the metal allow the conclusion that Mn does not alter the state of differentiation of SK-ER3 cells induced by the treatment with the hormone. The study underlines the importance of studying the effect of Mn in proliferating neural cells and demonstrates the toxic

role of micromolar concentrations of the metal in fully differentiated neural cells. Since other authors produced evidence of effects of the metal on cell death and proliferation only at millimolar concentrations, and none described its proliferative activity, the model utilized in the present study seems to be of particular interest. (C) 1996 Academic Press, Inc.

32. Dodd CA, Ward DL, Klein BG. (2005) Basal ganglia accumulation and motor assessment following manganese chloride exposure in the C57BL/6 mouse. International Journal of Toxicology 24(6):389-397.
Equivocal clinical evidence for involvement of manganese in development of Parkinson's disease necessitates experimental studies on this issue. The aged, 1-methyl-4-phenyl-1,2,3,6-tetrahyropyridine-treated C57BL/6 mouse is one of the most common models for Parkinson's disease. However, there is little information on brain bioaccumulation of manganese, and little or no information on clinical/behavioral manifestations of manganese neurotoxicity, in this strain. Male C57BL/6 retired breeder mice were given a single subcutaneous injection of either 0, 50, or 100 mg/kg of MnCl2 (single-dose regimen) or three injections of either of these doses over 7 days (multiple-dose regimen). Behavioral assessment was performed 24 h after final injection, followed by sacrifice, and body weight was recorded each day. There was a 105% increase in striatal manganese concentration 1 day after a single 100 mg/kg injection, and 421% and 647% increases, respectively, 1 day after multiple doses of 50 or 100 mg/kg of MnCl2. One day after a single injection, there were respective 30.9% and 38.9% decreases in horizontal movement (grid crossing) for the 50 and 100 mg/kg doses and a 43.2% decrease for the multiple dose of 100 mg/kg. There was no significant main effect of dose level on rearing, swimming, grip strength, or grip fatigue. Unlike previous work with the C57BL/6 strain using smaller intraperitoneal doses, this study established dosing regimens that produced significant increases in basal ganglia manganese concentration reminiscent of brain increases in the CD-1 mouse following subcutaneous doses close to our lowest. A decrease in locomotor behavior, significant but not severe in this study, has been reported following manganese exposure in other mouse strains. These data, particularly the significant increase in basal ganglia manganese concentration, provide guidance for designing studies of the potential role of manganese in Parkinson's disease using the most common animal model for the disorder.

33. Dorman DC. (2000) An integrative approach to neurotoxicology. Toxicologic Pathology 28(1):37-42.
Exposure of human populations to a wide variety of chemicals has generated concern about the potential neurotoxicity of new and existing chemicals. Experimental studies conducted in laboratory animals remain critical to the study of neurotoxicity. An integrative approach using pharmacokinetic, neuropathological, neurochemical, electrophysiological, and behavioral methods is needed to determine whether a chemical is neurotoxic. There are a number of factors that can affect the outcome of a neurotoxicity study, including the choice of animal species, dose and dosage regimen, route of administration, and the intrinsic sensitivity of the nervous system to the test chemical. The neurotoxicity of a chemical can vary at different stages of brain development and maturity. Evidence of neurotoxicity may be highly subjective and species specific and can be complicated by the presence of systemic disease. The aim of this paper is to give an overview of these and other factors involved in the assessment of the neurotoxic potential for chemicals. This article discusses the neurotoxicity of several neurotoxicants (eg, acrylamide, trimethyltin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, manganese, and

ivermectin), thereby highlighting a multidisciplinary approach to the assessment of chemically induced neurotoxicity in animals. These model chemicals produce a broad range of effects that includes peripheral axonopathy, selective neuronal damage within the nervous system, and impaired neuronal-glial metabolism.

34. Egyed M, Wood GC. (1996) Risk assessment for combustion products of the gasoline additive MMT in Canada. Science of the Total Environment 190:11-20.
Methylcyclopentadienyl manganese tricarbonyl (MMT) has been used as an octane enhancer in Canadian gasoline since 1976. The main potential health concern is from manganese oxides produced on combustion (mainly Mn3O4), given the known neurotoxicity of chronic inhalation of manganese (Mn) dust from mining and industrial use. Relevant epidemiological studies of occupational exposure to respirable Mn are briefly reviewed; an ambient air reference value of 0.1 mu g Mn/m(3), and associated inhalation tolerable daily intake (TDI) and tolerable daily uptake (TDU) of 0.035 and 0.021 mu g/kg b.w./day are derived. Ambient levels of PM(2.5) (respirable) Mn in Canadian cities have remained unchanged or have decreased between 1986 and 1992, and do not reflect large changes in MMT usage during that time. Ambient levels of PM(10) Mn in Canadian cities in 1992 were less than or equal to 0.025 mu g Mn/m(3). Mean, 90th and 98th percentiles of PM(10) Mn inhalation uptake based on ambient monitoring data from high traffic areas and from estimates of personal exposure are below the inhalation uptake criterion. An assessment of exposure from air, food, water and soil revealed that <1% of total daily Mn uptake is derived from inhalation for all age groups. Therefore, based on current information, Mn derived from the combustion of MMT-containing gasoline is unlikely to represent a significant health risk to Canadians.

35. Elbetieha A, Bataineh H, Darmani H, Al-Hamood MH. (2001) Effects of long-term exposure to manganese chloride on fertility of male and female mice. Toxicology Letters 119(3):193-201.
The effect of long-term ingestion of manganese (II) chloride tetrahydrate was investigated on fertility of male and female Swiss mice. Adult male or female mice ingested a solution of manganese chloride along with drinking water at concentrations of 1000, 2000, 4000 and 8000 mg/l for 12 weeks. Fertility was significantly reduced in male mice exposed to manganese chloride solution at a concentration of 8000 mg/l, but not at the other concentrations. There were no treatment-related effects on the number of implantation sites, viable fetuses or the number of resorptions in female rats impregnated by males who had ingested manganese chloride. Fertility was not significantly reduced in female mice exposed to manganese chloride solution at all concentrations used in this study. However, the numbers of implantations and viable fetuses were significantly reduced in females exposed to manganese chloride solution at a concentration of 8000 mg/l. There was no significant effect on the number of resorbed fetuses in females exposed to manganese chloride solution compared to their control counterparts. Absolute body weight was not significantly affected in females exposed to manganese chloride solutions. However, ovarian weight was significantly increased in females exposed to manganese chloride solution at concentrations of 4000 and 8000 mg/l. A significant increase in the uterine weight was also observed at all concentrations used in the study. These results indicate that ingestion of manganese chloride by adult male and female mice causes some adverse effects on fertility and reproduction.

36. EPA. 2004. Drinking Water Health Advisory for Manganese. U.S. Environmental Protection Agency Office of Water. Report nr EPA-822-R-04-003.

37. Ericson JE, Crinella FM, Clarke-Stewart KA, Allhusen VD, Chan T, Robertson RT. (2007) Prenatal manganese levels linked to childhood behavioral disinhibition. Neurotoxicology and Teratology 29(2):181-187.
Although manganese (Mn) is an essential mineral, high concentrations of the metal can result in a neurotoxic syndrome affecting dopamine balance and behavior control. We report an exploratory study showing an association between Mn deposits in tooth enamel, dating to the 20th and 62-64th gestational weeks, and childhood behavioral outcomes. In a sample of 27 children, 20th week Mn level was significantly and positively correlated with measures of behavioral disinhibition, specifically, play with a forbidden toy (36 months), impulsive errors on a continuous performance and a children's Stroop test (54 months), parents' and teachers' ratings of externalizing and attention problems on the Child Behavior Checklist (1st and 3rd grades), and, teacher ratings on the Disruptive Behavior Disorders Scale (3rd grade). By way of contrast, Mn level in tooth enamel formed at the 62-64th gestational week was correlated only with teachers' reports of externalizing behavior in 1st and 3rd grades. Although the source(s) of Mn exposure in this sample are unknown, one hypothesis, overabsorption of Mn secondary to gestational iron-deficiency anemia, is discussed. (c) 2006 Elsevier Inc. All rights reserved.

38. Erikson K, Aschner M. (2002) Manganese causes differential regulation of glutamate transporter (GLAST) taurine transporter and metallothionein in cultured rat astrocytes. Neurotoxicology 23(4-5):595-602.
Neurotoxicity due to excessive brain manganese (Mn) can occur due to environmental (air pollution, soil, water) and/or metabolic aberrations (decreased biliary excretion). Manganese is associated with oxidative stress, as well as alterations in neurotransmitter metabolism with concurrent neurobehavioral deficits. Based on the few existing studies that have examined brain regional [Mn], it is likely that in pathological conditions it can reach 100-500 muM. Amino acid (e.g. aspartate, glutamate, taurine), as well as divalent metal (e.g. zinc, manganese) concentrations are regulated by astrocytes in the brain. Recently, it has been reported that cultured rat primary astrocytes exposed to Mn displayed decreased glutamate uptake, thereby, increasing the excitotoxic potential of glutamate. Since the neurotoxic mechanism(s) Mn employs in terms of glutamate metabolism is unknown, a primary goal of this study was to link altered glutamate uptake in Mn exposed astrocytes to alterations in glutamate transporter message. Further we wanted to examine the gene expression of metallothionein (MT) and taurine transporter (tau-T) as markers of Mn exposure. Glutamate uptake was decreased by nearly 40% in accordance with a 48% decrease in glutamate/aspartate transporter (GLAST) mRNA. Taurine uptake was unaffected by Mn exposure even though tdu-T mRNA increased by 123%. MT mRNA decreased in these Mn exposed astrocytes possibly due to altered metal metabolism, although this was not examined. These data show that glutamate and taurine transport in Mn exposed astrocytes are temporally different. (C) 2002 Elsevier Science Inc. All rights reserved.

39. Erikson KM, Aschner M. (2003) Manganese neurotoxicity and glutamate-GABA interaction. Neurochemistry International 43(4-5):475-480.
Brain extracellular concentrations of amino acids (e.g. aspartate, glutamate, taurine) and divalent metals (e.g. zinc, copper, manganese) are primarily regulated by astrocytes. Adequate glutamate

homeostasis is essential for the normal functioning of the central nervous system (CNS). Glutamate is of central importance for nitrogen metabolism and, along with aspartate, is the primary mediator of the excitatory pathways in the brain. Similarly, the maintenance of proper manganese levels is important for normal brain functioning. Several in vivo and in vitro studies have linked increased manganese concentrations with alterations in the content and metabolism of neurotransmitters, namely dopamine, gamma-antinobutyric acid, and glutamate. It has been reported by our laboratory and others, that cultured rat primary astrocytes exposed to manganese displayed decreased glutamate uptake, thereby increasing the excitotoxic potential of glutamate. Furthermore, decreased uptake of glutamate has been associated with decreased gene expression of glutamate:aspartate transporter (GLAST) in manganese-exposed astroctyes. Additional studies have suggested that attenuation of astrocytic glutamate uptake by manganese may be a consequence of reactive oxygen species (ROS) generation. Collectively, these data suggest that excitotoxicity may occur due to manganese-induced altered glutamate metabolism, representing a proximate mechanism for manganese-induced neurotoxicity.

40. Erikson KM, Dorman DC, Fitsanakis V, Lash LH, Aschner M. (2006) Alterations of oxidative stress biomarkers due to in utero and neonatal exposures of airborne manganese. Biological Trace Element Research 111(1-3):199-215.
Neonatal rats were exposed to airborne manganese sulfate (MnSO4) (0, 0.05, 0.5, or 1.0 mg Mn/m(3)) during gestation (d 0-19) and postnatal days (PNDs) 1-18. On PND 19, rats were killed, and we assessed biochemical end points indicative of oxidative stress in five brain regions: cerebellum, hippocampus, hypothalamus, olfactory bulb, and striatum. Glutamine synthetase (GS) and tyrosine hydroxylase (TH) protein levels, metallothionein (MT), TH and GS mRNA levels, and reduced and oxidized glutathione (GSH and GSSG, respectively) levels were determined for all five regions. Mn exposure (all three doses) significantly ($p = 0.0021$) decreased GS protein levels in the cerebellum, and GS mRNA levels were significantly ($p = 0.0008$) decreased in the striatum. Both the median and high dose of Mn significantly ($p = 0.0114$) decreased MT mRNA in the striatum. Mn exposure had no effect on TH protein levels, but it significantly lowered TH mRNA levels in the olfactory bulb ($p = 0.0402$) and in the striatum ($p = 0.0493$). Mn exposure significantly lowered GSH levels at the median dose in the olfactory bulb ($p = 0.0032$) and at the median and high dose in the striatum ($p = 0.0346$). Significantly elevated ($p = 0.0247$) GSSG, which can be indicative of oxidative stress, was observed in the cerebellum of pups exposed to the high dose of Mn. These data reveal that alterations of oxidative stress biomarkers resulting from in utero and neonatal exposures of airborne Mn exist. Coupled with our previous study in which similarly exposed rats were allowed to recover from Mn exposure for 3 wk, it appears that many of these changes are reversible. It is important to note that the doses of Mn utilized represent levels that are a hundred- to a thousand-fold higher than the inhalation reference concentration set by the United States Environmental Protection Agency.

41. Erikson KM, Dorman DC, Lash LH, Aschner M. (2005) Persistent alterations in biomarkers of oxidative stress resulting from combined in utero and neonatal manganese inhalation. Biological Trace Element Research 104(2):151-163.
Neonatal female and male rats were exposed to airborne manganese sulfate (MnSO4) during gestation and postnatal d 1-18. Three weeks post-exposure, rats were killed and we assessed

biochemical end points indicative of oxidative stress in five brain regions: cerebellum, hippocampus, hypothalamus, olfactory bulb, and striatum. Glutamine synthetase (GS) protein levels, metallothionein (MT) and GS mRNA levels, and total glutathione (GSH) levels were determined for all five regions. Overall, there was a statistically significant effect of manganese exposure on decreasing brain GS protein levels (p=0.0061), although only the highest dose of manganese (1 mg Mn/m(3)) caused a significant increase in GS messenger RNA (mRNA) in both the hypothalamus and olfactory bulb of male rats and a significant decrease in GS mRNA in the striatum of female rats. This highest dose of manganese had no effect on MT mRNA in either males or females; however, the lowest dose (0.05 mg Mn/m(3)) decreased MT mRNA in the hippocampus, hypothalamus, and striatum in males. The median dose (0.5 mg Mn/m(3)) led to decreased MT mRNA in the hippocampus and hypothalamus of the males and olfactory bulb of the females. Overall, manganese exposure did not affect total GSH levels, a finding that is contrary to those in our previous studies. Only the cerebellum of manganese-exposed young male rats showed a significant reduction ($p < 0.05$) in total GSH levels compared to control levels. These data reveal that alterations in biomarkers of oxidative stress resulting from in utero and neonatal exposures of airborne manganese remain despite 3 wk of recovery; however, it is important to note that the doses of manganese utilized represent levels that are 100-fold to a 1000-fold higher than the inhalation reference concentration set by the US Environmental Protection Agency.

42. Erikson KM, Suber RL, Aschner M. (2002) Glutamate/aspartate transporter (GLAST), taurine transporter and metallothionein mRNA levels are differentially altered in astrocytes exposed to manganese chloride, manganese phosphate or manganese sulfate. Neurotoxicology 23(3):281-288.

Manganese (Mn)-induced neurotoxicity can occur due to environmental exposure (air pollution, soil, water) and/or metabolic aberrations (decreased biliary excretion). High brain manganese levels lead to oxidative stress, as well as alterations in neurotransmitter metabolism with concurrent neurobehavioral deficits. Based on the few existing studies that have examined brain regional Mn concentration, it is likely that in pathological conditions, Mn concentration can reach between 100 and 500 muM. Environmental Mn exposure as a result of methylcyclopentadienyl manganese tricarbonyl (MMT) combustion is in the form of phosphate or sulfate (MnPO4, MnSO4, respectively). Pharmacokinetic studies have shown that the Mn salt will determine the rate of transport into the brain: MnCl2 > MnSO4 > MnPO4. The salt-specific neurotoxicity of these species is unknown. The primary goal of this study was to examine gene expression of glutamate/aspartate transporter (GLAST), taurine transporter (tau-T), and metallothionein-I (MT-I) in astrocytes exposed to manganese chloride (MnCl2) manganese sulfate (MnSO4), and manganese phosphate (MnPO4). We hypothesized that the effects of MnPO4 and MnSO4 exposure on GLAST expression in astrocytes would be similar to those induced by MnCl2, since irrespective of salt species exposure, once internalized by astrocytes, the Mn ion would be identically complexed. At the same time, we hypothesized that the magnitude of the effect would be salt-dependent, since the chemical speciation would determine the rate of intracellular uptake of Mn. MnCl2 caused a significant overall decrease ($P < 0.0001$) in astrocytic GLAST mRNA levels with MnSO4 causing a moderate decrease. MnPO4 exposure did not alter GLAST mRNA in astrocytes. We also sought to examine astrocytic metallothionein and taurine transporter gene expression as markers of manganese exposure. Our findings suggest that manganese chloride significantly decreased ($P < 0.0001$) astrocytic metallothionein mRNA

compared to both the sulfate and phosphate species. However astrocytic taurine transporter mRNA was not affected by Mn exposure, irrespective of the salt species. These data are consistent with the hypothesis that astrocytic neurotoxicity due to Mn exposure is dependent upon its species, with solubility, and by inference, intracellular concentration, representing a major determinant of its neurotoxicity. (C) 2002 Elsevier Science Inc. All rights reserved.

43. Erikson KM, Thompson K, Aschner J, Aschner M. (2007) Manganese neurotoxicity: A focus on the neonate. Pharmacology & Therapeutics 113(2):369-377.
Manganese (Mn) is an essential trace metal found in all tissues, and it is required for normal amino acid, lipid, protein, and carbohydrate metabolism. While Mn deficiency is extremely rare in humans, toxicity due to overexposure of Mn is more prevalent. The brain appears to be especially vulnerable. Mn neurotoxicity is most commonly associated with occupational exposure to aerosols or dusts that contain extremely high levels (> 1-5 mg Mn/m(3)) of Mn, consumption of contaminated well water, or parenteral nutrition therapy in patients with liver disease or immature hepatic functioning such as the neonate. This review will focus primarily on the neurotoxicity of Mn in the neonate. We will discuss putative transporters of the metal in the neonatal brain and then focus on the implications of high Mn exposure to the neonate focusing on typical exposure modes (e.g., dietary and parenteral). Although Mn exposure via parenteral nutrition is uncommon in adults, in premature infants, it is more prevalent, so this mode of exposure becomes salient in this population. We will briefly review some of the mechanisms of Mn neurotoxicity and conclude with a discussion of ripe areas for research in this underreported area of neurotoxicity. (c) 2006 Elsevier Inc. All rights reserved.

44. Finley JW. (2004) Does environmental exposure to manganese pose a health risk to healthy adults? Nutrition Reviews 62(4):148-153.
Manganese is an essential nutrient that also may be toxic at high concentrations. Subjects chronically exposed to manganese-laden dust in industrial settings develop neuropsychological changes that resemble Parkinson's disease. Manganese has been proposed as an additive to gasoline (as a replacement for the catalytic properties of lead), which has generated increased research interest in the possible deleterious effects of environmental exposure to manganese. Low-level exposure to manganese has been implicated in neurologic changes, decreased learning ability in school-aged children, and increased propensity for violence in adults. However, a thorough review of the literature shows very weak cause-and-effect relationships that do not justify concern about environmental exposure to manganese for most of the North American population.

45. Fitsanakis VA, Zhang N, Avison MJ, Gore JC, Aschner JL, Aschner M. (2006) The use of magnetic resonance imaging (MRI) in the study of manganese neurotoxicity. Neurotoxicology 27(5):798-806.
Manganese (Mn), an element found in many foods, is an important and essential nutrient for proper health and maintenance. It is toxic in high doses, however, and exposure to excessive levels can result in the onset of a neurological disorder similar to, but distinct from, Parkinson's disease. Historically, Mn neurotoxicity was most commonly associated with various occupations, such as Mn mining, welding and steel production. More recently, increases in both blood and brain Mn levels have been observed in persons with liver disease or those receiving prolonged parenteral nutrition. Additionally, rodent data suggest that iron deficiency and anemia

may be risk factors for Mn neurotoxicity. Clinically, brain Mn accumulation can be monitored in vivo using non-invasive magnetic resonance imaging (MRI) due to the paramagnetic nature of this element. Indeed, MRI has been used in a variety of settings to evaluate the brain Mn deposition in various populations. This review focuses on the use of MRI technology in studies related specifically to Mn neurotoxicity. Thus, we will examine reports using MRI to confirm brain Mn accumulation in human populations, and conclude with data from non-human primate and rodent models of Mn neurotoxicity. (C) 2006 Elsevier Inc. All rights reserved.

46. Fitzgerald K, Mikalunas V, Rubin H, McCarthy R, Vanagunas A, Craig RM. (1999) Hypermanganesemia in patients receiving total parenteral nutrition. Journal of Parenteral and Enteral Nutrition 23(6):333-336.
Background: Manganese is one of the trace elements that is routinely administered to total parenteral nutrition (TPN) patients. The recommended daily IV dosage ranges from 100 to 800 mu g. We have used 500 mu g daily. Recent reports have suggested neurologic symptoms seen in some patients receiving home parenteral nutrition (HPN) may be due to hypermanganesemia. Therefore, HPN patients and some short-term inpatients receiving TPN were studied to ascertain the relationship between dose and blood levels. Methods: Red blood cell manganese levels were obtained by atomic absorptiometry. Results: The levels in 36 hospitalized, short-term patients obtained within 48 hours of initiating TPN were all normal. The 30 patients receiving TPN from 3 to 30 days had levels that ranged from 4.8 to 28 mu g/L (normal, 11 to 23 mu g/L). Two patients had abnormal levels, at days 14 and 18. Fifteen of the 21 patients receiving inpatient TPN or HPN for 36 to 5075 days had elevated Mn levels. Only one patient with hypermanganesemia, an inpatient, had abnormal biochemical liver tests (bilirubin and alkaline phosphatase). One of the patients with a high level had some vestibular symptoms attributed to aminoglycoside use and had increased signal density in the globus pallidus on T1-weighted images on magnetic resonance imaging (MRI). A second patient with Mn levels twice normal had no neurologic symptoms, but had similar MRI findings. A third had some basal ganglia symptoms, confirmed by a neurologic evaluation, seizures, and very high Mn levels. The MRI showed no signal enhancement, but motion artifacts limited the study technically. Conclusions: Hypermanganesemia is seen in HPN patients receiving 500 mu g manganese daily and may have resulted in some neurologic damage in three patients. Hypermanganesemia is sometimes seen after a short course of TPN in inpatients, as early as 14 days. Patients should be monitored for hypermanganesemia if they receive Mn in their TPN for >30 days. A 500 mu g/d dose of Mn is probably excessive, and 100 mu g/d should probably never be exceeded. Mn should be eliminated from the solution if the Mn level is elevated and should not be readministered unless the level returns to normal or subnormal. Mn should not be supplemented if the patient has liver disease with an elevated bilirubin.

47. Fortoul TI, Mendoza ML, Avila MD, Torres AQ, Osorio LS, Espejel GM, Fernandez GO. (2001) Manganese in lung tissue: Study of Mexico City residents' autopsy records from the 1960s and 1990s. Archives of Environmental Health 56(2):187-190.
During the conduct of autopsies performed on residents of Mexico City during the 1960s (20 males, 19 females) and 1990s (30 males and 18 females), concentrations of manganese in lung were studied with atomic absorption spectrometry. Concentrations of manganese were not significantly greater in the samples obtained in the 1990s (1.87 +/- 0.8 mug/gm [mean +/- standard deviation]) than in samples from the 1960s (1.72 +/- 1.2 mug/gm). Concentrations were

not correlated with gender, smoking habit, age, or cause of death; however, there was a correlation with occupation. The findings suggest that manganese exposure via air does not represent a health hazard to residents of Mexico City, given that lung concentrations of manganese remained stable during the 30-y period studied. Investigators should monitor concentrations of manganese in suspended particles to follow-up on these findings.

48. Fredstrom S, Rogosheske J, Gupta P, Burns LJ. (1995) Extrapyramidal Symptoms in a Bmt Recipient with Hyperintense Basal Ganglia and Elevated Manganese. Bone Marrow Transplantation 15(6):989-992.
Neurologic syndromes attributed to conditioning or medications have been reported in BMT recipients. A patient is presented who developed extrapyramidal symptoms on day +56 after allogeneic BMT. Brain magnetic resonance images of this patient demonstrated hyperintense basal ganglia, which has been associated with manganese (Mn) toxicity. The patient had received total parenteral nutrition (TPN) with standard trace element supplementation and had been cholestatic. Serum Mn was elevated, and continued to be so 5 months after BMT, long after discontinuation of TPN. Cholestatic patients and those on long-term TPN have been found to have high blood or serum levels of Mn, but generally are asymptomatic, When other cholestatic BMT patients were reviewed, all had elevated serum Mn. Manganese supplementation in TPN requires evaluation for BMT recipients.

49. FreelandGraves JH, Turnlund JR. (1996) Deliberations and evaluations of the approaches, endpoints and paradigms for manganese and molybdenum dietary recommendations. Journal of Nutrition 126(9):S2435-S2440.
The background of the current dietary recommendations for manganese and molybdenum are described. This article reviews how the previous and current estimated safe and adequate daily dietary intakes (ESADDI) were set, shortcomings in the methods used, concerns about the current recommendations, and brief summaries of new research reports. New approaches, endpoints and paradigms to use for the development of useful recommendations are given.

50. Friberg L, Nordberg GF, Vouk VB. (2007) Handbook of the Toxicology of Metals. 3rd ed. : Elsevier Science Publishing Company; pp. 476.
Handbook of the Toxicology of Metals is the standard reference work for physicians, toxicologists and engineers in the field of environmental and occupational health. This new edition is a comprehensive review of the effects on biological systems from metallic elements and their compounds. An entirely new structure and illustrations represent the vast array of advancements made since the last edition. Special emphasis has been placed on the toxic effects in humans with chapters on the diagnosis, treatment and prevention of metal poisoning. This up-to-date reference provides easy access to a broad range of basic toxicological data and also gives a general introduction to the toxicology of metallic compounds.

51. Gallez B, Baudelet C, Adline J, Geurts M, Delzenne N. (1997) Accumulation of manganese in the brain of mice after intravenous injection of manganese-based contrast agents. Chemical Research in Toxicology 10(4):360-363.
Because the manganese-based contrast agents used in magnetic resonance imaging are unstable in vivo, some concern exists about the potential toxicity coming from the Mn2+ released by the complexes. This potential problem arises because the manganese is known to accumulate in the

brain of people intoxicated by this metal (manganism): this central accumulation leads to neurological disorders (i.e., parkinsonism-like syndrome). The aim of this study was to assess the amount of Mn found in the brain after administration of MnCl2 or different chelates of Mn in normal mice as well as in mice with impaired biliary elimination. Male NMRI mice received an intravenous injection in a caudal vein of 5 mu mol/kg of Mn-54 compounds as MnCl2, manganese-diethylenetriaminepentaacetate (Mn-DTPA), or manganese-dipyridoxal diphosphate (Mn-DPDP). The radiolabeled complexes (1:1) were prepared by direct chelation (Mn-DTPA) or transchelation of preformed complex (Mn-DPDP), and the radiochemical purity was assessed by paper chromatography. The mice were killed at various times post-exposure (0-3 months), and the radioactivity present in the organs was determined by gamma counting. For each compound analyzed in the present study, we observed an accumulation of Mn (0.25-0.3% of the amount injected/g of tissue) in the mouse brain, reaching a plateau after 24 h, while the Mn content in the liver was decreasing with time. The amount of Mn accumulated in the brain remained unchanged 1 month later, but decreased to 40% of the maximum amount 3 months after the exposure. In mice whose bile ducts had been ligated 24 h before the administration of the manganese compound, we observed, 1 week after the injection, an amount of manganese accumulated in the brain 2 times higher than in normal mice.

52. Garrick MD, Dolan KG, Horbinski C, Ghio AJ, Higgins D, Porubcin M, Moore EG, Hainsworth LN, Umbreit JN, Conrad ME and others. (2003) DMT1: A mammalian transporter for multiple metals. Biometals 16(1):41-54.
DMT1 has four names, transports as many as eight metals, may have four or more isoforms and carries out its transport for multiple purposes. This review is a start at sorting out these multiplicities. A G185R mutation results in diminished gastrointestinal iron uptake and decreased endosomal iron exit in microcytic mice and Belgrade rats. Comparison of mutant to normal rodents is one analytical tool. Ectopic expression is another. Antibodies that distinguish the isoforms are also useful. Two mRNA isoforms differ in the 3' UTR: + IRE DMT1 has an IRE (Iron Responsive Element) but -IRE DMT1 lacks this feature. The +/- IRE proteins differ in the distal 18 or 25 amino acid residues after shared identity for the proximal 543 residues. A major function is serving as the apical iron transporter in the lumen of the gut. The + IRE isoform appears to have that role. Another role is endosomal exit of iron. Some evidence indicts the -IRE isoform for this function. In our ectopic expression assay for metal uptake, four metals - Fe2+,Mn2+,Ni2+ and Co2+ - respond to the normal DMT1 cDNA but not the G185 R mutant. Two metals did not - Cd2+ and Zn2+ -andtwo -Cu2+ and Pb2+ -remain to be tested. In competition experiments in the same assay, Cd2+,Cu2+ and Pb2+ inhibit Mn2+ uptake but Zn2+ did not. In rodent mutants, Fe and Mn appear more dependent on DMT1 than Cu and Zn. Experiments based on ectopic expression, specific antibodies that inhibit metal uptake and labeling data indicate that Fe3+ uptake depends on a different pathway in multiple cells. Two isoforms localize differently in a number of cell types. Unexpectedly, the -IRE isoform is in the nuclei of cells with neuronal properties. While the function of -IRE DMT1 in the nucleus is speculative, one may safely infer that this localization identifies new role(s) for this multifunctional transporter. Management of toxic challenges is another function related to metal homeostasis. Airways represent a gateway tissue for metal entry. Preliminary evidence using specific PCR primers and antibodies specific to the two isoforms indicates that -IRE mRNA and protein increase in response to exposure to metal in lungs and in a cell culture model; the + IRE form is unresponsive. Thus the -IRE form could be part of a detoxification system in which +

IRE DMT1 does not participate. How does iron status affect other metals' toxicity? In the case of Mn, iron deficiency may enhance cellular responses.

53. Gassmann B. (2001) Dietary reference intakes, report 4: Trace elements. Ernahrungs-Umschau 48(4):148-+.
Part 2 deals with a set of reference values established for chromium, copper, iodine, iron, manganese, molybdenum, and zinc to replace Recommended Dietary Allowances (RDAs), Estimated Safe and Adequate Daily Dietary Intakes published in 1989. In addition, the evidence of beneficial and adverse effects of arsenic, boron, nickel, silicon, and vanadium has been analyzed. AU RDAs, Adequate Intakes (AIs), and Tolerable Upper Intake Levels (ULs] reported are summarized, commented and compared with the DACH reference values 2000. Many questions that were raised about requirements for and recommended intakes of trace elements were not answered fully because of inadequacies in the published database. Thus RDAs have only been set for copper, iodine, iron, molybdenum, and zinc. Far most of the trace elements, there is no direct information allowing to estimate the amounts required by children, adolescents, the elderly, and pregnant and lactating women. Because of the lack of data to estimate average requirements of adults, AIs have to be set for chromium and manganese based on representative dietary intake data from healthy individuals in the United States. in the case of arsenic, boron, nickel, silicon, and vanadium, there is evidence that they have a beneficial role in physiological processes in some species. In some cases measurable responses of human subjects to changes in dietary intake have been demonstrated. However, the available data are not sufficient to determine average requirements. Nor could data available about dietary intake be used to establish an AI. For boron, copper, iodine, iron, manganese, molybdenum, nickel, vanadium, and zinc ULs have been established. For arsenic, chromium, and silicon data were sparse for setting ULs, precluding reliable estimates of how much can be ingested safely. Although there are some differences in their reference values, the Institute pf Medicine and DACH Societies used similar models for establishing reference intakes of trace elements.

54. Gavin CE, Gunter KK, Gunter TE. (1999) Manganese and calcium transport in mitochondria: Implications for manganese toxicity. Neurotoxicology 20(2-3):445-453.
Mn2+ is sequestered by liver and brain mitochondria via the mitochondrial Ca2+ uniporter. The mitochondrial Ca2+ uniporter is a cooperative transport mechanism possessing an external activation site and a transport site. Ca2+ binding to the activation site greatly increases the velocity of uptake of both Ca2+ and Mn2+. Electron paramagnetic resonance (EPR) shows that over 97% of the Mn2+ in the mitochondrial matrix is normally bound to the membrane or to matrix proteins. EPR measurements of manganese within living isolated mitochondria can be repeat-ed for hours, and during this time most of the manganese remains in the Mn2+ state. Mn2+ is transported out of mitochondria via the very slow Na+-independent efflux mechanism, which is an active (energy-requiring) mechanism. Mn2+ is not significantly transported over the Na+-dependent efflux mechanism, which is the dominant efflux mechanism in heart and brain mitochondria. Mn2+ inhibits the efflux of Ca2+ through both of these efflux mechanisms, having an apparent K-i of 7.9 nmol/mg protein on the Na+-independent efflux mechanism and an apparent K-i of 5.1 nmol/mg on the Na+-dependent efflux mechanism. Mn2+ inhibition of Ca2+ efflux may increase the probability of the mitochondria undergoing the mitochondrial permeability transition (MPT). Intramitochondrial Mn2+ also inhibits State 3 mitochondrial respiration using either succinate or malate plus glutamate as substrate. The data suggest that

Mn2+ depletes cellular energy supplies by interfering with oxidative phosphorylation at the level of the F(1)ATPase and at much higher concentrations, at Complex I. Effects such as these could lead to apoptosis in active neurons. (C) 1999 Inter Press, Inc.

55. Grandjean P, Landrigan PJ. (2006) Developmental neurotoxicity of industrial chemicals. Lancet 368(9553):2167-2178.
Neurodevelopmental disorders such as autism, attention deficit disorder, mental retardation, and cerebral palsy are common, costly, and can cause lifelong disability. Their causes are mostly unknown. A few industrial chemicals (eg, lead, methylmercury, polychlorinated biphenyls [PCBs], arsenic, and toluene) are recognised causes of neurodevelopmental disorders and subclinical brain dysfunction. Exposure to these chemicals during early fetal development can cause brain injury at doses much lower than those affecting adult brain function. Recognition of these risks has led to evidence-based programmes of prevention, such as elimination of lead additives in petrol. Although these prevention campaigns are highly successful, most were initiated only after substantial delays. Another 200 chemicals are known to cause clinical neurotoxic effects in adults. Despite an absence of systematic testing, many additional chemicals have been shown to be neurotoxic in laboratory models. The toxic effects of such chemicals in the developing human brain are not known and they are not regulated to protect children. The two main impediments to prevention of neurodevelopmental deficits of chemical origin are the great gaps in testing chemicals for developmental neurotoxicity and the high level of proof required for regulation. New, precautionary approaches that recognise the unique vulnerability of the developing brain are needed for testing and control of chemicals.

56. Halatek T, Opalska B, Rydzynski K, Bernard A. (2006) Pulmonary response to methylcyclopentadienyl manganese tricarbonyl treatment in rats: injury and repair evaluation. Histology and Histopathology 21(11):1181-1192.
Methylcyclopentadienyl manganese tricarbonyl (MMT), an organometallic compound, used as an antiknock additive in fuels, may produce alveolar inflammation and bronchiolar cell injury. The aim of the experimental study on female rats was to determine by morphological examination and sensitive biomarkers, the course of the injury and repair process following a single i.p. injection of 5 mg/kg MMT. The animals were sacrificed 12, 24, 48 hours or 7 days post-exposure (PE). The first biochemical changes 12 h PE showed an increase in GSH-S-transferase (GST) activity in the lung parallel to the earliest observed morphological changes-vacuolation and swollen cytoplasm in type I pneumocytes. Alterations in type I pneumocytes were most prevalent in rat lung 24 h PE. Clara cells with dilated smooth endoplasmic reticulum membranes and cytoplasmic vacuolation could be observed. Compared to the values found for controls, Clara cell protein (CC16) in the bronchoalveolar lavage fluid (BALF) at 24 and 48 h PE decreased by 58% and 55%, respectively. At the same time (at 24 and 48 h), the total protein concentration in BALF increased 5 and 7 times, respectively. A significant rise in hyaluronic acid (HA) level was observed 24 and 48 h PE. Divided type II pneumocyte cells and Clara cells in their mitotic phase were observed in immunocytochemistry (detecting BrdU binding into DNA) 48 h PE. Seven days after MMT administration, fibroblasts, macrophages, collagen and elastin fibres could be seen in the alveolar walls as well as neutrophils, lymphocytes, and alveoli macrophages in the alveolar lumen. We conclude that injury and repair of bronchial epithelium cells, especially of Clara cells and type II pneumocyte cells, play an important part in MMT toxicity, probably depending on the antioxidant status of these cells. The sensitive biomarkers of

CC16 and hyaluronic acid in BALF and serum reflect lung injury and indicate the time course of pulmonary damage and repair processes.

57. Hernandez EH, Discalzi G, Dassi P, Jarre L, Pira E. (2003) Manganese intoxication: The cause of an inexplicable epileptic syndrome in a 3 year old child. Neurotoxicology 24(4-5):633-639.
Excess manganese (Mn) can cause several neurotoxic effects, however only a few studies have reported epileptic syndromes related to manganese intoxication. We describe an epileptic syndrome due to manganese intoxication in a 3 year old male child. His blood manganese was elevated, but no other abnormal values or toxic substances were found in blood or urine. The electroencephalogram (EEG) showed a picture of progressive encephalopathy, while brain magnetic resonance was normal. The patient's conditions rapidly worsened to epileptic status despite the use of antiepileptic drugs. Chelating treatment with CaNa(2)EDTA was initiated to remove excess manganese and promptly succeeded in reverting epileptic symptoms. Concurrently, manganese blood levels and electroencephalogram progressively normalized. Thereafter it has been possible to discontinue antiepileptic treatment, and the patient remains in excellent conditions without any treatment.

58. Hirata Y, Adachi E, Kiuchi K. (1998) Activation of JNK pathway and induction of apoptosis by manganese in PC12 cells. Journal of Neurochemistry 71(4):1607-1615.
Manganese is known to induce neurological disorders similar to parkinsonisms. A dopamine deficiency has been demonstrated in Parkinson's disease and in chronic manganese poisoning, suggesting that the mechanisms underlying the neurotoxic effects of the metal ion are related to a functional abnormality of the extrapyramidal system. However, the details have yet to be elucidated. Here we report that manganese causes characteristic internucleosomal DNA fragmentation, a biochemical hallmark of apoptosis, in PC12 cells. It was transcription dependent, relatively specific for manganese, and blocked in Bcl-2-overexpressed PC12 cells, The results indicate that apoptosis may play a role in the dopaminergic neurotoxicity associated with manganese, the first metal to be reported to induce this form of cell death. The early biochemical events show the impairment of energy metabolism, and the process may require new synthesis of proteins such as c-Fos and c-Jun. In addition, manganese induces phosphorylation of c-Jun at Ser(63) and Ser(73) and SEK1/MKK4 (c-Jun N-terminal kinase kinase) at Thr(258) and tyrosine phosphorylation of several proteins. These results indicate that manganese activates specific signal cascades including the c-Jun N-terminal kinase pathway

59. Hirata Y, Kiuchi K, Nagatsu T. (2001) Manganese mimics the action of 1-methyl-4-phenylpyridinium ion, a dopaminergic neurotoxin, in rat striatal tissue slices. Neuroscience Letters 311(1):53-56.
Manganese and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) are known to induce neurological pathologies similar to that of parkinsonism. Previous studies performed in rat striatal slices have shown that MPTP and related compounds inhibit tyrosine hydroxylation, a rate-limiting step of dopamine biosynthesis. Here, we reported that manganese inhibited tyrosine hydroxylation in rat striatal slices. In addition, manganese caused increase in the levels of lactate indicating that aerobic glycolysis was inhibited in striatal slices. This inhibition was unique to manganese since other divalent cations, such as magnesium and zinc, did not increase lactate concentrations. These results suggest that the mechanisms by which manganese produces

dysfunction of the nervous system are similar to those of MPTP. (C) 2001 Elsevier Science Ireland Ltd. All rights reserved.

60. Hsieh CT, Liang JS, Peng SSF, Lee WT. (2007) Seizure associated with total parenteral nutrition-related hypermanganesemia. Pediatric Neurology 36(3):181-183.
The trace element manganese is usually supplied when total parenteral nutrition is used. However, long-term parenteral administration of manganese, which bypasses the normal. regulatory mechanism, may cause hypermanganesemia. Manganese poisoning presents clinically with parkinsonian-like symptoms and psychological changes. Seizures are a rare presentation of this disease. This report describes a 10-year-old female who had received total parenteral nutrition for 3 months because of short bowel syndrome, and presented with tonic-clonic seizure, decreased level of consciousness, and fever. The serum electrolytes, glucose and the cerebrospinal fluid examination were normal. The blood culture grew Pantoea agglomerans. The brain magnetic resonance imaging disclosed no evidence of central nervous system infection. However, symmetric high-intensity signal on T-1-weighted images was documented in the basal ganglia, especially in the globus pallidus. Her whole blood manganese level was 3.7 mu g/dL, which was significantly higher than the normal range (0.4-1.4 mu g/dL). Diagnosis of hypermanganesemia related to total parenteral nutrition was made. (c) 2007 by Elsevier Inc. All rights reserved.

61. Kafritsa Y, Fell J, Long S, Bynevelt M, Taylor W, Milla P. (1998) Long term outcome of brain manganese deposition in patients in home parenteral nutrition. Archives of Disease in Childhood 79(3):263-265.
BIOSIS COPYRIGHT: BIOL ABS. Manganese intoxication has been described in children on long term parenteral nutrition presenting with liver and nervous system disorders. Cases are reported of a brother and sister on long term parenteral nutrition with hypermanganesaemia and basal ganglia manganese deposition, detected by magnetic resonance imaging (MRI), without overt neurological signs. Following reduction of manganese intake, basal ganglia manganese was monitored by repeated MRI, and neurological and developmental examinations. An MRI intensity index of the globus pallidus declined over a three year period from 0.318 and 0.385 to 0.205 and 0.134 with concomitant falls in whole blood manganese from 323 and 516 to 226 and 209 nmol/l (normal range, 73-210 nmol/l). Unlike adult experience these children developed normally without neurological signs. In conclusion, deposited manganese is removed from neural tissue over time and the prognosis is good when neurological manifestations and liver disease ar

62. Kessler KR, Wunderlich G, Hefter H, Seitz RJ. (2003) Secondary progressive chronic manganism associated with markedly decreased striatal D2 receptor density. Movement Disorders 18(2):216-218.
We describe a patient with chronic manganism due to intoxication 40 years ago. Whereas previous reports on acute or subacute intoxication have shown no or only small reductions in striatal D2 receptor density, we found markedly decreased D2 receptor density using F-18-methylspiperone PET in this very late stage of chronic manganism, supporting the hypothesis that manganese intoxication may trigger a neuro-degenerative disease process. (C) 2002 Movement Disorder Society.

63. Kim JW, Kim Y, Cheong HK, Ito K. (1998) Manganese induced Parkinsonism: A case report. Journal of Korean Medical Science 13(4):437-439.
BIOSIS COPYRIGHT: BIOL ABS. Manganese (Mn) intoxication is known to induce parkinsonism. Mn-induced parkinsonism preferentially affect the globus pallidus in contrast to idiopathic parkinsonism where degeneration predominantly involves the nigral pars compacta. We describe a 51-year-old man who had been occupationally exposed to Mn. He had parkinsonian features including masked face, resting tremor, and bradykinesia. He also had a cock walk and a particular propensity to fall in a backward gait. There was no sustained therapeutic response to levodopa. A fluorodopa PET scan was normal. This case indicates that Mn-induced parkinsonism can be differentiated from idiopathic parkinsonism in that the former has unique clinical features and a normal fluorodopa PET scan.

64. Kondoh H, Iwase K, Higaki J, Tanaka Y, Yoshikawa M, Hori S, Osuga K, Kamiike W. (1999) Manganese deposition in the brain following parenteral manganese administration in association with radical operation for esophageal cencer: Report of a case. Surgery Today-the Japanese Journal of Surgery 29(8):773-776.
We report herein the case of a patient in whom manganese (Mn) deposition in the basal ganglia was detected by magnetic resonance imaging (MRI) subsequent to thoracic esophagectomy, performed following perioperative parenteral nutrition. A multi-trace-element supplement solution which included 20 mu mol of Mn per day had been parenterally administered for 7 days preoperatively and 21 days postoperatively. The serum level of total bilirubin reached a maximum value of 5.1mg/dl postoperatively. The T1-weighted MRI on the 32nd postoperative day demonstrated bilateral and symmetrical hyperintense lesions in the globus pallidus and the whole-blood Mn level on the 34th postoperative day was 4.9 mu g/l, the normal range being 0.8-2.5 mu g/l. This hyperintensity on T1-weighted MRI was gradually improved following normalization of the blood Mn level. This case report serves to demonstrate that even short-term perioperative parenteral nutrition may result in Mn deposition in the brain following radical surgery for esophageal cancer, especially in patients with hyperbilirubinemia.

65. Kucera J, Bencko V, Sabbioni E, Vandervenne MT. (1995) Review of Trace-Elements in Blood, Serum and Urine for the Czech and Slovak Populations and Critical-Evaluation of Their Possible Use as Reference Values. Science of the Total Environment 166(1-3):211-234.
The availability of accurate trace element reference values in human tissues represents an important indicator to the health status of the general population and occupational groups exposed to trace elements. The EURO TERVIHT project (Trace Element Reference Values in Human Tissues) aims to establish and compare trace element reference values in tissues from inhabitants of the European countries as baseline values for clinical/toxicological assessment studies [3]. In this context, one of the first steps considered is the critical evaluation (state of the art) of existing literature on trace element reference values in blood, serum and urine in the general population of each European country. This paper reviews the Czech and Slovak situation by assessing studies carried out in these countries for Al, As, Cd, Co, Cr, Cu, F, Mn, Hg, Ni, Pb, Rb, Sc, Se, V and Zn in blood, serum and urine. These studies show that most of the data available do not meet criteria designed recently for deriving reference intervals, especially regarding the number of subjects, the age of population sample studies as well as the use of appropriate sampling techniques and quality assurance procedures. Elements which present the highest potential risk for health in Czech and Slovak populations and for which reference values

should be urgently established are: Cd, Hg, Pb (major pollutants); As, Cr, Ni (carcinogenic metals); Al, F, Mn, Tl, V (released into the environment by coal combustion and other industrial activities); Pt (increasing use of Pt catalyst in petrol-driven automobiles); essential trace elements such as I, Se and Zn for which a deficiency in Czech and Slovak populations was detected or is suspected.

66. Lambert LB, Singer TM, Boucher SE, Douglas GR. (2005) Detailed review of transgenic rodent mutation assays. Mutation Research-Reviews in Mutation Research 590(1-3):1-280. Induced chromosomal and gene mutations play a role in carcinogenesis and may be involved in the production of birth defects and other disease conditions. While it is widely accepted that in vivo mutation assays are more relevant to the human condition than are in vitro assays, our ability to evaluate mutagenesis in vivo in a broad range of tissues has historically been quite limited. The development of transgenic rodent (TGR) mutation models has given us the ability to detect, quantify, and sequence mutations in a range of somatic and germ cells. This document provides a comprehensive review of the TGR mutation assay literature and assesses the potential use of these assays in a regulatory context. The information is arranged as follows. (1) TGR mutagenicity models and their use for the analysis of gene and chromosomal mutation are fully described. (2) The principles underlying current OECD tests for the assessment of genotoxicity in vitro and in vivo, and also nontransgenic assays available for assessment of gene mutation, are described. (3) All available information pertaining to the conduct of TGR assays and important parameters of assay performance have been tabulated and analyzed. (4) The performance of TGR assays, both in isolation and as part of a battery of in vitro and in vivo short-term genotoxicity tests, in predicting carcinogenicity is described. (5) Recommendations are made regarding the experimental parameters for TGR assays, and the use of TGR assays in a regulatory context. 1. The TGR mutation assay is based on transgenic rats and mice that contain multiple copies of chromosomally integrated plasmid and phage shuttle vectors that harbour reporter genes for detection of mutation. Mutagenic events arising in the rodent are scored by recovering the shuttle vector and analyzing the phenotype of the reporter gene in a bacterial host. TGR gene mutation assays allow mutations induced in a genetically neutral transgene to be scored in any tissue of the rodent, and therefore circumvent many of the existing limitations to the study of in vivo gene mutation. TGR models for which sufficient data are available to permit evaluation include Muta (TM) mouse, Big Blue (R) mouse and rat, LacZ plasmid mouse, and the gpt delta mouse. Mutagenesis in the TGR models is normally assessed as a mutant frequency (MF); however, if required, molecular analysis can provide additional information., 2. OECD guidelines exist for a range of in vitro mutation assays that are capable of detecting both chromosomal and gene mutations. In vivo assays are required components of a thorough genetic toxicity testing programme. For somatic cells, those assays that are most commonly conducted, for which OECD guidelines are currently available, assess induced chromosomal mutation. In addition there are non-transgenic assays that can be used for analysis of gene mutation; none of these have an OECD test guideline. Existing in vivo assays are limited by a range of different factors, including cost of the assay, the number of tissues in which genotoxicity may be measured, the state of understanding of the endpoint, and the nature of the chemicals that will be detected. 3. As of July 2004, 163 agents have been evaluated using TGR assays. The majority of experimental records have assessed a subset of these chemicals, most of which are strong mutagens and carcinogens. Of the 103 agents whose carcinogenicity has been evaluated 90 are carcinogens and only 13 are noncarcinogens. The following conclusions may be drawn from the

existing TGR mutation data. The ability to use all routes of administration has been demonstrated. Experiments can be tailored to use the most relevant route of administration. The ability to examine mutation in virtually all tissues has-been demonstrated. TGR assays have most commonly examined mutagenicity in the liver and bone marrow. The majority of the experiments have used shorter administration times than is currently recommended by the International Workshops on Genotoxicity Testing (IWGT); there are limited data available to assess the effects of longer sampling time except at extremely short administration times. Although it is recognized that a number of factors may influence the tissue specificity of mutation, including cell turnover, DNA repair, toxicokinetics, and the nature of the genetic target, there are currently limited experimental data specific to transgenes that are available to inform the discussion. Limited data are available to evaluate the results of TGR assays in known target tissues for carcinogenicity. A case-by-case analysis of instances in which discrepancies are apparent suggests that in the majority of cases, factors such as nongenotoxic mechanism of action, inappropriate mode of administration, or inadequate study design may account for the observed negative result in the tissue of interest. Qualitatively similar results have been obtained in the majority of experiments that have assayed different transgenes using similar experimental parameters. The spontaneous mutant frequency (SMF) in most somatic tissues of TGR animals is 5-10-fold higher than observed in available endogenous loci using the same animals. Factors such as the age of the animal, the tissue, and the animal model influence the absolute value of the SMF. In most somatic tissues, with the exception of brain, there is an age related increase in mutation frequency throughout the life of the animal. Most, but not all, studies suggest that the SMF in male germline tissues remains low and constant throughout the life of the animal. Multiple treatments of a mutagen appear to increase mutant frequencies in neutral transgenes in an approximately additive manner. However, extremely long treatment times of 12 weeks or longer may produce an apparent increase in MF through clonal expansion, genomic instability in developing preneoplastic foci or tumours, or through oxidation damage of DNA resulting from chronic induction of cytochrome P-450 monooxygenases. The time required to reach the maximum mutant frequency is tissue-specific, and appears to be related to the turnover time of the cell population: the optimal sampling time differs according to tissue, with liver and bone marrow at opposite extremes among proliferating somatic tissues: in bone marrow, the mutant frequency appears to reach a maximum at extremely short sampling times and then decreases over 28 days following an acute treatment; in liver the induced mutation frequency increases over the month following exposure, reaches a maximum, and remains relatively constant thereafter. There are insufficient data available for other tissues to support any conclusion regarding optimal sampling time. The results of studies carried out on a given chemical using similar experimental protocols suggest that the TGR assays show good qualitative reproducibility in both somatic and germ cells, and quantitative reproducibility over a limited range of conditions and laboratories. The data are insufficient to draw conclusions regarding the quantitative reproducibility of the assays over a wider range of conditions. Although there exists a theoretical possibility that ex vivo and in vitro mutations may arise during the course of a TGR experiment, these types of mutations are expected to be extremely rare in a properly conducted experiment using the major TGR models. For positive selection systems, any such mutations will not be detected. The weight of evidence suggests that transgenes and endogenous genes respond in approximately the same manner to mutagens in the few instances where direct comparisons are possible. Sensitivity is determined in large part by the SMF: the higher SMF in transgenes, as compared to testable endogenous genes, appears to reduce their sensitivity, especially when

acute treatments are used. The sensitivity of transgenes can be enhanced by increasing the administration time. Mutagens that induce deletions are likely to be detected more easily in certain endogenous genes than in transgenes due to phenotypic selection issues. A very high proportion of the TGR experiments carried out to date have examined the activity of compounds that are known to be strong mutagens. A limited number of noncarcinogens have been evaluated with TGRs. The specificity of the TGR assay for predicting carcinogenicity is generally higher than other assays evaluated in this paper. However, additional data from TGR assays on noncarcinogens is required. Molecular analysis of induced mutations in transgenic targets is possible and provides additional information in situations where high interindividual variation is observed and clonal expansion is suspected, when weak responses are obtained, or when mechanistic information is desired. However, DNA sequence analysis of mutants is laborious and adds to the cost of the experiment; sequencing would not normally be required when testing drugs or chemicals for regulatory applications, particularly where a clear positive or negative result is obtained. 4. Analysis of the predictivity of TGR assays for carcinogenicity is hindered somewhat by the fact that TGR data are available for only a small number of noncarcinogens. Of the 90 carcinogens and 13 noncarcinogens that have been assessed using TGR assays, the following conclusions can be drawn regarding the predictivity and complementarity of TGR assays in comparison to a range of other OECD in vitro and in vivo genotoxicity tests.. The TGR assay has high sensitivity and positive predictivity, meaning that most carcinogens have positive results in TGR and there is a high probability that a chemical with a positive result in TGR is a carcinogen. As is the case with most genotoxicity assays, the TGR assay exhibits low specificity and negative predictivity, meaning that relatively few noncarcinogens were negative in TGR and there is a low probability that a chemical with a negative result in TGR is a noncarcinogen; however, it was no worse than the Salmonella mutagenicity assay in this regard. Considering all the best batteries and single assays examined using the current dataset, best positive and negative predictivity was obtained from the TGR assay alone, the Salmonella mutagenicity assay alone, and a battery in which a positive result in TGR or Salmonella was considered positive and negative results in both assays was considerd negative. Despite the lack of substantial increases in predictive values of the test batteries compared with the component assays alone, the test batteries had a much lower false negative rate. TGR and the in vivo micronucleus (MN) assay exhibited significant complementary - i.e. they offered greater predictivity for the detection of mutagens when combined than when alone - consistent with the fact that these two assays measure different genotoxic endpoints. TGR was usually positive for those carcinogens that were positive in Salmonella and the in vitro chromosomal aberration (CA) assay. In contrast, in vivo MN had a much higher false negative rate for the same chemicals. If in vivo confirmation of positive results from both Salmonella and in vitro CA is warranted, TGR is likely a better choice than in vivo MN. For chemicals having positive Salmonella and negative in vitro CA results (presumptive gene mutagens), selecting either TGR or in vivo MN as the in vivo confirmation assay did not markedly affect the proportion of correct carcinogenicity predictions. For chemicals having positive in vitro CA and negative Salmonella results (presumptive clastogens), selecting in vivo MN as the in vivo confirmation assay led to a slightly higher proportion of correct carcinogenicity predictions than did selecting TGR. For those carcinogens with negative results in both Salmonella and in vitro CA, adding either TGR or in vivo MN to the test battery did not improve the overall predictivity, since neither assay identified the carcinogens missed by the in vitro assays. 5. Recommendations, based on internationally harmonized criteria, are made regarding the proper conduct of a TGR assay. These

recommendations relate to accepted characteristics of a transgenic rodent mutation assay, treatment protocols, and post treatment sampling procedures. Of particular importance in optimizing TGR protocols are two experimental variables - the administration time and the sampling time. Based on observations that mutations accumulate with each treatment, a repeated-dose regimen for a period of 28 days is strongly encouraged, with sampling at 3 days following the final treatment. If slowly proliferating tissues are of particular importance, then a longer sampling time may be more appropriate. Additional confidence in the recommended test protocol will be provided by research that examines the following: The influence of the administration time on the observed mutation frequency for weak mutagens. It has not conclusively been determined if data (especially negative results) from experiments using an administration time of less than 28 days should be discounted, if a 28 day treatment period is sufficiently long to permit the detection of weak mutagen-induced mutations in all tissues, or if weak mutagens could in fact be detected using treatment times shorter than 28 days. The influence of the frequency of treatment on the observed mutation frequency. The difference between weekly and daily administrations on mutant frequency and on the ultimate conclusions of transgenic rodent experiments has not yet been thoroughly investigated. The influence of sampling time following repeat administrations on the mutant frequency in both slowly and rapidly dividing tissue, particularly when examining weak mutagens. At the current time there are insufficient comparative data available for a range of tissues. Recommendations are made regarding how a TGR assay might be used within a short-term test battery for assessing new compounds. The test battery consists of various combinations of four assays - Salmonella, in vitro CA, in vivo MN and TGR. This proposed strategy is based on the conclusions obtained from the predictivity analysis, and the relative costs of the in vivo assays. TGR assays may also be used to resolve conflicts between in vitro and in vivo tests that are currently components of the standard genotoxicity test battery - Salmonella, in vitro CA and in vivo MN. In situations where the standard test battery has been conducted and there are conflicting results -particularly in situations where Salmonella has a positive result but in vivo MN is negative - TGR may be conducted as an additional test to resolve the conflict. Recommended test strategies are based on an analysis of the existing data. Confidence in these recommendations would be enhanced by additional experimental data in the following areas. TGR data for additional non-carcinogens to increase the proportion of non-carcinogens in the data set. Additional testing to fill data gaps for chemicals having known TGR assay but missing data from the Salmonella, in vitro CA, or in vivo MN assays. The testing of additional chemicals using an accepted test guideline for TGR mutation assays. Based on the information and analyses in this review, there is sufficient evidence to support the recommendation that the OECD undertake the development of a Test Guideline on Transgenic Rodent Gene Mutation Assays. Accordingly, it is recommended that the OECD establish an Expert Working Group to develop such a Test Guideline, and serve as an international forum for undertaking any additional research that would lead to the development of a fuller understanding of the variables surrounding the conduct of TGR mutation assays.

67. Laurant P, Chanut E, Bobillier-Chaumont S, Gaillard E, Jacquot C, Trouvin JH, Berthelot A. (2003) Attenuation of the development of DOCA salt hypertension by a high Mn intake in the rat. Trace Elements and Electrolytes 20(3):172-180.
The effects of a high Mn intake on blood pressure, vascular reactivity and central catecholamine levels were studied in DOCA salt-hypertensive rats. High Mn intake inhibited blood pressure

elevation in DOCA salt rats but did not modify it in normotensive rats. The blood pressure-lowering effect of Mn was associated with inhibited cardiac hypertrophy and increased natriuresis. Pharmacological studies in blood vessels showed that high Mn intake normalized vasoconstriction and sensitivity to norepinephrine of isolated and perfused mesenteric vascular beds from DOCA salt rats. Furthermore, high Mn intake improved the endothelium- and NO-dependent relaxation in isolated aortae from DOCA salt-hypertensive rats but not in those from normotensive rats. Norepinephrine levels were higher in the hypothalamus of DOCA salt-hypertensive rats than in those of normotensive rats, and high Mn intake decreased norepinephrine levels in hypothalamus of DOCA salt rats. In conclusion, a high Mn intake attenuated the development of hypertension with beneficial vascular and central effects. Mechanisms related to the pathophysiological development of DOCA salt hypertension may be involved.

68. Lee B, Hiney JK, Pine MD, Srivastava VK, Dees WL. (2007) Manganese stimulates luteinizing hormone releasing hormone secretion in prepubertal female rats: hypothalamic site and mechanism of action. Journal of Physiology-London 578(3):765-772.
We have shown recently that Mn2+ stimulates gonadotropin secretion via an action at the hypothalamic level, and a diet supplemented with a low dose of the element is capable of advancing the time of female puberty. In this study, we used an in vitro approach to investigate the mechanism by which Mn2+ induces luteinizing hormone-releasing hormone (LHRH) secretion from prepubertal female rats. Themedial basal hypothalamus from 30-day-old rats was incubated in Locke solution for 30 min to assess basal LHRH secretion, then incubated with buffer alone or buffer plus either a nitric oxide synthase (NOS) inhibitor (N-monomethyl-L-arginine (NMMA); 300 or 500 mu M) or a soluble guanylyl cyclase (sGC) inhibitor (1H-[1,2,4] oxadiazolo[4,3- a] quinoxalin-1-one(ODQ); 100 or 250 mu M) for another 30 min. Finally, the incubation continued for a further 30 min, but in the presence of MnCl2 (50 or 250 mu M) to assess the effect of the blockers on stimulated LHRH secretion. Both 50 and 250 mu M MnCl2 stimulated LHRH release ($P < 0.05$ and $P < 0.01$, respectively). The addition of 300-500 mu M NMMA to the medium did not block Mn2+-stimulated release of LHRH, even with the higher dose of MnCl2. Furthermore, while 50, 100 and 250 mu M MnCl2 all significantly induced LHRH release, the two lowest doses did not stimulate total nitrite released from the same tissue, an effect only observed with the highest dose. Taken together, these data suggest that Mn2+ is not an effective stimulator of NO. Conversely, inhibiting sGC with ODQ blocked the Mn2+-stimulated secretion of LHRH in a dose-dependent manner, indicating that GC is the site of action of Mn2+. Additionally, we showed that Mn2+ stimulated cGMP and LHRH from the same tissues, and that downstream blocking of protein kinase G formation with KT5823 (10 mu M) inhibited Mn2+-induced LHRH release. These data demonstrate that the principal action of Mn2+ within the hypothalamus is to activate sGC directly and/or as a cofactor with available NO, hence generating cGMP and resulting in prepubertal LHRH release.

69. Lee B, Pine M, Johnson L, Rettori V, Hiney JK, Dees WL. (2006) Manganese acts centrally to activate reproductive hormone secretion and pubertal development in male rats. Reproductive Toxicology 22(4):580-585.
Manganese (Mn) is an important element for normal growth and reproduction. Because Mn accumulates in the hypothalamus and is capable of stimulating puberty-related hormones in female rats, we assessed whether this metal could cause similar effects in male rats. We have

demonstrated that MnCl2, when administered acutely into the third ventricle of the brain, acts dose dependently to stimulate luteinizing hormone (LH) release. Furthermore, there was a dose dependent stimulation in the secretion of LH-releasing hormone (LHRH) from the medial basal hypothalamus in vitro, and administration of an LHRH receptor antagonist in vivo blocks Mn-induced LH release. To assess potential chronic effects of the metal, male pups were supplemented with 10 or 25 mg MnCl2 per kg by gastric gavage from day 15 until days 48 or 55, at which times developmental signs of spermatogenesis were assessed. Results demonstrate that while significant effects were not observed with the 10 mg/kg dose, the animals receiving the 25 mg/kg dose showed increased LH ($p < 0.05$), FSH ($p < 0.01$) and testosterone ($p < 0.01$) levels at 55 days of age. Furthermore, there was a concomitant increase in both daily sperm production ($p < 0.05$) and efficiency of spermatogenesis ($p < 0.05$), demonstrating a Mn-induced acceleration in spermatogenesis. Our results suggest Mn is a stimulator of prepubertal LHRH/LH secretion and may facilitate the normal onset of male puberty. These data also suggest that the metal may contribute to male precocious pubertal development should an individual be exposed to low but elevated levels of Mn too early in life.

70. Malecki EA, Devenyi AG, Barron TF, Mosher TJ, Eslinger P, Flaherty-Craig CV, Rossaro L. (1999) Iron and manganese homeostasis in chronic liver disease: Relationship to pallidal T1-weighted magnetic resonance signal hyperintensity. Neurotoxicology 20(4):647-652.
The hyperintense signal in the globus pallidus of cirrhotic patients on T1-weighted magnetic resonance (MR) imaging has been postulated to arise from deposition of paramagnetic manganese(2+) (Mn). Intestinal absorption of both iron and Mn are increased in iron deficiency; iron deficiency may therefore increase susceptibility to Mn neurotoxicity. To investigate the relationships between MR signal abnormalities and Mn and Fe status, 21 patients with chronic liver disease were enrolled (alcoholic liver disease, 5; primary biliary cirrhosis, 9; primary sclerosing cholangitis, 3; hepatitis B virus, 2; hepatitis C virus, 1; alpha 1-antitrypsin deficiency 1). Signal hyperintensity in the pallidum on axial T1 weighted images repetition time/evolution time: 500 ms/15ms was observed in 13 of 21 subjects: four patients had mild hyperintensity, three moderate, and six exhibited marked hyperintensity. Erythrocyte Mn concentrations were positively correlated with the degree of the MR hyperintensity (Kendall's tau-b=0.52, $P<0.005$). The log of erythrocyte Mn concentration was also inversely correlated with all measures of iron status: hemoglobin (Pearson's R=-0.73, $P<0.0005$); hematocrit (R=-0.62, $P<0.005$); serum Fe concentrations (R=-0.65, $P<0.005$); and TIBC saturation (R=-0.62, $P<0.005$). These findings confirm the association of Mn with the development of pallidal hyperintensity in patients with liver disease. We further found that iron deficiency is an exacerbating factor probably because of increased intestinal absorption of Mn. We therefore recommend that patients with chronic liver disease avoid Mn supplements without concurrent iron supplementation.

71. Malecki EA, Lo HC, Yang H, Davis CD, Ney DM, Greger JL. (1995) Tissue Manganese Concentrations and Antioxidant Enzyme-Activities in Rats Given Total Parenteral-Nutrition with and without Supplemental Manganese. Journal of Parenteral and Enteral Nutrition 19(3):222-226.
Background: Manganese is an essential but potentially toxic mineral. Parenteral administration of manganese via total parenteral nutrition (TPN) bypasses homeostatic mechanisms (intestinal absorption and presystemic hepatic elimination). Our objective in this study was to determine the

effect of supplemental manganese in TPN solutions on manganese status in a rat model. Methods: Male Sprague-Dawley rats underwent jugular catheterization and were given 61.0 +/- 0.4 g/d TPN solution providing 0.5 +/- 0.2 nmol manganese/g (Mn-; n = 6) or 16 +/- 3 nmol manganese/g (Mn+; n = 7) for 7 days. Reference rats (RF; n = 8) were fed a purified diet containing 1.3 mmol manganese/g. Results: Liver manganese decreased in both TPN groups, but tibia, spleen, and pancreas manganese concentrations were greater in Mn+ rats than in Mn- or RF rats. Although no treatment differences were seen in heart or liver manganese superoxide dismutase activity, heart copper-zinc superoxide dismutase activity was lower in the Mn+ rats than in Mn- or RF rats ($p < .05$). Glutathione peroxidase activity was depressed in livers of both Mn- and Mn+ rats relative to RF rats ($p < .001$), which was not due to selenium deficiency. Conclusions: Supplemental parenteral manganese is taken up to a greater extent by peripheral tissues than the liver. In this first report of antioxidant enzyme activities in animals maintained with TPN, we found that TPN as well as supplemental manganese can influence antioxidant enzyme activities. We conclude that it is generally unnecessary and potentially toxic to supplement TPN solutions with manganese during short-term usage.

72. Masumoto K, Suita S, Taguchi T, Yamanouchi T, Nagano M, Ogita K, Nakamura M, Mihara F. (2001) Manganese intoxication during intermittent parenteral nutrition: Report of two cases. Journal of Parenteral and Enteral Nutrition 25(2):95-99.
Background and Methods: The administration of trace elements is thought to be needed in patients receiving long-term parenteral nutrition. Recently, manganese intoxication or deposition was documented in such patients. We report two cases of manganese intoxication during intermittent parenteral nutrition including manganese. Manganese had been administered for 4 years at a frequency of one or two times per week in one case and for 5 years at a frequency of one or two times per month in the other case. Both cases showed mild symptoms with headache and dizziness. One case had mild hepatic dysfunction and the other did not. The whole-blood manganese level increased in one case, but not in the other case. T1-weighted magnetic resonance images revealed symmetrical high-intensity areas in basal ganglia and thalamus in both cases. After the administration of manganese was stopped, these symptoms all disappeared and the magnetic resonance images abnormalities gradually improved in both patients. Mild long-term manganese intoxication is thus considered to occur regardless of the frequency of using a manganese supplement. Conclusions: Patients should be carefully monitored when receiving long-term parenteral nutrition including manganese, even when the manganese dose is small and the frequency of receiving a manganese supplement is low.

73. Mergler D, Baldwin M. (1997) Early manifestations of manganese neurotoxicity in humans: An update. Environmental Research 73(1-2):92-100.
BIOSIS COPYRIGHT: BIOL ABS. It is possible to detect early signs of neurotoxic dysfunction associated with occupational and environmental exposure to manganese; neurophysiologic and neurobehavioral tests can be used in the absence of clinical manifestations. Although outcomes from individual studies vary, they collectively show a pattern of slowing motor functions, increased tremor, reduced response speed, enhanced olfactory sense, possible memory and intellectual deficits, and mood changes. This overall portrait is consistent with the action of manganese on the central nervous system. In reports to date, there is little consistency in dose-effect relationships between internal parameters of manganese exposure (blood manganese,

urinary manganese, hair manganese) and external measures and neurologic outcomes. Several studies suggest the existence of dose-effect relationships, but additional clarification is needed.

74. Miller KB, Caton JS, Finley JW. (2006) Manganese depresses rat heart muscle respiration. Biofactors 28(1):33-46.
It has previously been reported that moderately high dietary manganese (Mn) in combination with marginal magnesium (Mg) resulted in ultrastructural damage to heart mitochondria. Manganese may replace Mg in biological functions, including the role of enzyme cofactor. Manganese may accumulate and substitute for Mg during the condition of Mg-deficiency. The objective of the current study was to determine whether high Mn alters heart muscle respiration and Mg-enzyme activity as well as whole body Mn retention under marginal Mg. An additional objective was to determine whether high Mn results in increased oxidative stress. In experiment 1: forty-eight rats were fed a 2 x 3 factorial arrangement of Mn (10, 100, or 1000 mg/kg) and Mg (200 or 500 mg/kg). In experiment 2: thirty-two rats were fed one of four diets in a 2 x 2 factorial arrangement of Mn (10 or 250 mg/kg) and Mg (200 or 500 mg/kg). In experiment 3: thirty-two rats were fed one of four diets in a 2 x 2 factorial arrangement of Mn (10 or 650 mg/kg) and Mg (200 or 500 mg/kg). In experiment 2, high Mn and marginal Mg reduced ($P < 0.05$) oxygen consumption of left ventricle muscle. Marginal Mg, but not Mn, reduced ($P < 0.05$) activity of sarcoplasmic reticulum calcium-ATPase enzyme. Dietary Mg had no affect on Mn-54 kinetics, but high dietary Mn decreased ($P < 0.01$) absorption, retention, and rate of excretion of Mn-54. Neither cellular stress, measured by Comet assay, nor antioxidant activities were increased by high Mn. A strong interaction ($P < 0.001$) between increasing Mn and adequate Mg on hematology was observed. These results confirm previous research in swine that high Mn alters myocardial integrity as well as function, but not as a result of altered calcium transport or oxidative stress.

75. Oikawa S, Hirosawa I, Tada-Oikawa S, Furukawa A, Nishiura K, Kawanishi S. (2006) Mechanism for manganese enhancement of dopamine-induced oxidative DNA damage and neuronal cell death. Free Radical Biology and Medicine 41(5):748-756.
Although the cause of dopammergic cell death in Parkinson's disease is still poorly understood, there is accumulating evidence suggesting that metal ions can be involved in the processes. We investigated the effect of manganese on cell death and DNA damage in Pd12 ells treated with dopamine. Mn(II) enhanced cell death induced by dopamine. Mn(II) also increased the 8-oxo-7,8-dihydro-2-deoxyguanosine (8-oxodG) contents of DNA in PC12 cells treated with dopamine. To clarify the mechanism of cellular DNA damage, we investigated DNA damage induced by dopamine and Mn(II) using (32)p-labeled DNA fragments. Mn(II) enhanced Cu(II)-dependent DNA damage by dopamine. The Mn(II)-enhanced DNA damage was greatly increased by NADH. Piperidine and forrnamidopyrimidine-DNA glycosylase treatment induced cleavage sites mainly at T and G of the 5'-TG-3' sequence, respectively. Bathocuproine, a Cu(I) chelator, and catalase inhibited the DNA damage. Oxygen consumption and UV-visible spectroscopic measurements showed that Mn(II) enhanced autoxidation of dopamine with H2O2 formation. These results suggest that reactive species derived from the reaction of H2O2 with Cu(I) participates in Mn(II)-enhanced DNA damage by dopamine plus Cu(II). Therefore, it is concluded that oxidative DNA damage induced by dopamine in the presence of Mn(II), NADH, and Cu(II) is possibly linked to the degeneration of dopaminergic neurons.

76. Ostiguy C, Asselin P, Malo S. (2006) The emergence of manganese-related health problems in Quebec: An integrated approach to evaluation, diagnosis, management and control. Neurotoxicology 27(3):350-356.
This paper describes the strategy developed in Quebec to deal with an emerging problem: manganism in welders. Only two cases of manganism had been reported to the Commission de la sante et de la securite du travail (CSST, Workers Compensation Board in Quebec) before 2000. In the fall of 200 1, the CSST was informed of a possible cluster of manganism and received 20 compensation claims from one plant. Action was rapidly taken to understand and tackle this emerging problem. Under the leadership of the CSST, a coordinating working group implemented medical and environmental subcommittees involving representatives of the different partners of the prevention network. After a literature review to document the health risks associated with manganese and the lack of some important information, a panel of international experts was formed to try to reach agreement on the parameters to consider in the diagnosis and management of manganism. The CSST compensation management policies would be adjusted accordingly. Simultaneously, all the available industrial hygiene data were analyzed to estimate where and at what levels workers were exposed to manganese. To complete these data, the exposure of workers in more than 50 industrial plants was evaluated and existing control measures were documented. All these data have been presented for a revision of the Quebec permissible exposure limit (PEL). In this integrated approach, the next step targets the formation of neurologists and neuropsychologists for a standardized medical evaluation, to complete workplace evaluation in the high risk sectors, inform workers and employers and recommend control measures where required, based on a revised PEL. Many strategies will be used to inform the prevention network (about 1000 people), employers and employees of the risks of overexposure to manganese and of the measures to control exposure in all the plants where workers are susceptible to be exposed to manganese.

77. Park J, Yoo CI, Sim CS, Kim HK, Kim JW, Jeon BS, Kim KR, Bang OY, Lee WY, Yi Y and others. (2005) Occupations and Parkinson's disease: A multi-center case-control study in South Korea. Neurotoxicology 26(1):99-105.
Objective: We performed a hospital based case-control study in South Korea (1) to clarify the role of occupational exposure, and especially manganese (Mn) exposure in the etiology of Parkinson's disease (PD) and (2) to discover the association between any occupations and PD. Methods: We selected two groups, PD patient group (NI) and controls (N-2). Three hundred sixty-seven consecutive outpatients with PD (177 men, 190 women) and 309 controls were interviewed about life style, past history, family history, education level, and occupational history etc. We employed a range of industrial categories as defined by section (the most broad category) and division (sub-category) of the Korea Standard Industry Code (KSIC) Manual. Along with KSIC, we also used the Korea Standard Classification of Occupations (KSCO) as proxies of occupational exposure. The odds ratios (ORs) and 95% confidence intervals (CA), adjusted for age, sex, smoking status, and education level are presented. Results: As regarding the exposure to hazardous materials, especially Mn, more subjects in the control group than the PD patient group 'have worked in the occupations with potential exposure to Mn ($P < 0.001$). Ever having worked in 'agriculture, hunting, and forestry' section of industry was positively associated with PD (OR 1.88), and 'agriculture production crops (OR 1.96)'division of industry

was positively associated with PD. On the other hand, ever having worked in the 'manufacturing (OR 0.56)', 'transportation (OR 0.28)' section of industry, and 'transporting (OR 0.20)' division of industry were negatively associated with PD. 'Drivers (OR 0.13)'division of occupation also was negatively associated with PD. Conclusions: To our knowledge, this is the first case-control studies to find an inverse relationship between 'transporting' or 'technicians like machinery engineers' as his/her longest job and PD risk. Because of this unexpected finding, our work should be replicated in various populations.

78. Park RM, Bowler RM, Eggerth DE, Diamond E, Spencer KJ, Smith D, Gwiazda R. (2006) Issues in neurological risk assessment for occupational exposures: The Bay Bridge welders. Neurotoxicology 27(3):373-384.
The goal of occupational risk assessment is often to estimate excess lifetime risk for some disabling or fatal health outcome in relation to a fixed workplace exposure lasting a working lifetime. For sub-chronic or sub-clinical health effects measured as continuous variables, the benchmark dose method can be applied, but poses issues in defining impairment and in specifying acceptable levels of excess risk. Such risks may also exhibit a dose-rate effect and partial reversibility such that effects depend on how the dose is distributed over time. Neurological deficits as measured by a variety of increasingly sensitive neurobehavioral tests represent one such outcome, and the development of a parkinsonian syndrome among welders exposed to manganese fume presents a specific instance. Welders employed in the construction of piers for a new San Francisco-Oakland Bay Bridge in San Francisco were previously evaluated using a broad spectrum of tests. Results for four of those tests (Rey-Osterrieth Complex Figure Test, Working Memory Index, Stroop Color Word Test and Auditory Consonant Trigrams Test) were used in the benchmark dose procedure. Across the four outcomes analyzed, benchmark dose estimates were generally within a factor of 2.0, and decreased as the percentile of normal performance defining impairment increased. Estimated excess prevalence of impairment, defined as performance below the 5th percentile of normal, after 2 years of exposure at the current California standard (0.2 mg/m(3), 8 h TWA), ranged 15-32% for the outcomes studied. Because these exposures occurred over a 1-2-year period, generalization to lifetime excess risk requires further consideration of the form of the exposure response and whether short-term responses can be generalized to equivalent 45-year period. These results indicate unacceptable risks at the current OSHA PEL for manganese (5.0 mg/m(3) 15 min) and likely at the Cal OSHA PEL as well.

79. Pecze L, Papp A, Nagymajtenyi L. (2004) Changes in the spontaneous and stimulus-evoked activity in the somatosensory cortex of rats on acute manganese administration. Toxicology Letters 148(1-2):125-131.
In this work, acute effects of inorganic manganese exposure on nervous electrical activity of rats were investigated. Young adult male Wistar rats were prepared for recording in anaesthesia and spontaneous cortical as well as stimulus-evoked cortical and peripheral nervous activity was recorded before and after i.p. administration of 25 and 50 mg/kg Mn2+. The alterations found resulted possibly from several known neuronal effects of manganese. The frequency shift of spontaneous cortical activity, and increased latency and decreased amplitude of the peripheral nerve action potential, were probably due to the Mn2+-induced impairment of the mitochondria, whereas the increased amplitude of the evoked cortical response, to the effect on glutamatergic transmission.

80. Ramesh GT, Ghosh D, Gunasekar PG. (2002) Activation of early signaling transcription factor, NF-kappa B following low-level manganese exposure. Toxicology Letters 136(2):151-158.
Occupational and environmental exposure to manganese (Mn2+) is an increasing problem. It manifests neuronal degeneration characterized by dyskinesia resembling Parkinson's disease. The study was performed to test the hypotheses whether exposure to Mn2+ alters cellular physiology and promotes intracellular signaling mechanism in dopaminergic neuronal cell line. Since transcription factors have been shown to play an essential role in the control of cellular proliferation and survival, catecholaminergic rich pheochromocytoma (PC12) cells were used to measure changes in the DNA binding activities of nuclear factor kappa B (NF-kappaB) by electrophoretic mobility shift assay (EMSA) following Mn2+ (0.1-10 muM) exposure. Cells that were exposed to Mn2+ produced five-fold-activation of transcription factor NF-kappaB DNA binding activity. This remarkable increase was seen within 30-60 min period of Mn2+ exposure. Activation of NF-kappaB DNA binding activity by Mn2+ at 1.0 muM correlated with proteolytic degradation of the inhibitory subunit IkappaBalpha as evidenced in cytosol. Additional experiments on NF-kappaB reporter gene assay also showed increased NF-kappaB gene expression at 1.0 and 5.0 muM Mn2+ and this was completely blocked in the presence of NF-kappaB translocation inhibitor, IkappaBalpha-DN supporting that NF-kappaB induction occurred during Mn2+ exposure. In addition, Mn2+ exposure to PC 12 cells led to activation of signal responsive mitogen activated proteinexposure. In addition, Mn2+ exposure to PC 12 cells led to activation of signal responsive mitogen activated protein kinase kinase (MAPKK). These results suggest that Mn2+ at a low dose appears to induce the expression of immediate early gene, NF-kappaB through MAPKK by a mechanism in which IKBoc phosphorylation may be involved.) (C) 2002 Elsevier Science Ireland Ltd. All rights reserved.

81. Rao KVR, Norenberg MD. (2004) Manganese induces the mitochondrial permeability transition in cultured astrocytes. Journal of Biological Chemistry 279(31):32333-32338.
Manganese is known to cause central nervous system injury leading to parkinsonism and to contribute to the pathogenesis of hepatic encephalopathy. Although mechanisms of manganese neurotoxicity are not completely understood, chronic exposure of various cell types to manganese has shown oxidative stress and mitochondrial energy failure, factors that are often implicated in the induction of the mitochondrial permeability transition (MPT). In this study, we examined whether exposure of cultured neurons and astrocytes to manganese induces the MPT. Cells were treated with manganese acetate (10-100 muM), and the MPT was assessed by changes in the mitochondrial membrane potential and in mitochondrial calcein fluorescence. In astrocytes, manganese caused a dissipation of the mitochondrial membrane potential and decreased the mitochondrial calcein fluorescence in a concentration- and time-dependent manner. These changes were completely blocked by pretreatment with cyclosporin A, consistent with induction of the MPT. On the other hand, similarly treated cultured cortical neurons had a delayed or reduced MPT as compared with astrocytes. The manganese-induced MPT in astrocytes was blocked by pretreatment with antioxidants, suggesting the potential involvement of oxidative stress in this process. Induction of the MPT by manganese and associated mitochondrial dysfunction in astrocytes may represent key mechanisms in manganese neurotoxicity.

82. Reaney SH, Kwik-Uribe CL, Smith DR. (2002) Manganese oxidation state and its implications for toxicity. Chemical Research in Toxicology 15(9):1119-1126.
Manganese (Mn) is ubiquitous in mammalian systems and is essential for proper development and function, though it can also be toxic at elevated exposures. While essential biologic functions of Mn depend on its oxidation state [e.g., Mn(II), Mn(III)], little is known about how the oxidation state of elevated Mn exposures affect cellular uptake, and function/toxicity. Here we report the dynamics of EPR measurable Mn(II) in fresh human plasma and cultured PC12 cell lysates as a function of exposure to either manganese(II) chloride or manganese(III) pyrophosphate, and the effects of exposure to Mn(II) versus Mn(III) on total cellular aconitase activity and cellular Mn uptake. The results indicate that Mn(II) or Mn(III) added in vitro to fresh human plasma or cell lysates yielded similar amounts of EPR measurable Mn(II). In contrast, Mn added as Mn(III) was significantly more effective in inhibiting total cellular aconitase activity, and intact PC 12 cells accumulated significantly more Mn when exposures occurred as Mn(III)., Collectively, these data reflect the dynamic nature of Mn speciation in simple biological systems, and the importance of Mn oxidation/speciation state in mediating potential cellular toxicity. This study supports concern over increased environmental exposures to Mn in different oxidation states [Mn(II), Mn(III), and Mn(IV)] that may arise from combustion products of. the gasoline antiknock additive methycyclopentadienyl manganese tricarbonyl (MMT).

83. Rico H, Gomez-Raso N, Revilla M, Hernandez ER, Seco C, Paez E, Crespo E. (2000) Effects on bone loss of manganese alone or with copper supplement in ovariectomized rats - A morphometric and densitomeric study. European Journal of Obstetrics Gynecology and Reproductive Biology 90(1):97-101.
Objective: The aim of this study was to examine the effect of manganese (Mn) alone and with the addition of copper (Cu) in the inhibition of osteopenia induced by ovariectomy (OVX) in rats. Study conditions: Four lots of 100-day-old female Wistar rats were divided into experimental groups of 15 each. One group received a diet supplemented with 40 mg/kg of Mn per kilogram of feed (OVX+Mn). The second group received the same diet as the first, but with an additional 15 mg/kg of copper (OVX+Mn+Cu). The third group of 15 OVX and the fourth group of 15 Sham-OVX received no supplements. At the conclusion of the 30-day experiment, the rats were slaughtered and their femurs and fifth lumbar vertebrae were dissected. Femoral and vertebral length were measured with caliper and bones were weighed on a precision balance. The bone mineral content (BMC) and bone density (BMD) of the femur (F-BMC, mg and F-BMD, mg/cm(2)) and the fifth lumbar vertebra (V-BMC, mg and V-BMD, mg/cm(2)) were measured separately with dual energy X-ray absorptiometry. Results: The F-BMD, mg/cm(2) was lower in the OVX than in the Sham-OVX group ($P<0.0001$) and in the other two groups receiving mineral supplements ($P<0.005$ in both). F-BMC, mg was significantly lower in the OVX group than in the other three ($P<0.0001$ in all cases), Calculations for V-BMC, mg and V-BMD, mg/cm(2) are similar to findings in the femur. Conclusions: These data show that a Mn supplement is an effective inhibitor of loss of bone mass after OVX, both on the axial and the peripheral levels, although this effect is not enhanced with the addition of Cu.

84. Ross C, O'Reilly DS, McKee R. (2006) Potentially clinically toxic concentrations of whole blood manganese in a patient fed enterally with a high tea consumption. Annals of Clinical Biochemistry 43:226-228.
This report describes a 37-year-old female patient who after seven years on intermittent overnight enteral feeding supplementation was noted to have an increased whole blood manganese concentration. Manganese toxicity is well documented after pathological absorption through inhalation via the lungs, or after intravenous administration to patients on long-term total parenteral nutrition. A dietary history revealed high tea consumption. The association between high blood manganese concentrations and enteral/oral nutrition does not appear to have previously been described.

85. Seth P, Husain MM, Gupta P, Schoneboom BA, Grieder FB, Mani H, Maheshwari RK. (2003) Early onset of virus infection and up-regulation of cytokines in mice treated with cadmium and manganese. Biometals 16(2):359-368.
A substantial database indicates that a large number of environmental pollutants, chemicals and therapeutic agents to which organisms are exposed cause immunotoxicity. The suppression of immune functions may cause increased susceptibility of the host to a variety of microbial pathogens potentially resulting in a life-threatening state. Evaluation of the immunotoxic potential of chemical xenobiotics is of great concern and, therefore, we have investigated the impact of exposure of inorganic metals, specifically cadmium (Cd) and manganese (Mn) on Encephalomyocarditis virus (EMCV), Semliki Forest virus (SFV), and Venezuelan Equine Encephalitis virus (VEEV) infection. Pretreatment with a single, oral dose of Cd or Mn increased the susceptibility of mice to a sub-lethal infection of these viruses as observed by increased severity of symptoms and mortality compared to untreated controls. An early onset of virus infection was found in brains of Cd and Mn treated animals. Histopathological observations of the brain indicate evidence of inflammation and greater tissue pathology in Cd- or Mn-exposed mice compared to control animals. Meningitis and vascular congestion was seen in virus infected mice in all the metal treated groups, and further, the perivascular inflammation appeared earlier in treated mice compared to control. Encephalitis was maximum in Cd pretreated mice. Widespread environmental contamination of metals and the potential for their exposure and subsequent infection of humans or animals is indicative that further studies of these and all other metals are important to understand the effect of environmental pollution on human health.

86. Sjogren B, Iregren A, Frech W, Hagman M, Johansson L, Tesarz M, Wennberg A. (1996) Effects on the nervous system among welders exposed to aluminium and manganese. Occupational and Environmental Medicine 53(1):32-40.
Objectives-The purpose was to study the effects on the nervous system in welders exposed to aluminium and manganese. Methods-The investigation included questionnaires on symptoms, psychological methods (simple reaction time, finger tapping speed and endurance, digit span, vocabulary, tracking, symbol digit, cylinders, olfactory threshold, Luria-Nebraska motor scale), neurophysiological methods (electroencephalography, event related auditory evoked potential (P-300), brainstem auditory evoked potential, and diadochokinesometry) and assessments of blood and urine concentrations of metals (aluminium, lead, and manganese). Results-The welders exposed to aluminium (n = 38) reported more symptoms from the central nervous system than the control group (n = 39). They also had a decreased motor function in five tests. The effect was dose related in two of these five tests. The median exposure of aluminium

welders was 7065 hours and they had about seven times higher concentrations of aluminium in urine than the controls. The welders exposed to manganese (n = 12) had a decreased motor function in five tests. An increased latency of event related auditory evoked potential was also found in this group. The median manganese exposure was 270 hours. These welders did not have higher concentrations of manganese in blood than the controls. Conclusions-The neurotoxic effects found in the groups of welders exposed to aluminium and manganese are probably caused by the aluminium and manganese exposure, respectively. These effects indicate a need for improvements in the work environments of these welders.

87. Sunderman FW. (2001) Review: Nasal toxicity, carcinogenicity, and olfactory uptake of metals. Annals of Clinical and Laboratory Science 31(1):3-24.
Occupational exposures to inhalation of certain metal dusts or aerosols can cause loss of olfactory acuity, atrophy of the nasal mucosa, mucosal ulcers, perforated nasal septum, or sinonasal cancer. Anosmia and hyposmia have been observed in workers exposed to Ni- or Cd-containing dusts in alkaline battery factories, nickel refineries, and cadmium industries. Ulcers of the nasal mucosa and perforated nasal septum have been reported in workers exposed to Cr(VI) in chromate production and chrome plating, or to As(III) in arsenic smelters. Atrophy of the olfactory epithelium has been observed in rodents following inhalation of NiSO4 or alpha Ni3S2. Cancers of the nose and nasal sinuses have been reported in workers exposed to Ni compounds in nickel refining, cutlery factories, and alkaline battery manufacture, or to Cr(VI) in chromate production and chrome plating. III animals, several metals (eg, Al, Cd, Co, Hg, Mn, Ni, Zn) have been shown to pass via olfactory receptor neurons from the nasal lumen through the cribriform plate to the olfactory bulb. Some metals (eg. Mn, Ni, Zn) can cross synapses in the olfactory bulb and migrate via secondary olfactory neurons to distant nuclei of the brain. After nasal instillation of a metal-containing solution, transport of the metal via olfactory axons can occur rapidly within hours or a few days (eg, Mn), or slowly other days or weeks (eg, Ni). The olfactory bulb tends to accumulate certain metals (eg, Al, Bi, Cu, Mn, Zn) with greater avidity than other regions of the brain. The molecular mechanisms responsible for metal translocation in olfactory neurons and deposition in the olfactory bulb are unclear, but complexation by metal-binding molecules such as carnosine (beta -alanyl-L-histidine) may be involved.

88. Takeda A. (2004) Essential trace metals and brain function. Yakugaku Zasshi-Journal of the Pharmaceutical Society of Japan 124(9):577-585.
Trace metals such as zinc, manganese, and iron are necessary for the growth and function of the brain. The transport of trace metals into the brain is strictly regulated by the brain barrier system, i.e., the blood-brain and blood-cerebrospinal fluid barriers. Trace metals usually serve the function of metalloproteins in neurons and glial cells, while a portion of trace metals exists in the presynaptic vesicles and may be released with neurotransmitters into the synaptic cleft. Zinc and manganese influence the concentration of neurotransmitters in the synaptic cleft, probably via the action against neurotransmitter receptors and transporters and ion channels. Zinc may be an inhibitory neuromodulator of glutamate release in the hippocampus, while neuromodulation by manganese might mean functional and toxic aspects in the synapse. Dietary zinc deficiency affects zinc homeostasis in the brain, followed by an enhanced susceptibility to the excitotoxicity of glutamate in the hippocampus. Transferrin may be involved in the physiological transport of iron and manganese into the brain and their utilization there. It is reported that the brain transferrin concentration is decreased in neurodegenerative diseases such as Alzheimer's disease

and Parkinson's disease and that brain iron metabolism is also altered. The homeostasis of trace metals in the brain is important for brain function and also for the prevention of brain diseases.

89. TERA. 2008. ITER Database. Concurrent Technologies Corporation and Toxicology Excellence for Risk Assessment (TERA).
Chemical Name: Manganese CAS Registry Number: 7439-96-5

90. Wasserman GA, Liu XH, Parvez F, Ahsan H, Levy D, Factor-Litvak P, Kline J, van Geen A, Slavkovich V, Lolacono NJ and others. (2006) Water manganese exposure and children's intellectual function in Araihazar, Bangladesh. Environmental Health Perspectives 114(1):124-129.
Exposure to manganese via inhalation has long been known to elicit neurotoxicity in adults, but little is known about possible consequences of exposure via drinking water. In this study, we report results of a cross-sectional investigation of intellectual function in 142 10-year-old children in Araihaza, Bangladesh, who had been consuming tube-well water with an average concentration of 793 mu g Mn/L and 3 mu g arsenic/L. Children and mothers came to our field clinic, where children received a medical examination in which weight, height, and head circumference were measured. Children's intellectual function was assessed on tests drawn from the Wechsler Intelligence Scale for Children, version III, by summing weighted items across domains to create Verbal, Performance, and Full-Scale raw scores. Children provided urine specimens for measuring urinary As and creatinine and were asked to provide blood samples for measuring blood lead, As, Mn, and hemoglobin concentrations. After adjustment for sociodemographic covariates, water Mn was associated with reduced Full-Scale, Performance, and Verbal raw scores, in a dose-response fashion; the low level of As in water had no effect. In the United States, roughly 6% of domestic household wells have Mn concentrations that exceed 300 mu g Mn/L, the current U.S. Environmental Protection Agency, lifetime health advisory level. We conclude that in both Bangladesh and the United States, some children are at risk for Mn-induced neurotoxicity.

91. Yokel RA, Lasley SM, Dorman DC. (2006) The speciation of metals in mammals influences their toxicokinetics and toxicodynamics and therefore human health risk assessment. Journal of Toxicology and Environmental Health-Part B-Critical Reviews 9(1):63-85.
Chemical form (i.e., species) can influence metal toxicokinetics and toxicodynamics and should be considered to improve human health risk assessment. Factors that influence metal speciation (and examples) include: (1) carrier-mediated processes for specific metal species (arsenic, chromium, lead and manganese), (2) valence state (arsenic, chromium, manganese and mercury), (3) particle size (lead and manganese), (4) the nature of metal binding ligands (aluminum, arsenic, chromium, lead, and manganese), (5) whether the metal is an organic versus inorganic species (arsenic, lead, and mercury), and (6) biotransformation of metal species (aluminum, arsenic, chromium, lead, manganese and mercury). The influence of speciation on metal toxicokinetics and toxicodynamics in mammals, and therefore the adverse effects of metals, is reviewed to illustrate how the physicochemical characteristics of metals and their handling in the body (toxicokinetics) can influence toxicity (toxicodynamics). Generalizing from mercury, arsenic, lead, aluminum, chromium, and manganese, it is clear that metal speciation influences mammalian toxicity. Methods used in aquatic toxicology to predict the interaction among metal speciation, uptake, and toxicity are evaluated. A classification system is presented to show that

the chemical nature of the metal can predict metal ion toxicokinetics and toxicodynamics. Essential metals, such as iron, are considered. These metals produce low oral toxicity under most exposure conditions but become toxic when biological processes that utilize or transport them are overwhelmed, or bypassed. Risk assessments for essential and nonessential metals should consider toxicokinetic and toxicodynamic factors in setting exposure standards. Because speciation can influence a metal's fate and toxicity, different exposure standards should be established for different metal species. Many examples are provided which consider metal essentiality and toxicity and that illustrate how consideration of metal speciation can improve the risk assessment process. More examples are available at a website established as a repository for summaries of the literature on how the speciation of metals affects their toxicokinetics.

92. Yoritaka A, Hattori N, Mori H, Kato K, Mizuno Y. (1997) An immunohistochemical study on manganese superoxide dismutase in Parkinson's disease. Journal of the Neurological Sciences 148(2):181-186.
We report an immunohistochemical study on manganese superoxide dismutase (Mn SOD) in Parkinson's disease (PD) patients and age-matched control subjects. Overall appearance of immunostaining intensity of nigral neurons did not differ significantly between the PD patients and the control subjects. However, when the immunostaining intensity of each neuron was semiquantitatively analyzed, both very intensely stained (more than normal) neurons as well as neurons stained only weakly were more frequently detected in the lateral part than in the medial and the central parts of the substantia nigra in PD patients. As a result, the proportion of normally stained neurons was significantly smaller in the lateral part of the substantia nigra in PD patients; however, the overall distribution of the neurons among the three rating grades for immunostaining did not differ significantly. The immunostaining intensity of the neuropils in the medial and the central part of the substantia nigra tended to be more intense in PD patients than in the control subjects. Our results suggest up-regulation of Mn SOD mainly in the dendritic processes of the less involved nigral neurons. (C) 1997 Elsevier Science B.V.

93. Zheng W, Aschner M, Ghersi-Egea JF. (2003) Brain barrier systems: a new frontier in metal neurotoxicological research. Toxicology and Applied Pharmacology 192(1):1-11.
The concept of brain barriers or a brain barrier system embraces the blood-brain interface, referred to as the blood-brain barrier, and the blood-cerebrospinal fluid (CSF) interface, referred to as the blood-CSF barrier. These brain barriers protect the CNS against chemical insults, by different complementary mechanisms. Toxic metal molecules can either bypass these mechanisms or be sequestered in and therefore potentially deleterious to brain barriers. Supportive evidence suggests that damage to blood-brain interfaces can lead to chemical-induced neurotoxicities. This review article examines the unique structure, specialization, and function of the brain barrier system, with particular emphasis on its toxicological implications. Typical examples of metal transport and toxicity at the barriers, such as lead (Pb), mercury (Hg), iron (Fe), and manganese (Mn), are discussed in detail with a special focus on the relevance to their toxic neurological consequences. Based on these discussions, the emerging research needs, such as construction of the new concept of blood-brain regional barriers, understanding of chemical effect on aged or immature barriers, and elucidation of the susceptibility of tight junctions to toxicants, are identified and addressed in this newly evolving field of neurotoxicology. They represent both clear challenges and fruitful research domains not only in

neurotoxicology, but also in neurophysiology and pharmacology. (C) 2003 Elsevier Science (USA). All rights reserved.

4.4 OTHER ENDPOINT-SPECIFIC STUDIES [e.g., in vivo neurological, immunological studies]

Key References (0)

There were no key references identified for this section.

Supporting References (0)

There were no supporting references identified for this section.

4.5 MECHANISTIC DATA AND OTHER STUDIES IN SUPPORT OF THE MODE OF ACTION

Key References (25)

1. Ali SF, Duhart HM, Newport GD, Lipe GW, Slikker W. (1995) Manganese-Induced Reactive Oxygen Species - Comparison between Mn+2 and Mn+3. Neurodegeneration 4(3):329-334.
Manganese (Mn) is an essential element, the deficiency or excess of which is known to cause neurotoxicity in experimental animals and man. The mechanism of action of Mn neurotoxicity is still unclear. The present study was designed to evaluate whether in vitro or in vivo exposure to Mn produced reactive oxygen species (ROS). We also sought to determine if a single injection of Mn produces changes in monoamines concentration in different regions of rat brain. Adult Sprague-Dawley rats were dosed with 0, 50 or 100 mg/kg, ip with either MnCl2 (Mn+2) or MnOAc (Mn+3) and were sacrificed 1 h after the dose was administered. Brains were quickly removed and dissected for neurochemical analysis. ROS were measured by a molecular probe, 2',7'-dichlorofluorescein diacetate (DCFH-DA), and monoamines and their metabolites were measured by HPLC/EC. In vitro exposure to MnCl2 (1-1000 mu M) produced dose-dependent increases of ROS in striatum whereas MnOAc produced similar increases at much lower concentrations (1-100 mu M) In vivo exposure to MnOAc (Mn+3) produced significant increases of ROS in caudate nucleus and hippocampus, whereas MnCl2 (Mn+2) produced significant effects only in hippocampus. Concentrations of dopamine, serotonin and their metabolites (DOPAC, HVA and 5-HIAA) were not altered with acute injections of either MnCl2 or MnOAc. These data suggest that both divalent and trivalent manganese induce ROS, however, Mn+3 is an order of magnitude more potent than Mn+2. (C) 1995 Academic Press Limited

2. Brown S, Taylor NL. (1999) Could mitochondrial dysfunction play a role in manganese toxicity? Environmental Toxicology and Pharmacology 7(1):49-57.
Individuals suffering from manganese toxicity exhibit several symptoms, including mitochondrial dysfunction, which are similar to those frequently observed in cases of Parkinson's disease. We review the literature concerning manganese toxicity and mitochondrial function, and

propose a simple conceptual model of the aetiology of manganese toxicity which involves an interaction between inhibition of mitochondrial energy transduction, generation of free radicals and mutations of the mitochondrial genome. This conceptual model prompts a number of relatively simple experiments which would provide a test of the model. (C) 1999 Elsevier Science B.V. All rights reserved.

3. Chetty CS, Reddy GR, Suresh A, Desaiah D, Ali SF, Slikker WJ. (2001) Effects of manganese on inositol polyphosphate receptors and nitric oxide synthase activity in rat brain. International Journal of Toxicology 20(5):275-280.
The neurotoxic effects of excessive exposure to manganese (Mn) include degeneration of dopaminergic neurons, impairment of energy metabolism, and perturbations in phosphoinositide (PI) hydrolysis leading to altered calcium (Ca2+) homeostasis. This study is designed to assess the in vitro and in vivo effects of Mn on Ca2+/calmodulin-dependent neuronal nitric oxide synthase (nNOS) activity and on the regulation of inositol 1,4,5-trisphosphate (InsP(3)) and inositol 1,3,4,5-tetrakisphosphate (InsP(4)) receptors involved in intracellular and extracellular mobilization of Ca2+. In vivo Mn exposure significantly increased H-3-InsP(3) and H-3-InsP(4) binding in the cerebellum and the cerebral cortex in a dose-dependent manner. However, in vitro Mn decreased H-3-InsP(3) binding and increased H-3-InsP(4) binding. In vitro and in vivo exposure of Mn inhibited nNOS activity in the cerebellum and the cerebral cortex. Immunohistochemical studies also showed a notable decrease in nNOS immunoreactivity in the granule cell layer of the cerebellum, whereas no significant changes were observed in the cerebral cortex. These data suggest that Mn neurotoxicity may be due to altered calcium homeostasis by its modulation of inositol polyphosphate receptors. Further, the inhibition of nNOS by Mn is of considerable importance because NO regulates a number of neurotransmitter functions.

4. Clegg MS, Donovan SM, Monaco MH, Baly DL, Ensunsa JL, Keen CL. (1998) The influence of manganese deficiency on serum IGF-1 and IGF binding proteins in the male rat. Proceedings of the Society for Experimental Biology and Medicine 219(1):41-47.
Young male rats subjected to a dietary manganese (Mn) deficiency respond to the deficiency by reducing their growth rate. The growth hormone (GH)/insulin-like growth factor (IGF) axis is critical for linear growth; this system is exquisitely sensitive to the nutritional state of the animal, In this study, we examined circulating GH, IGF-1, and insulin levels in Mn-deficient (-Mn; fed a 0.5 mu g Mn/g diet) and sufficient (+Mn; fed a 45 mu g Mn/g diet) male Sprague-Dawley rats. Additionally, we examined the distribution of circulating IGF binding proteins (IGFBPs) in animals of both dietary groups as these proteins modulate IGF-1 action in vivo and in vitro, and have been demonstrated to be altered in a number of nutritional and physiological states. Body weight was significantly reduced in -Mn relative to +Mn rats. Consistent with other studies, daily food intake was not altered. However, cumulative food intake (over 3 months) was marginally lower in -Mn versus +Mn animals. -Mn animals displayed lower circulating concentrations of IGF-1 (66% of control levels) and insulin (60% of control levels) despite having significant elevations in circulating GH levels relative to +Mn animals (140% of control levels), The IGFBP profile of -Mn animals reflected their elevated GH status, as we observed increased binding of tracer (I-125-IGF-1) to the circulating IGFBP-3 complex (120% of control binding) using native chromatography techniques, Interestingly, the lower circulating insulin concentrations of -Mn animals did not result in dramatic elevations in lower-molecular-weight

binding proteins. In summary, we demonstrate that in young male rats, Mn deficiency is associated with alterations in IGF metabolism. These alterations may contribute to the growth and bone abnormalities observed in -Mn animals.

5. Diaz-Veliz G, Mora S, Gomez P, Dossi MT, Montiel J, Arriagada C, Aboitiz F, Segura-Aguilar J. (2004) Behavioral effects of manganese injected in the rat substantia nigra are potentiated by dicumarol, a DT-diaphorase inhibitor. Pharmacology Biochemistry and Behavior 77(2):245-251.
The purpose of this study was to evaluate the contribution of DT-diaphorase inhibition to in vivo neurodegenerative effects of dopamine (DA) oxidation to the corresponding o-quinones. The neurotoxicity to nigrostriatal DA neurons was induced by injection of manganese pyrophosphate (Mn3+) complex as a prooxidizing agent alone or together with the DT-diaphorase inhibitor dicumarol into the right rat substantia nigra. The behavioral effects were compared with those induced after selective lesions of dopaminergic neurons with 6-hydroxydopamine (6-OHDA). Intranigral injection of Mn3+ and Mn3+ plus dicumarol produced significant impairment in motor behavior compared with control animals. However, the effect seen in the Mn3+ plus dicumarol injected group was significantly more severe than that observed in the Mn3+ alone injected group. In motor activity and rearing behavior, the simultaneous injection of Mn3+ plus dicumarol produced a 6-OHDA-like impairment. Similar effects were observed in the acquisition of a conditioned avoidance response (CAR). Dicumarol significantly impaired avoidance conditioning although without affecting the motor behavior. The behavioral effects were correlated to the extent of striatal tyrosine hydroxylase (TH)-positive fiber loss. Rats receiving unilateral intranigral Mn3+ and Mn3+ plus dicumarol injections exhibited a significant reduction in nigrostriatal TH-positive fiber density in medial forebrain bundle compared with the contralateral noninjected side. In conclusion, this study provides evidence that the neurotoxicity of Mn3+ in vivo is potentiated by DT-diaphorase inhibition, suggesting that this enzyme could play a neuroprotective role in the nigrostriatal DA systems.

6. Erikson KM, Dobson AW, Dorman DC, Aschner M. (2004) Manganese exposure and induced oxidative stress in the rat brain. Science of the Total Environment 334-35:409-416.
Neurotoxicity linked to excessive brain manganese levels can occur as a result of high level Mn exposures and/or metabolic aberrations (liver disease and decreased biliary excretion). Increased brain manganese levels have been reported to induce oxidative stress, as well as alterations in neurotransmitter metabolism with concurrent neurobehavioral and motor deficits. Two putative mechanisms in which manganese can produce oxidative stress in the brain are: (1) via its oxidation of dopamine, and (2) interference with normal mitochondrial respiration. Measurements of antioxidant species (e.g., glutathione and metallothionein), and the abundance of proteins (enzymes) exquisitely sensitive to oxidation (e.g., glutamine synthetase) have been commonly used as biomarkers of oxidative stress, particularly in rat brain tissue. This paper examines the link between manganese neurotoxicity in the rat brain and common pathways to oxidative stress.

7. Erikson KM, Jones SR, Aschner M. (2005) Brain manganese accumulation due to toxic exposure is mediated by the dopamine transporter. Faseb Journal 19(5):A1033-A1034.

8. Gonzalez-Reyes RE, Gutierrez-Alvarez AM, Moreno CB. (2007) Manganese and epilepsy: A systematic review of the literature. Brain Research Reviews 53(2):332-336.
Manganese is an essential trace element for the development and function of the central nervous system. Alterations in manganese concentrations, whether excessive or deficient, can be accompanied by convulsions. This article represents a systematic review of available quantitative evidence that might clarify this issue. We searched The Cochrane Library, Medline and LILACS databases from January 1966 through June 2006 and reviewed all resulting English and Spanish language publications, as well as those possibly relevant in other languages based on their abstracts. The final selection included for this review comprises all investigations in humans and animals that compared manganese levels in any tissue of a group with spontaneous or induced convulsions (with or without antiepileptic treatment) and a convulsion-free control group. The literature search identified thirteen publications since then relevant to the issue, four of which failed to meet our criteria for inclusion. of the remaining nine, six were in humans and three in rodents. At present, there is no satisfactory explanation for the relationship between low manganese levels and the presence of convulsions. There is a documented correlation between low blood manganese levels and the presence of convulsions in both humans and animals. The lack of evidence indicating whether this is a cause or an effect of the convulsions clearly justifies more detailed follow-up investigations in humans.

9. HaMai D, Bondy SC. (2004) Oxidative basis of manganese neurotoxicity. Redox-Active Metals in Neurological Disorders. NEW YORK: NEW YORK ACAD SCIENCES. pp 129-141.
Exposure to excessive levels of manganese, an essential trace element, can evoke severe psychiatric and extrapyramidal motor dysfunction closely resembling Parkinson's disease. The clinical manifestations of manganese toxicity arise from focal injury to the basal ganglia. This region, characterized by intense consumption of oxygen and significant dopamine content, can incur mitochondrial dysfunction, depletion of levels of peroxidase and catalase, and catecholamine biochemical imbalances following manganese exposure. The site specificity of the pathology and the nature of the cellular damage caused by manganese have been attributed to its capacity to produce cytotoxic levels of free radicals. However, support for such a pro-oxidant role for manganese has been largely limited to inferences drawn from histopathological observations. More recently, research efforts into the molecular details of manganese toxicity have provided evidence of an etiological relationship between oxidative stress and manganese-related neurodegeneration. This review focuses on studies that evaluate the redox chemistry of manganese during the neurodegenerative process and its molecular consequences.

10. Hussain SM, Javorina AK, Schrand AM, Duhart HM, Ali SF, Schlager JJ. (2006) The interaction of manganese nanoparticles with PC-12 cells induces dopamine depletion. Toxicological Sciences 92(2):456-463.
This investigation was designed to determine whether nano-sized manganese oxide (Mn-40nm) particles would induce dopamine (DA) depletion in a cultured neuronal phenotype, PC-12 cells, similar to free ionic manganese (Mn2+). Cells were exposed to Mn-40nm, Mn2+ (acetate), or known cytotoxic silver nanoparticles (Ag-15nm) for 24 h. Phase-contrast microscopy studies show that Mn-40nm or Mn2+ exposure did not greatly change morphology of PC-12 cells. However, Ag-15nm and AgNO3 produce cell shrinkage and irregular membrane borders compared to control cells. Further microscopic studies at higher resolution demonstrated that Mn-40nm nanoparticles and agglomerates were effectively internalized by PC-12 cells.

Mitochondrial reduction activity, a sensitive measure of particle and metal cytotoxicity, showed only moderate toxicity for Mn-40nm compared to similar Ag-15nm and Mn2+ doses. Mn-40nm and Mn2+ dose dependently depleted DA and its metabolites, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), while Ag-15nm only significantly reduced DA and DOPAC at concentrations of 50 mu g/ml. Therefore, the DA depletion of Mn-40nm was most similar to Mn2+, which is known to induce concentration-dependent DA depletion. There was a significant increase (> 10-fold) in reactive oxygen species (ROS) with Mn-40nm exposure, suggesting that increased ROS levels may participate in DA depletion. These results clearly demonstrate that nanoscale manganese can deplete DA, DOPAC, and HVA in a dose-dependent manner. Further study is required to evaluate the specific intracellular distribution of Mn-40nm nanoparticles, metal dissolution rates in cells and cellular matrices, if DA depletion is induced in vivo, and the propensity of Mn nanoparticles to cross the blood-brain barrier or be selectively uptaken by nasal epithelium.

11. Malecki EA, Devenyi AG, Beard JL, Connor JR. (1999) Existing and emerging mechanisms for transport of iron and manganese to the brain. Journal of Neuroscience Research 56(2):113-122.
The metals iron (Fe) and manganese (Mn) are essential for normal functioning of the brain. This review focuses on recent developments in the literature pertaining to Fe and Mn transport, These metals are treated together because they appear to share several transport mechanisms. In addition, several neurological diseases such as Alzheimer's Disease, Parkinson's Disease, and Huntington's Disease are all associated with Fe mismanagement in the brain, particularly in the striatum and basal ganglia. Similarly, Mn accumulation in brain also appears to target the same brain regions. Therefore, stringent regulation of the concentration of these metals in the brain is essential, The homeostatic mechanisms for these metals must be understood in order to design neurotoxicity prevention strategies. J, Neurosci, Res. 56:113-122, 1999, (C) 1999 Wiley-Liss, Inc.

12. Martin CJ. (2006) Manganese neurotoxicity: Connecting the dots along the continuum of dysfunction. Neurotoxicology 27(3):347-349.
Three different manifestations of manganese neurotoxicity have been described. The first, and historically most prominent, is often termed manganism: a dramatic extrapyramidal syndrome following acute, overwhelming exposure. While resembling Idiopathic Parkinson's Disease (IPD), most authorities have regarded the two conditions as clinically and pathophysiologically distinct. The second manifestation, reported by several investigators starting in the 1980s, consisted of subclinical and subfunctional declines in the performance of specialized neuropsychological tests. The implication of these cross-sectional findings was that, when superimposed upon age-related attritional effects, increased rates of clinical disease could result. In this decade, it has been proposed that manganese exposure may play a role in the development of IPD itself. Investigating the relationship between these three manifestations should be a priority for future research. (c) 2005 Elsevier Inc. All rights reserved.

13. Normandin L, Hazell AS. (2002) Manganese neurotoxicity: An update of pathophysiologic mechanisms. Metabolic Brain Disease 17(4):375-387.
The central nervous system, and the basal ganglia in particular, is an important target in manganese neurotoxicity, a disorder producing neurological symptoms similar to that of

Parkinson's disease. Increasing evidence suggests that astrocytes are a site of early dysfunction and damage; chronic exposure to manganese leads to selective dopaminergic dysfunction, neuronal loss, and gliosis in basal ganglia structures together with characteristic astrocytic changes known as Alzheimer type II astrocytosis. Astrocytes possess a high affinity, high capacity, specific transport system for manganese facilitating its uptake, and sequestration in mitochondria, leading to a disruption of oxidative phosphorylation. In addition, manganese causes a number of other functional changes in astrocytes including an impairment of glutamate transport, alterations of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase, production of nitric oxide, and increased densities of binding sites for the "peripheral-type" benzodiazepine receptor (a class of receptor predominantly localized to mitochondria of astrocytes and involved in oxidative metabolism, mitochondrial proliferation, and neurosteroid synthesis). Such effects can lead to compromised energy metabolism, resulting in altered cellular morphology, production of reactive oxygen species, and increased extracellular glutamate concentration. These consequences may result in impaired astrocytic-neuronal interactions and play a major role in the pathophysiology of manganese neurotoxicity.

14. Pamphlett R, McQuilty R, Zarkos K. (2001) Blood levels of toxic and essential metals in motor neuron disease. Neurotoxicology 22(3):401-410.
Toxic and essential metals have been implicated in the pathogenesis of sporadic motor neuron disease (SMND), but attempts to measure blood levels of these metals have led to contradictory results. We, therefore, measured blood levels of various metals using paired SMND/controls. In 20 subjects with SMND (15 males, five females, mean age 56.8 years) and 20 partner controls (15 females, five males, mean age 55.0 years) cadmium, lead, mercury, copper, zinc and selenium levels were measured in blood, plasma and red cells with inductively coupled plasma mass spectrometry and manganese levels with atomic absorption spectrophotometry. Results were analysed using non-parametric tests. Hypoosmotic red blood cell fragility was estimated in six SMND/control pairs to see if hemolysis could account for increased metal levels. The plasma cadmium level was significantly raised in SMND cases (P = 0.005), but with considerable overlap between SMND and controls. No other metal levels were significantly different, though plasma lead in SMND had a tendency to be higher than controls. No difference in red cell fragility was found between groups. In conclusion, plasma levels of cadmium were raised in this SMND group, but the biological significant of this is uncertain. The measurement of metals in the blood of SMND cases seems unwarranted for routine diagnostic testing. (C) 2001 Published by Elsevier Science Inc.

15. Ranasinghe JGS, Liu MC, Sakakibara Y, Suiko M. (2000) Manganese administration induces the increased production of dopamine sulfate and depletion of dopamine in Sprague-Dawley rats. Journal of Biochemistry 128(3):477-480.
Sprague-Dawley rats were used as an experimental model for investigating the effects of manganese poisoning on the serum levels of unsulfated and sulfated forms of dopamine and its biosynthetic precursors, L-Dopa and L-p-tyrosine. Groups of rats were treated daily with Mn2+ (20 mg or 40 mg; in the form of MnSO4) or Na+ (20 mg; in the form of Na2SO4). High performance liquid chromatography (HPLC) analysis of the serum samples taken after a 50-day experimental period revealed that the serum level of dopamine sulfate increased by more than 10 times compared with untreated control rats or rats treated with sodium sulfate. In contrast, there was a dramatic decrease (by as much as 4.8 times) in the serum level of unsulfated dopamine in

manganese-treated rats. The serum levels of L-Dopa sulfate and L-p-tyrosine sulfate were also markedly elevated, although not as much as those of dopamine sulfate. Meanwhile, the serum levels of unsulfated L-Dopa and L-p-tyrosine showed no dramatic changes. Atomic absorption spectrophotometric analysis revealed in general an accumulation of manganese in the four organ samples taken from manganese-treated rats. Compared with liver, heart, and kidney, the highest degree of manganese accumulation in manganese-treated rats appeared to be in brain. These results together suggested a role for manganese in stimulating the dopamine-sulfating sulfotransferases in brain, thereby leading to the depletion of dopamine in vivo.

16. Rovetta F, Catalani S, Steimberg N, Bonlottl J, Gilberti ME, Mariggio MA, Mazzoleni G. (2007) Organ-specific manganese toxicity: a comparative in vitro study on five cellular models exposed to MnCl2. Toxicology in Vitro 21(2):284-292.
Manganese (Mn) is both an essential nutrient and a toxicant, with specific effects on liver and kidney (acute exposure) and on central nervous system (CNS) (chronic exposure). Mn neurotoxicity includes neurobehavioral disorders and extra-pyramidal motor dysfunctions (manganism), possibly due to focal injuries to the basal ganglia. Even if widely investigated, the molecular mechanisms responsible for Mn toxicity remain to be clarified. Aim of this study was to identify suitable in vitro models to investigate these molecular pathways. To this purpose we compared the effect of manganese chloride on four cell lines, representative of the main target organs of Mn toxicity in vivo. HepG2 and MDCK cell lines were selected for liver and kidney, respectively; glial GL15 and neuronal SHSY5Y cells were used as models of CNS components. To complete the "motor system" model, skeletal muscle C2Cl2 cells were also included. Our results demonstrate that hepatic, renal, glial and neuronal cell types differently react to Mn, mirroring the specific in vivo response of the tissue they represent. This confirms their value as suitable in vitro models to study Mn-related toxic events. Interestingly, also muscle C2Cl2 cells showed a noticeable sensitivity to Mn, preferential targets being differentiated myotubes.

17. Sloot WN, Korf J, Koster JF, DeWit LEA, Gramsbergen JBP. (1996) Manganese-induced hydroxyl radical formation in rat striatum is not attenuated by dopamine depletion or iron chelation in vivo. Experimental Neurology 138(2):236-245.
The present studies were aimed at investigating the possible roles of dopamine (DA) and iron in production of hydroxyl radicals ((OH)-O-.) in rat striatum after Mn2+ intoxication. For this purpose, DA depletions were assessed concomitant with in vivo 2,3- and 2,5-dihydroxybenzoic acid (DHBA) formation from the reaction of salicylate with (OH)-O-., of which 2,3-DHBA is a nonenzymatic adduct. Following intrastriatal Mn2+ injection, marked 2,3-DHBA increases were observed in a time- and dose-dependent fashion reaching maximum levels at 6-18 h and a plateau beyond 0.4 mu mol (fourfold increase). The delayed increase of 2,3-DHBA levels suggests that Mn2+ induces (OH)-O-. formation in the living brain by an indirect process. The early DA depletion (2 h) and relatively late (OH)-O-. formation (6 h) indicate independent processes by Mn2+. In addition, depletion of DA (about 90%) by reserpine pretreatment did not significantly alter Mn2+-induced 2,3-DHBA formation or the extent of DA depletion, suggesting that DA or DA autoxidation are not participating in Mn2+ induced (OH)-O-. formation in vivo. Furthermore, Mn2+ injection did not significantly alter the low molecular weight iron pool in striatum, and co-injections of the iron-chelator deferoxamine with Mn2+ into striatum did not significantly attenuate Mn2+-induced 2,3-DHBA formation. These findings suggest no role of

chelatable iron in generation of Mn2+-induced (OH)-O-., but do not exclude a role for mitochondrial heme-iron or peroxynitrite (Fe-independent) in Mn2+-induced (OH)-O-. formation. (C) 1996 Academic Press, Inc.

18. Takeda A. (2003) Manganese action in brain function. Brain Research Reviews 41(1):79-87.
Manganese, an essential trace metal, is supplied to the brain via both the blood-brain and the blood-cerebrospinal fluid barriers. There are some mechanisms in this process and transferrin may be involved in manganese transport into the brain. A large portion of manganese is bound to manganese metalloproteins, especially glutamine synthetase in astrocytes. A portion of manganese probably exists in the synaptic vesicles in glutamatergic neurons and the manganese is dynamically coupled to the electrophysiological activity of the neurons. Manganese released into the synaptic cleft may influence synaptic neurotransmission. Dietary manganese deficiency, which may enhance susceptibility to epileptic functions, appears to affect manganese homeostasis in the brain, probably followed by alteration of neural activity. On the other hand, manganese also acts as a toxicant to the brain because this metal has prooxidant activity. Abnormal concentrations of manganese in the brain, especially in the basal ganglia, are associated with neurological disorders similar to Parkinson's disease. Understanding the movement and action of manganese in synapses may be important to clarify the function and toxicity of manganese in the brain. (C) 2002 Elsevier Science B.V. All rights reserved.

19. Takeda A. (2004) Analysis of brain function and prevention of brain diseases: the action of trace metals. Journal of Health Science 50(5):429-442.
Trace metals such as zinc, manganese, and iron are necessary for the growth and function of the brain. The transport of trace metals into the brain is strictly regulated by the brain barrier system, i.e., the blood-brain and blood-cerebrospinal fluid barriers. The alteration of homeostasis of trace metals in the brain is associated with brain diseases. Trace metals usually serve the function of metalloproteins in neurons and glial cells, while a portion of trace metals exists in the presynaptic vesicles and may be released with neurotransmitters into the synaptic cleft. Zinc and manganese influence the concentration of neurotransmitters in the synaptic cleft, probably via the action against neurotransmitter receptors and transporters and ion channels. Zinc may be an inhibitory neuromodulator of glutamate release in the hippocampus, while neuromodulation by manganese might have both functional and toxic aspects in the synapse. Dietary zinc deficiency affects zinc homeostasis in the brain, followed by an enhanced excitotoxicity of glutamate in the hippocampus. Transferrin may be involved in the physiologic transport of iron and manganese into the brain and their utilization there.

20. Takeda A, Sotogaku N, Oku N. (2002) Manganese influences the levels of neurotransmitters in synapses in rat brain. Neuroscience 114(3):669-674.
previously taken up by the amygdala is released along with known neurotransmitters into the extracellular space during stimulation with 100 mM KCl. The possibility of manganese release from neuron terminals in a calcium- and impulse-dependent manner was examined by using the in vivo microdialysis method in the present study. The increase of Mn-54 release into the amygdalar extracellular space during stimulation with high K+ was inhibited by addition of 1 muM tetrodotoxin. This increase of Mn-54 release into the extracellular space by stimulation with high K was also observed in the hippocampus, but not in the substantia nigra. The increment of glutamate in the extracellular space during stimulation with high K+ was highly

correlated with that of Mn-54, suggesting that manganese is concurrently released with glutamate from neuron terminals. The level of Mn-54 in the extracellullar space in the hippocampus was increased with that of glutamate, but not with those of GABA and glycine, during stimulation with 100 mM KCl in the presence of 30 muM kainate. This increase was more marked than during stimulation with 30 muM kainate alone. It is likely that manganese is released from glutamatergic neuron terminals. When the rat hippocampus was perfused with artificial cerebrospinal fluid containing 20 or 200 nM MnCl2, the levels of glutamate, aspartate and GABA in the perfusate were dose-dependently decreased during perfusion with manganese. The present findings demonstrate that manganese released into the synaptic cleft may influence synaptic neurotransmission.

21. Tjalkens R. (2005) Neuro-Glial Interactions In Basal Ganglia Dysfunction: Insights From Manganese Neurotoxicity. Toxicol Sci 84(1-S):337.
During periods of stress or injury, astroglia can undergo phenotypic transformation into an activated state whereupon expression of inflammatory mediators is dramatically increased, to the detriment of associated neurons. Neuronal injury in several disorders of the basal ganglia, including manganism and Parkinsons disease, is associated with regional increases in expression of inflammatory mediators and activation of astroglia, with subsequent overproduction of nitric oxide (NO). The present studies explore the role of astroglial activation in basal ganglia dysfunction by examining a prototypic neurotoxicant of the basal ganglia, manganese, and its capacity to elicit expression of inflammatory genes in astroglia. Although playing various essential physiological roles in the central nervous system, manganese in excess is the cause of an extrapyramidal neurodegenerative disorder in humans that produces progressive dyskinesia, emotional lability, and certain neurological deficits resembling Parkinsons disease. It is postulated that astroglial-derived NO mediates neuronal injury induced by manganese exposure and that manganese potentiates the effects of pro-inflammatory cytokines on induction of nitric oxide synthase in astroglial cells. This hypothesis is tested utilizing: 1) subchronic in vivo exposure to manganese in mice; 2) an astroglial-neuronal co-culture system; and 3) primary astrocyte cultures to examine molecular signaling events relevant to inflammatory gene expression.Manganese potentiates cytokine-induced expression of nitric oxide synthase in astrocytes that increases apoptosis in co-cultured neurons in an NFkappaB- dependent fashion. Dysregulation of intracellular calcium and mitochondrial dysfunction in astroglia mitochondria appear to be pivotal to induction of nitric oxide production. Thus, therapeutic strategies that target the molecular signaling pathways regulating expression of nitric oxide synthase in astroglia may be effective in mitigating neuronal injury in degenerative conditions of the basal ganglia.

22. Villalobos V, Estevez J, Novo E, Bonilla E. (2001) Effects of chronic manganese treatment on mouse brain (H-3) spiroperidol binding parameters: In vivo and in vitro studies. Revista Cientifica-Facultad De Ciencias Veterinarias 11(4):306-313.
The in vivo and in vitro effects of Mn on the binding of (H-3) spiroperidol to mouse brain was assessed. (H-3) spiroperidol bind ing parameters (Kd and Bmax) in striatum, hypothalamus and olfactory bulb did not change by Mn administration (5mg/kg/day) for 9 weeks. On the other hand, preincubation of mouse brain homogenates with increasing concentrations of Mn (0.05-10 mM) and dopamine (10 mM) resulted in a significant rise in the (H-3) spiroperidol specific

binding with a Mn concentration of 75 muM or higher. Binding assays carried out using homogenates preincubated with 10 mM dopamine and 75 muM Mn showed an increase in Bmax and Kd. These studies demonstrated that Mn administration does not after the binding pattern of (H-3) spiroperidol. The increase in Bmax and Kd observed in the in vitro assays, when dopamine and Mn are added to the incubation medium seem to be originated from changes in cell membranes, leading to the exposure of new and different binding sites.

23. Yavorskaya V, Pelekhova O, Grebenyuk G, Chernyshova T. (2006) Manganese toxic encephalopathy with parkinsonism. European Journal of Neurology 13:289-290.

24. Zheng W, Ren S, Graziano JH. (1998) Manganese inhibits mitochondrial aconitase: A mechanism of manganese neurotoxicity. Brain Research 799(2):334-342.
The symptoms of Mn-induced neurotoxicity resemble those of Parkinson's diseases. Since iron (Fe) appears to play a pivotal role in pathophysiology of Parkinson's disease, we set out to test the hypothesis that alterations in Fe-requiring enzymes such as aconitase contribute to Mn-induced neurotoxicity. Mitochondrial fractions prepared from rat brain were preincubated with MnCl2 in vitro, followed by the enzyme assay. Mn treatment significantly inhibited mitochondrial aconitase activity (24% inhibition at 625 mu M to 81% at 2.5 mM, $p < 0.05$). The inhibitory effect was reversible and Mn-concentration dependent, and was reversed by the addition of Fe (0.05-1 mM) to the reaction mixture. In an in vivo chronic Mn exposure model, rats received intraperitoneal injection of 6 mg/kg Mn as MnCl2 once daily for 30 consecutive days. Mn exposure led to a region-specific alteration in total aconitase (i.e., mitochondrial + cytoplasmic): 48.5% reduction of the enzyme activity in frontal cortex ($p < 0.01$), 33.7% in striatum ($p < 0.0963$), and 20.6% in substantia nigra ($p < 0.139$). Chronic Mn exposure increased Mn concentrations in serum, CSF, and brain tissues. The elevation of Mn in all selected brain regions (range between 3.1 and 3.9 fold) was similar in magnitude to that in CSF (3.1 fold) rather than serum (6.1 fold). The present results suggest that Mn alters brain aconitase activity, which may lead to the disruption of mitochondrial energy production and cellular Fe metabolism in the brain.

25. Zwingmann C, Leibfritz D, Hazell AS. (2004) Brain energy metabolism in a sub-acute rat model of manganese neurotoxicity: An ex vivo nuclear magnetic resonance study using [1-C-13]glucose. Neurotoxicology 25(4):573-587.
Ex vivo high-resolution NMR spectroscopy combined with in vivo injection of [1-C-13]glucose was applied to gain insight into the mechanism(s) leading to energy failure in manganese neurotoxicity. In rats treated for 4 days with 50 mg/kg MnCl2 (intraperitoneally, i.p.), the concentration of C-13-labeled lactate increased to 154% compared to control rats. Changes in the absolute amounts of lactate were much less, resulting in increased fractional C-13-enrichments in lactate (indicating relative changes of de novo synthesis from glucose via the glycolytic pathway) to 143% of control values ($P < 0.001$). Analysis of samples obtained from blood plasma and peripheral organs demonstrate a selective increase of lactate synthesis from [1-C-13]glucose in the brain, which is released into the circulation. In parallel, manganese treatment resulted. in stimulation of flux through pyruvate dehydrogenase (PDH), leading to accumulation of [4-C-13]glutamate, [4-C-13]glutamine and [2-C-13]GABA to 168, 247 and 144% of control, respectively. The relative flux of glucose through astrocytic pyruvate carboxylase (PC), on the other hand, was impaired by manganese, as evident from a decreased ratio of [2-C-13]/[4-C-

13]glutamate or [2-C-13]/[4-C-13]glutamine. Consistent with stimulated glucose oxidative metabolism, the firactional C-13-enrichment in [2-C-13]acetyl-CoA entering the tricarboxylic acid (TCA) cycle and contributing to glutamate and glutamine synthesis increased to 138 and 156% of control, respectively ($P < 0.001$). In parallel, the TCA cycling ratio increased to 134% compared to control rats, prior to the label ending up in glutamate. In contrast, glutamine is synthesized mainly during the first TCA cycle turn. The present data provide new evidence in support of changes in brain energy metabolism playing an important role in manganese neurotoxicity. In particular, increased glycolytic flux and lactate synthesis may contribute to the deleterious effects of manganese in the brain. Furthermore, stimulated astrocytic glucose oxidation and glutamine synthesis may be associated with astrocytic pathology and altered astrocytic-neuronal metabolic trafficking in manganese neurotoxicity.

Supporting References (146)

1. Reaney SH, Smith DR. (2005) Manganese oxidation state mediates toxicity in PC12 cells. Toxicology and Applied Pharmacology 205(3):271-281.
The role of the manganese (Mn) oxidation state on cellular Mn uptake and toxicity is not well understood. Therefore, undifferentiated PC12 cells were exposed to 0-200 mu M Mn(II)-chloride or Mn(III)-pyrophosphate for 24 h, after which cellular manganese levels were measured along with measures of cell viability, function, and cytotoxicity (trypan blue exclusion, medium lactate dehydrogenase (LDH), 8-isoprostanes, cellular ATP, dopamine, serotonin, H-ferritin, transferrin receptor (TfR), Mn-superoxide dismutase (MnSOD), and copper-zinc superoxide dismutase (CuZnSOD) protein levels). Exposures to Mn(III) > 10 mu M produced 2- to 5-fold higher cellular manganese levels than equimolar exposures to Mn(II). Cell viability and ATP levels both decreased at the highest Mn(II) and Mn(III) exposures (150-200 mu M), while Mn(III) exposures produced increases in LDH activity at lower exposures (>= 50 mu M) than did Mn(II) (200 mu M only). Mn(II) reduced cellular dopamine levels more than Mn(III), especially at the highest exposures (50% reduced at 200 mu M Mn(II)). In contrast, Mn(III) produced a > 70% reduction in cellular serotonin at all exposures compared to Mn(II). Different cellular responses to Mn(II) exposures compared to Mn(III) were also observed for H-ferritin, TfR, and MnSOD protein levels. Notably, these differential effects of Mn(II) versus Mn(III) exposures on cellular toxicity could not simply be accounted for by the different cellular levels of manganese. These results suggest that the oxidation state of manganese exposures plays an important role in mediating manganese cytotoxicity. (c) 2004 Elsevier Inc. All rights reserved.

2. Alcaraz-Zubeldia M, Montes S, Rios C. (2001) Participation of manganese-superoxide dismutase in the neuroprotection exerted by copper sulfate against 1-methyl 4-phenylpyridinium neurotoxicity. Brain Research Bulletin 55(2):277-279.
Neurodegenerative effects of 1-methyl-4-phenylpyridinium (MPP+), the main metabolite of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) include enhancement of lipid peroxidation in the striatum of mice, associated to overproduction of free radicals. Copper acts as a prosthetic group of several copper-dependent antioxidant enzymes, and we previously showed the neuroprotective effect of CuSO4 pretreatment against the MPP+-induced neurotoxicity. In those studies, acute administration of CuSO4 (2.5 mg/kg) blocked MPP+-induced striatal lipid peroxidation, suggesting the activation of Cu-dependent proteins that defend neurons from

damage elicited by free radicals. In the present study, we evaluated the activity of superoxide dismutase in mice pretreated with CuSO4 16 h or 24 h prior to MPP+ administration. Copper administration produced a specific and significant increase in manganese superoxide dismutase activity in both the CuSO4/saline (fivefold increase) and the CuSO4/MPP+ groups of animals (sevenfold increase). The Na2SO4/MPP+ group showed a twofold increase in manganese superoxide dismutase activity versus control levels. The results suggest that the load of copper activating manganese-dependent superoxide dismutase could be responsible for neuroprotection against the MPP+ insult. (C) 2001 Elsevier Science Inc.

3. Alinovi R, Vettori MV, Mutti A, Cavazzini S, Bacchini A, Bergamaschi E. (1996) Dopamine (DA) metabolism in PC12 cells exposed to manganese (Mn) at different oxidation states. Neurotoxicology (Little Rock) 17(3-4):743-750.
BIOSIS COPYRIGHT: BIOL ABS. The present study was aimed at assessing the role of Mn valency state in Mn-induced changes in DA metabolism by PC12 cells. Mn(II)Cl2, Mn(III)Acetate, and Mn(V)O2 were used for these experiments. PC12 cells were incubated for 3, 24 and 72 hours to Mn nominal concentrations ranging from 10-8 to 10-4 M in 24-well plates containing 2l. Supernatants and cellular materials were then separated and immediately processed for the analysis of dopamine (DA), and its metabolite 3,4-di-hydroxyphenylacetic acid (DOPAC). Lactate dehydrogenase (LDH) activity and MTT cleavage were measured as indices of cell death. In parallel experiments, Mn-containing medium (10-5 M) was removed and cells incubated for further periods with Mn-free medium to evaluate the reversibility of observed changes. At the end of the experimental periods, none of Mn-exposed cultures showed appreciable reduction in cell viability as compared to their respective controls. After exposure to Mn(II) and Mn(III), irre

4. Anantharam V, Kitazawa M, Latchoumycandane C, Kanthasamy A, Kanthasamy AG. (2004) Blockade of PKC delta proteolytic activation by loss of function mutants rescues mesencephalic dopaminergic neurons from methylcyclopentadienyl manganese tricarbonyl (MMT)-induced apoptotic cell death. Protective Strategies for Neurodegenerative Diseases. NEW YORK: NEW YORK ACAD SCIENCES. pp 271-289.
The use of methytcyclopentadienyl manganese tricarbonyl (MMT) as a gasoline additive has raised health concerns and increased interest in understanding the neurotoxic effects of manganese. Chronic exposure to inorganic manganese causes Manganism, a neurological disorder somewhat similar to Parkinson's disease. However, the cellular mechanism by which MMT, an organic manganese compound, induces neurotoxicity in dopaminergic neuronal cells remains unclear. Therefore, we systematically investigated apoptotic cell-signaling events following exposure to 3-200 mu M MMT in mesencephalic dopaminergic neuronal (N27) cells. MMT treatment resulted in a time- and dose-dependent increase in reactive oxygen species generation and cell death in N27 cells. The cell death was preceded by sequential activation of mitochondrial-dependent proapoptotic events including cytochrome c release, caspase-3 activation, and DNA fragmentation, indicating that the mitochondrial-dependent apoptotic cascade primarily triggers MMT-induced apoptotic cell death. Importantly, MMT induced proteolytic cleavage of protein kinase C delta (PKC delta), resulting in persistently increased kinase activity. The proteolytic activation of PKC delta was suppressed by treatment with 100 mu M Z-VAD-FMK and 100 mu M Z-DEVD-FMK, suggesting that caspase-3 mediates the proteolytic activation of PKC delta. Pretreatment with 100 mu M Z-DEVD-FMK and 5 mu M

rottlerin (a PKC delta inhibitor) also significantly attenuated MMT-induced DNA fragmentation. Furthermore, overexpression of either the kinase inactive dominant negative PKC delta(K376R) mutant or the caspase cleavage resistant PKC delta(D327A) mutant rescued N27 cells from MMT-induced DNA fragmentation. Collectively, these results demonstrate that the mitochondrial-dependent apoptotic cascade mediates apoptosis via proteolytic activation of PKC delta in MMT-induced dopaminergic degeneration and suggest that PKC delta may serve as an attractive therapeutic target in Parkinson-related neurological diseases.

5. Anantharam V, Kitazawa M, Wagner J, Kaul S, Kanthasamy AG. (2002) Caspase-3-dependent proteolytic cleavage of protein kinase C delta is essential for oxidative stress-mediated dopaminergic cell death after exposure to methylcyclopentadienyl manganese tricarbonyl. Journal of Neuroscience 22(5):1738-1751.
In the present study, we characterized oxidative stress-dependent cellular events in dopaminergic cells after exposure to an organic form of manganese compound, methylcyclopentadienyl manganese tricarbonyl (MMT). In pheochromocytoma cells, MMT exposure resulted in rapid increase in generation of reactive oxygen species (ROS) within 5-15 min, followed by release of mitochondrial cytochrome C into cytoplasm and subsequent activation of cysteine proteases, caspase-9 (twofold to threefold) and caspase-3 (15- to 25-fold), but not caspase-8, in a time- and dose-dependent manner. Interestingly, we also found that MMT exposure induces a time- and dose-dependent proteolytic cleavage of native protein kinase Cdelta (PKCdelta, 72-74 kDa) to yield 41 kDa catalytically active and 38 kDa regulatory fragments. Pretreatment with caspase inhibitors (Z-DEVD-FMK or Z-VAD-FMK) blocked MMT-induced proteolytic cleavage of PKCdelta, indicating that cleavage is mediated by caspase-3. Furthermore, inhibition of PKCdelta activity with a specific inhibitor, rottlerin, significantly inhibited caspase-3 activation in a dose-dependent manner along with a reduction in PKCdelta cleavage products, indicating a possible positive feedback activation of caspase-3 activity by PKCdelta. The presence of such a positive feedback loop was also confirmed by delivering the catalytically active PKCdelta fragment. Attenuation of ROS generation, caspase-3 activation, and PKCdelta activity before MMT treatment almost completely suppressed DNA fragmentation. Additionally, overexpression of catalytically inactive PKCdelta(K376R) (dominant-negative mutant) prevented MMT-induced apoptosis in immortalized mesencephalic dopaminergic cells. For the first time, these data demonstrate that caspase-3-dependent proteolytic activation of PKCdelta plays a key role in oxidative stress-mediated apoptosis in dopaminergic cells after exposure to an environmental neurotoxic agent.

6. Anastassopoulou J, Theophanides T. (2002) Magnesium-DNA interactions and the possible relation of magnesium to carcinogenesis. Irradiation and free radicals. Critical Reviews in Oncology Hematology 42(1):79-91.
Magnesium deficiency causes renal complications. The appearance of several diseases is related to its depletion in the human body. In radiotherapy, as well as in chemotherapy, especially in treatment of cancers with cis-platinum, hypomagnesaemia is observed. The site effects of chemotherapy that are due to hypomagnesaemia are decreased using Mg supplements. The role of magnesium in DNA stabilization is concentration dependent. At high concentrations there is an accumulation of Mg binding, which induces conformational changes leading to Z-DNA, while at low concentration there is deficiency and destabilization of DNA. The biological and clinical consequences of abnormal concentrations are DNA cleavage leading to diseases and

cancer. Carcinogenesis and cell growth are also magnesium-ion concentration dependent. Several reports point out that the interaction of magnesium in the presence of other metal ions showed that there is synergism with Li and Mn, but there is magnesium antagonism in DNA binding with the essential metal ions in the order: Zn > Mg > Ca. In the case of toxic metals such as Cd, Ga and Ni there is also antagonism for DNA binding. It was found from radiolysis of deaerated aqueous solutions of the nucleoside 5'-guanosine monophosphate (5'-GMP) in the presence as well as in the absence of magnesium ions that, although the addition of hydroxyl radicals ((OH)-O-.) has been increased by 2-fold, the opening of the imidazole ring of the guanine base was prevented. This effect was due to the binding of Mg2+ ions to N7 site of the molecule by stabilizing the five-member ring imitating cis-platinum. It was also observed using Fourier Transform Infrared spectroscopy, Raman spectroscopy and Fast Atom Bombardment mass spectrometry that (OH)-O-. radicals subtract H atoms from the C1', C4' and C5' sites of the nucleotide. Irradiation of 5'-GMP in the presence of oxygen (2.5 x 10(-4) M) shows that magnesium is released from the complex. There is spectroscopic evidence that superoxide anions (O-2(-.)) react with magnesium ions leading to magnesium release from the complex. From radiolysis data it was suggested that magnesium ions can act as radiosensitizers in the absence of oxygen, while in the presence of oxygen they act as protectors and stabilizers of DNA.

7. Anderson JG, Cooney PT, Erikson KM. (2007) Brain manganese accumulation is inversely related to gamma-amino butyric acid uptake in male and female rats. Toxicological Sciences 95(1):188-195.
Iron (Fe) is an essential trace metal involved in numerous cellular processes. Iron deficiency (ID) is reported as the most prevalent nutritional problem worldwide. Increasing evidence suggests that ID is associated with altered neurotransmitter metabolism and a risk factor for manganese (Mn) neurotoxicity. Though recent studies have established differences in which the female brain responds to ID-related neurochemical alterations versus the male brain, little is known about the interactions of dietary ID, Mn exposure, and sex on gamma-amino butyric acid (GABA). Male and female Sprague-Dawley rats were randomly divided into four dietary treatment groups: control (CN), control/ Mn supplemented, ID, and ID/Mn supplemented. After 6 weeks of treatment, both ID diets caused a highly significant decrease in Fe concentrations across all brain regions compared to CN in both sexes. Both ID and Mn supplementation led to significant accumulation of Mn across all brain regions in both sexes. There was no main effect of sex on Fe or Mn accumulation. Striatal synaptosomes were utilized to examine the effect of dietary intervention on H-3-GABA uptake. At 4 weeks, there was a significant correlation between Fe concentration and H-3-GABA uptake in male rats ($p < 0.05$). At 6 weeks, there was a significant inverse correlation between Mn concentration and 3H-GABA uptake in male and female rats and a postitive correlation between Fe concentration and H-3-GABA uptake in female rats ($p < 0.05$). In conclusion, ID-associated Mn accumulation is similar in both sexes, with Mn levels affecting GABA uptake in both sexes in a comparable fashion.

8. Anderson JG, Fordahl SC, Cooney PT, Erikson KM. (2007) Iron deficiency and manganese exposure are associated with decreases in neurotransmitter uptake. Faseb Journal 21(6):A1065-A1065.

9. Antonini JM, Santaimaria AB, Jenkins NT, Albini E, Lucchini R. (2006) Fate of manganese associated with the inhalation of welding fumes: Potential neurological effects. Neurotoxicology 27(3):304-310.
Welding fumes are a complex mixture composed of different metals. Most welding fumes contain a small percentage of manganese. There is an emerging concern among occupational health officials about the potential neurological effects associated with the exposure to manganese in welding fumes. Little is known about the fate of manganese that is complexed with other metals in the welding particles after inhalation. Depending on the welding process and the composition of the welding electrode, manganese may be present in different oxidation states and have different solubility properties. These differences may affect the biological responses to manganese after the inhalation of welding fumes. Manganese intoxication and the associated neurological symptoms have been reported in individual cases of welders who have been exposed to high concentrations of manganese-containing welding fumes due to work in poorly ventilated areas. However, the question remains as to whether welders who are exposed to low levels of welding fumes over long periods of time are at risk for the development of neurological diseases. For the most part, questions remain unanswered. There is still paucity of adequate scientific reports on welders who suffered significant neurotoxicity, hence there is a need for well-designed epidemiology studies that combine complete information on the occupational exposure of welders with both behavioral and biochemical endpoints of neurotoxicity. Published by Elsevier Inc.

10. Baek SY, Kim YH, Oh SO, Lee CR, Yoo CI, Lee JH, Lee H, Sim CS, Park J, Kim JW and others. (2007) Manganese does not alter the severe neurotoxicity of MPTP. Human & Experimental Toxicology 26(3):203-211.
We utilized a mice model of Parkinsonism: (1) to evaluate 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-induced neurotoxicity; and (2) to evaluate whether manganese (Mn) exposure can affect MPTP-induced neurotoxicity. A 2 X 3 experimental design (MPTP x +/-Mn) was as follows: SS, MPTP(-) x Mn(-); SLMn, MPTP(-) x low Mn(+); SHMn, MPTP(-) x high Mn(+); MpS, MPTP(+) x Mn(-); MpLMn, MPTP(+) x low Mn(+); MpHMn, MPTP(+) x high Mn(+). We administered MPTP (30 mg/kg per day) to male C57BL/6 mice intraperitoneally, once a day for 5 days. Subsequently, mice were treated with either 2 or 8 mg/kg of MnCl2 center dot 4H(2)O intraperitoneally, once a day for 3 weeks. Blood and striatal Mn levels were elevated in the Mn-exposed groups. The number of tyrosine hydroxylase (TH)-immunoreactive (ir) neurons in the substantia nigra pars compacta were decreased significantly in the MPTP-exposed groups. The densities of TH-ir axon terminals in caudate-putamen (CPU) were significantly decreased in the MPTP-treated groups. However, Mn treatment did not affect MPTP neurotoxicity. The densities of glial fibrillary acidic protein (GFAP)-ir astrocytes in the CPU or globus pallidus were significantly increased in the MPTP-treated groups. Concentrations of dopamine in the striatum were decreased significantly in the MPTP-exposed groups only, but Mn had no effect.

11. Baek SY, Lee MJ, Jung HS, Kim HJ, Lee CR, Yoo C, Lee JH, Lee H, Yoon CS, Kim YH and others. (2003) Effect of manganese exposure on MPTP neurotoxicities. Neurotoxicology 24(4-5):657-665.
We used a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-treated mice model to evaluate whether manganese (Mn) exposure can affect MPTP-induced neurotoxicity. We randomly

assigned adult male C57BL/6 mice (n = 5-7 per group) the following treatments: SO, Mn(-) MPTP(-); MO, Mn(+) MPTP(-); SM, Mn(-) MPTP(+); MM, Mn(+) MPTP(+). Mn (MnCl(2)4H(2)O) was administered intraperitoneally at a dose of 2 mg/kg daily for 3 weeks. MPTP was then administered intraperitoneally at a dose of 30 mg/kg daily for 5 days in the SM and MM groups. Seven days after the last MPTP injection, the animals were sacrificed. Blood Mn levels were elevated in the Mn-exposed groups. Striatal Mn levels were not influenced by Mn treatment alone, however they were decreased following MPTR Tyrosine hydroxylase (TH)-immunoreactive (ir) neurons in the substantia nigra pars compacta (SNpc) were decreased significantly in the MPTP-exposed groups. Densities of TH- and dopamine transporter (DAT)-ir axon terminals in the caudate-putamen (CPU) were also decreased in the MPTP-treated groups. Furthermore, glial fibrillary acidic protein (GFAP)-ir astrocytes increased in the CPU with MPTP treatment. However no effects were observed with Mn exposure. Concentrations of dopamine (DA), 3,4-dihydrophenyl acetic acid (DOPAC) and homovanillic acid (HVA) in the corpus striatum were also decreased significantly with MPTP treatment alone, but Mn had no effect. Thus, decreased dopaminergic activities with MPTP led to decreased DA and its metabolites. Significant hypertrophies of GFAP-ir astrocytes in the globus pallidus (GP) were observed in Mn-exposed groups, especially in the MM group. MPTP targeted dopaminergic systems whereas Mn neurotoxicities occurred in the GP In conclusion, our data suggest that Mn does not potentiate the neurotoxicity of MPTP. (C) 2003 Elsevier Science Inc. All rights reserved.

12. Bairati C, Goi G, Bollini D, Roggi C, Luca M, Apostoli P, Lombardo A. (1997) Effects of lead and manganese on the release of lysosomal enzymes in vitro and in vivo. Clinica Chimica Acta 261(1):91-101.
BIOSIS COPYRIGHT: BIOL ABS. In this study we evaluated the effects of two heavy metals, lead and manganese, on the release of some glycohydrolases of lysosomal origin, N-acetyl-beta-D-glucosaminidase and its major isoenzymes, beta-D-glucuronidase and alpha-D-galactosidase. We have studied release of these enzymes in vitro from peripheral mitogen-activated lymphocytes from healthy subjects after addition of Pb or Mn to the medium and their plasma levels in individuals exposed at work to Pb (31 subjects) or to manganese (36 subjects), versus matched controls. We also determined the plasma levels in a general population (417 subjects). The enzymatic activities were assayed fluorimetrically with 4-methylumbelliferyl-glycosides as substrates. Particular attention was given to some technical aspects: enzymatic activity was preserved by addition of ethylene glycol and stable liquid material was employed for calibration purposes. N-acetyl-beta-D-glucosaminidase isoenzymes were separated by a routine chrom

13. Blakey DH, Bayley JM. (1995) Induction of chromosomal aberrations by the fuel addictive methylcyclopentadienyl-manganese tricarbonyl mmt in chinese hamster ovary cells. 26th Annual Meeting of the Environmental Mutagen Society, St. Louis, Missouri, USA, March 12-16, 1995. Environmental and Molecular Mutagenesis 25(SUPPL. 25):6.
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14. Bredow S, Falgout MM, Divine KK. (2005) A Potential Mechanism For Pulmonary Manganese-Toxicity: Manganese Induces Pulmonary VEGF Expression In Vitro. Toxicol Sci 84(1-S):234.

The respiratory tract constitutes a major route of entry and absorption for airborne Manganese (Mn) dust and fume particles. Although chronic Mn-exposure causes toxic responses in lung, little is known about the underlying mechanisms that mediate these effects. In non-pulmonary cell lines Mn induces cellular expression of Vascular Endothelial Growth Factor (VEGF) in vitro. VEGF is perhaps the most important positive regulator of angiogenesis, the sprouting and growth of new blood vessels from the existing vasculature. Angiogenic activity, which is usually low under normal physiological conditions, contributes to the pathogenesis of many diseases, and elevated VEGF levels frequently correlate with poor prognosis and disease outcome. Here we demonstrate that Mn increases VEGF expression in vitro in several human pulmonary epithelial cell lines (A549, Calu-3, NCI-H292). Cells were transiently transfected with a reporter plasmid containing the gene for firefly luciferase under the control of the VEGF wild type-promoter. Twenty-eight hours later, MnCl2 was directly added to the medium in concentrations ranging from 50 to 1000 µM. The cells were incubated for another 20 hours and then lyzed. Analysis of the cell lysates for firefly activity revealed cell- and dose-dependent increases in promoter activity between 1.5 and 3.5-fold. Interestingly in comparison to non-treated controls, exposure to 0.25 mM MnCl2 for 20 hours increases promoter activity 2-fold for up to 24 hours after Mn is removed. Further, growing the cells in the presence of 0.25 mM MnCl2 for 2 weeks did not affect their viability. These data suggest that Mn might promote changes in pulmonary angiogenic growth factor expression, which, over time, could affect lung vasculature morphology, leading to enhanced susceptibility to disease. Further studies may provide an insight into the pathogenesis of, and therapeutic targets for, lung diseases such as asthma and other chronic inflammatory airway diseases.

15. Brurok H, Schjott J, Berg K, Karlsson JOG, Jynge P. (1997) Manganese and the heart: Acute cardiodepression and myocardial accumulation of manganese. Acta Physiologica Scandinavica 159(1):33-40.
The aim of study was to assess acute effects oi the divalent manganese ion (Mn2+) in an intact bur isolated heart preparation. Rat hearts were perfused in the Langendorff mode at constant flow rate. Left ventricular (LV) developed pressure (LVDP), LV pressure first derivatives (LVdp/dt max and min), heart rate (HR) and aortic pressure (AoP) were recorded. Ventricular contents of high energy phosphate compounds (HEP) and Mn metal were measured at the end of experiment. Infusion of MnCl2 for 5 min with perfusate concentrations 1-3000 mu M induced an immediate depression of contractile function at and above 33 mu M and negative chronotropy at and above 300 mu M. These EC(50) values were found (mu M): LVDP 250: LVdp/dt max 160. LVdp/dp min 120, HR 1000; and increase in AoP 80. Recovery of function during a 14 min washout period was rapid and extensive. except for Mn2+ 300 mu M. Somewhat unexpected, Mn2+ 30-1000 mu M raised coronary vascular resistance up to about twice the control level, whereas the vasoconstrictory response was overcome at 3000 mu M. Mn2+ 3000 mu M reduced tissue HEP. Ventricular Mn content rose stepwise for perfusate Mn2+ above 1 mu M UP to about 55 times the control level for perfusate Mn2+ 3000 mu M, it is concluded that: acute effects of Mn2+ like depression of contractility and rate is rapidly reversible: and rat hearts accumulate and buffer large amounts of Mn2+ without affecting cardiac function or energy metabolism in the acute stage.

16. Btaiche IF, Khalidi N. (2004) Metabolic complications of parenteral nutrition in adults, part 1. American Journal of Health-System Pharmacy 61(18):1938-1949.

Purpose. Common metabolic complications associated with parenteral nutrition (PN) are reviewed, and the consequences of overfeeding and variables for patient monitoring are discussed. Summary. Although PN is a lifesaving therapy in patients with gastrointestinal failure, its use may be associated with metabolic, infectious, and technical complications. The metabolic complications associated with PN in adult patients include hyperglycemia, hypoglycemia, hyperlipidemia, hypercapnia, refeeding syndrome, acid-base disturbances, liver complications, manganese toxicity, and metabolic bone disease. These complications may occur in the acute care or chronic care patient. The frequency and severity of these complications depend on patient- and PN-specific factors. Proper assessment of the patient's nutritional status; tailoring the macronutrient, micronutrient, fluid, and electrolyte requirements on the basis of the patient's underlying diseases, clinical status, and drug therapy; and monitoring the patient's tolerance of and response to nutritional support are essential in avoiding these complications. Early recognition of the signs and symptoms of complications and knowledge of the available pharmacologic and nonpharmacologic therapies are essential to proper management. PN should be used for the shortest period possible, and oral or enteral feeding should be initiated as soon as is clinically feasible. The gastrointestinal route remains the most physiologically appropriate and cost-effective way of providing nutritional support. Conclusion. PN can lead to serious complications, many of which are associated with overfeeding. Close management is necessary to recognize and manage these complications.

17. Btaiche IF, Khalidi N. (2004) Metabolic complications of parenteral nutrition in adults, part 2. American Journal of Health-System Pharmacy 61(19):2050-2057.
Purpose. Common metabolic complications associated with parenteral nutrition (PN) are reviewed, and the consequences of overfeeding and variables for patient monitoring are discussed. Summary. Although PN is a lifesaving therapy in patients with gastrointestinal failure, its use may be associated with metabolic, infectious, and technical complications. The metabolic complications associated with PN in adult patients include hyperglycemia, hypoglycemia, hyperlipidemia, hypercapnia, refeeding syndrome, acid-base disturbances, liver complications, manganese toxicity, and metabolic bone disease. These complications may occur in the acute care or chronic care patient. The frequency and severity of these complications depend on patient- and PN-specific factors. Proper assessment of the patient's nutritional status; tailoring the macronutrient, micronutrient, fluid, and electrolyte requirements on the basis of the patient's underlying diseases, clinical status, and drug therapy; and monitoring the patient's tolerance of and response to nutritional support are essential in avoiding these complications. Early recognition of the signs and symptoms of complications and knowledge of the available pharmacologic and,nonpharmacologic therapies are essential to proper management. PN should be used for the shortest period possible, and oral or enteral feeding should be initiated as soon as is clinically feasible. The gastrointestinal route remains the most physiologically appropriate and cost-effective way of providing nutritional support. Conclusion. PN can lead to serious complications, many of which are associated with overfeeding. Close management is necessary to recognize and manage these complications..

18. Butterworth RF, Spahr L, Fontaine S, Layrargues GP. (1995) Manganese toxicity, dopaminergic dysfunction and hepatic encephalopathy. Metabolic Brain Disease 10(4):259-267.
Patients with chronic liver disease manifest a high incidence (>75%) of pallidal signal hyperintensity on T-1-weighted Magnetic Resonance Imaging (MRI), the intensity of which

correlates with blood manganese levels and the presence of extrapyramidal symptoms. A major cause of pallidal hyperintensity on T-1-weighted MRI is manganese deposition; chronic manganese intoxication in the absence of liver disease results in pallidal MR signal hyperintensity, in extrapyramidal symptoms and in selective effects on the dopaminergic neurotransmitter system in basal ganglia. Direct measurements in globus pallidus obtained at autopsy from patients with chronic liver disease who died in hepatic coma reveal 2 to 7-fold increases of pallidal manganese and a concomitant loss of dopamine D-2 binding sites. Liver transplantation results in normalization of pallidal MR signals and of blood manganese levels. These findings suggest that (1) pallidal MR signal hyperintensity in patients with chronic liver disease is the result of manganese deposition and (2) alterations of dopaminergic function due to the toxic effects of manganese may contribute to the extrapyramidal symptoms in these patients.

19. Cano G, SuarezRoca H, Bonilla E. (1997) Alterations of excitatory amino acid receptors in the brain of manganese-treated mice. Molecular and Chemical Neuropathology 30(1-2):41-52.
An excessive activation of excitatory amino acid (EAA) receptors has been associated with oxidative stress, which is considered the primary cause of manganese (Mn) poisoning neurotoxicity. Therefore, the EAA receptor distribution was analyzed by autoradiographic methods in several brain regions during Mn intoxication. We found that chronic treatment of mice with MnCl2, during 8 wk significantly alters the L-[H-3]glutamate (L-[H-3]Glu) binding to total glutamate (Glu) receptors, as well as to N-methyl-D-aspartate (NMDA) and quisqualate (QA) receptor subtypes. A generalized decrease of 16-24% of the L-[H-3]Glu binding to total Glu receptors was found in all cortex, hippocampus, basal ganglia (except globus pallidus), and cerebellum. Saturation studies showed a significant reduction of the maximal number of receptors (B-max) in Mn-treated mice, whereas the affinity (K-d) was not altered. L-[H-3]Glu binding to NMDA sites was mainly decreased (10-21%) in a few cortical regions, basal ganglia (except globus pallidus), and hippocampus, whereas binding to QA receptor subtype was diminished (16-30%) in cortex, hippocampus, and cerebellum. The decrease of Glu receptor binding sites during Mn poisoning could reflect a receptor downregulation more than neuronal loss, since these reductions are moderate and diffuse. Thus, this downregulation might mean a protection mechanism against an excitotoxic process associated with Mn toxicity.

20. Cardozo-Pelaez F, Cox DP, Bolin C. (2005) Lack of the DNA repair enzyme OGG1 sensitizes dopamine neurons to manganese toxicity during development. Gene Expression 12(4-6):315-323.
Onset of Parkinson's disease (PD) and Parkinson-like syndromes has been associated with exposure to diverse environmental stimuli. Epidemiological studies have demonstrated that exposure to elevated levels of manganese produces neuropathological changes localized to the basal ganglia, including neuronal loss and depletions in striatal dopamine content. However, understanding the mechanisms associated with manganese neurotoxicity has been hampered by the lack of a good rodent model. Elevated levels of 8-hydroxy-2'-deoxyguanosine (oxo(8)dG) have been found in brain areas affected in PD. Whether increased DNA damage is responsible for neuronal degeneration or is a mere epiphenomena of neuronal loss remains to be elucidated. Thus, by using mice deficient in the ability to remove oxo(8)dG we aimed to determine if dysregulation of DNA repair coupled to manganese exposure would be detrimental to dopaminergic neurons. Wild-type and OGG1 knockout mice were exposed to manganese from conception to postnatal day 30; in both groups, exposure to manganese led to alterations in the

neurochemistry of the nigrostriatal system. After exposure, dopamine levels were elevated in the caudate of wild-type mice. Dopamine was reduced in the caudate of OGG1 knockout mice, a loss that was paralleled by an increase in the dopamine index of turnover. In addition, the reduction of dopamine in caudate putamen correlated with the accumulation of oxo(8)dG in midbrain. We conclude that OGG1 function is essential in maintaining neuronal stability during development and identify DNA damage as a common pathway in neuronal loss after a toxicological challenge.

21. Centonze D, Gubellini P, Bernardi G, Calabresi P. (2001) Impaired excitatory transmission in the striatum of rats chronically intoxicated with manganese. Experimental Neurology 172(2):469-476.
Chronic exposure to manganese (Mn) is known to produce a parkinsonian or dystonic state in humans caused by a rather selective involvement of the basal ganglia. Experimental observations suggest that secondary excitotoxic mechanisms play a crucial role in the development of Mn-induced neurodegeneration in the striatum, although the site of interference of Mn with glutamatergic transmission in this brain area is still unknown. To answer this question, in the present in vitro study, we investigated the physiological characteristics of striatal excitatory synaptic transmission in a rat model of Mn intoxication. We found that chronic Mn greatly increased both frequency and amplitude of spontaneous excitatory postsynaptic potentials, in the absence of appreciable changes of intrinsic membrane properties of striatal cells. The sensitivity of striatal neurons to glutamate AMPA and NMDA receptor stimulation was unaffected by Mn poisoning, as demonstrated by comparing the membrane responses produced in control and treated rats to the application of selective agonists of these receptors and to the direct activation of corticostriatal glutamatergic fibers. In addition, also paired-pulse facilitation was unaltered by Mn treatment, indicating that this toxin does not affect the pre- and postsynaptic mechanisms responsible for the appearance of this short-term form of synaptic plasticity at corticostriatal synapses. It is concluded, therefore, that hyperactivity of corticostriatal neurons, rather than increased postsynaptic sensitivity to glutamate, accounts for the abnormal excitation of striatal neurons in the course of Mn intoxication. (C) 2001 Elsevier Science.

22. Chang JY, Liu LZ. (1999) Manganese potentiates nitric oxide production by microglia. Molecular Brain Research 68(1-2):22-28.
Manganese toxicity has been associated with clinical symptoms of neurotoxicity which are similar to the symptoms observed in Parkinson's disease. Earlier reports indicated that reactive microglia was present in the substantia nigra of patients with Parkinson's disease. Using N9 microglial cells, the current study was designed to determine whether high levels of manganese were associated with microglial activation. Results indicated that manganese significantly increased the bacterial lipopolysaccharide-induced nitric oxide production. This potent activity of manganese was not shared by other transition metals tested, including iron, cobalt, nickel, copper and zinc. Immunohistochemical staining and Western blot analysis indicated that manganese increased the cellular production of inducible nitric oxide synthase. Northern blot analysis indicated that manganese Likely increased iNOS gene transcription since this agent increased the mRNA level of the inducible nitric oxide synthase. In contrast to other transition metals tested, manganese did not appear to be cytotoxic to microglial cells. These results suggested that manganese could induce sustained production of neurotoxic nitric oxide by

activated microglial cells, which might cause detrimental consequences to surrounding neurons. (C) 1999 Elsevier Science B.V. All rights reserved.

23. Chen CJ, Liao SL. (2002) Oxidative stress involves in astrocytic alterations induced by manganese. Experimental Neurology 175(1):216-225.
It is hypothesized that manganese neurotoxicity could be secondary to a diminuition of cellular protective and scavenger mechanisms. Since manganese is known to be sequestered in glial cells, we investigated possible neurotoxic mechanisms involving astrocytes in vitro. Astrocytes differentiated into process-bearing stellate cells in response to manganese treatment. Manganese concentration dependently decreased cellular DNA synthesis, glial fibrillary acidic protein expression, energy production, antioxidant capacity, and glutamate transporter activity. In contrast, manganese increased glutamine synthetase protein expression and cytokine-stimulated interleukin 6 mRNA expression. Under the concentration of 0.1 mM manganese chloride caused no significant astrocyte death even up to 48 h after treatment. That is, these astrocytic alterations proceeded before the onset of cell demise. As a possible mediator of manganese-derived alterations, we determined intracellular redox state in astrocytes. Manganese time-dependently changed intracellular redox potential into oxidized state. The influx of manganese and its resultant oxidative stress was essential to most of the alterations, except for the action on stellation. Astrocytes are central component of the brain's antioxidant defense. Therefore, the observations suggest that dysfunction of astrocytes possibly involved in neurotoxic action of Manganese. (C) 2002 Elsevier Science (USA).

24. Chen CJ, Ou YC, Lin SY, Liao SL, Chen SY, Chen JH. (2006) Manganese modulates pro-inflammatory gene expression in activated glia. Neurochemistry International 49(1):62-71.
Redox-active metals are of paramount importance for biological functions. Their impact and cellular activities participate in the physiological and pathophysiological processes of the central nervous system (CNS), including inflammatory responses. Manganese is an essential trace element and it is required for normal biological activities and ubiquitous enzymatic reactions. However, excessive chronic exposure to manganese results in neurobehavioral deficits. Recent evidence suggests that manganese neurotoxicity involves activation of microglia or astrocytes, representative CNS immune cells. In this study, we assessed the molecular basis of the effects of manganese on the modulation of pro-inflammatory cytokines and nitric oxide (NO) production in primary rat cortical glial cells. Cultured glial cells consisted of 85% of astrocytes and 15% of microglia. Within the assayed concentrations, manganese was unable to induce tumor necrosis factor alpha (TNF-alpha) and inducible nitric oxide synthase (iNOS) expression, whereas it potentiated iNOS and TNF-alpha gene expression by lipopol gamma-saccharide/interferon-gamma-activated glial cells. The enhancement was accompanied by elevation of free manganese, generation of oxidative stress, activation of mitogen-activated protein kinases, and increased NF-KB and AP-1 binding activities. The potentiated degradation of inhibitory molecule IKB-alpha was one of underlying mechanisms for the increased activation of NF-KB by manganese. However, manganese decreased iNOS enzymatic activity possibly through the depletion of cofactor since exogenous tetrahydrobiopterin reversed manganese's action. These data indicate that manganese could modulate glial inflammation through variable strategies. (c) 2006 Elsevier Ltd. All rights reserved.

25. Chen JY, Tsao GC, Zhao QQ, Zheng W. (2001) Differential cytotoxicity of Mn(II) and Mn(III): Special reference mitochondrial [Fe-S] containing enzymes. Toxicology and Applied Pharmacology 175(2):160-168.
Manganese (Mn)-induced neurodegenerative toxicity has been associated with a distorted iron (Fe) metabolism at both systemic and cellular levels. In the current study, we examined whether the oxidation states of Mn produced differential effects on certain mitochondrial [Fe-S] containing enzymes in vitro. When mitochondrial aconitase, which possesses a [4Fe-4S] cluster, was incubated with either Mn(II) or Mn(III), both Mn species inhibited the activities of aconitase. However, the IC10 (concentration to cause a 10% enzyme inhibition) for Mn(HI) was ninefold lower than that for Mn(II). Following exposure of mitochondrial fractions with Mn(II) or Mn(III), there was a significant inhibition by either Mn species in activities of Complex I whose active site contains five to eight [Fe-S] clusters. The dose-time response curves reveal that Mn(III) was more effective in blocking Complex I activity than Mn(II). Northern blotting was used to examine the expression of mRNAs encoding transferrin receptor (TfR), which is regulated by cytosolic aconitase. Treatment of cultured PC12 cells with Mn(II) and Mn(III) at 100 muM for 3 days resulted in 21 and 58% increases, respectively, in the expression of TfR mRNA. Further studies on cell growth dynamics after exposure to 25-50 muM Mn in culture media demonstrated that the cell numbers were much reduced in Mn(III)- treated groups compared to Mn(II)-treated groups, suggesting that Mn(III) is more effective than Mn(II) in cell killing. In cells exposed to Mn(II) and Mn(IH), mitochondrial DNA (mtDNA) was significantly decreased by 24 and 16%, respectively. In contrast, rotenone and MPP+ did not seem to alter mtDNA levels. These in vitro results suggest that Mn(IH) species appears to be more cytotoxic than Mn(II) species, possibly due to higher oxidative reactivity and closer radius resemblance to Fe. (C) 2001 Academic Press.

26. Chen MT, Sheu JY, Lin TH. (2000) Protective effects of manganese against lipid peroxidation. Journal of Toxicology and Environmental Health-Part A 61(7):569-577.
The aim of this study was to investigate the effects of chronic, daily, 30-d administration of manganese chloride (MnCl2) to male Sprague-Dawley rats on lipid peroxidation in various tissues. Rats were intraperitoneally injected with MnCl2 (20 mg/kg) once daily for 30 consecutive days. The Mn accumulated in liver, spleen, adrenal glands, heart, kidneys, lung, and testes. This was associated with decreased lipid peroxidation in liver, spleen, and adrenal glands and a decrease in the levels of Fe in these tissues. In a second group of animals, Mn (20 mg/kg/d) and glutathione (GSH, 15 mg/kg/d) were administered ip for 30 d. GSH counteracted the Mn-induced protective fall in lipid peroxidation, but Fe levels remained lower in liver and spleen. Mn decreases lipid peroxidation in certain tissues, which may involve lowering Fe content, but interaction with Fe is not the sole mechanism.

27. Cheng J, Fu JL, Zhou ZC. (2003) The inhibitory effects of manganese on steroidogenesis in rat primary Leydig cells by disrupting steroidogenic acute regulatory (StAR) protein expression. Toxicology 187(2-3):139-148.
Manganese is known to impede the male reproductive function, however, the mechanisms through which the adverse effects are mediated are not clearly elucidated. In order to get insight into those mechanisms, the effects of manganese on the biosynthesis of testosterone by primary rat Leydig cells were examined. Primary Leydig cells were exposed to various concentrations of manganese chloride for different periods of time. Dose and time-dependent reductions of human

chorionic gonadotropin (hCG)-stimulated testosterone level were observed in the culture medium. The expression of Steroidogenic Acute Regulatory (StAR) protein and the activities of P450 side-chain cleavage (P450scc) and 3beta-hydroxysteroid dehydrogenase (3beta-HSD) enzymes were also detected. The expression of StAR protein stimulated by hCG was suppressed by manganese chloride at all concentrations (0.01, 0.1, 1.0 mM) and time points (2, 4, 24, 48 h) tested. Progesterone productions treated with 22R-hydroxycholesterol or pregnenolone were reduced after treated by manganese chloride for 24 or 48 h, respectively. The manganese exposure effect on cell viability was significant at 1.0 and 1.5 mM at 24 h, while at 48 It it was significant at every concentration tested. The decreasing effect of manganese on mitochondrial membrane potential was significant at every concentration measured and every time point tested. These data suggest that manganese exposure for 2 and 4 h inhibited rat primary Leydig cell steroidogenesis by decreasing StAR protein expression while 24 and 48 h exposure of manganese chloride caused adverse effects on both StAR protein and P450scc and 3beta-HSD enzyme activity to reduce steroidogenesis. Manganese may also disrupt StAR expression and/or function secondary to mitochondrial dysfunction.

28. Cheng J, Fu JL, Zhou ZC. (2005) The mechanism of manganese-induced inhibition of steroidogenesis in rat primary Leydig cells. Toxicology 211(1-2):1-11.
In previous studies in cultured primary rat Leydig cells, manganese was shown to inhibit hCG-stimulated steroidogenesis of Leydig cells, and the data showed that while the inhibition of StAR protein expression and/or function and mitochondrial dysfunction contribute to the acute reduction of steroidogenesis (2 and 4h manganese treatment), the enzyme activities of P450scc and 3 beta-HSD were only reduced after 24 h manganese treatment, we hypothesize that there were different mechanisms for its effect at later stage (24 and 48 h manganese treatment). We further our study by examining StAR mRNA level in cultured primary rat Leydig cells to understand if inhibition of StAR protein expression occurs at the level of transcription of StAR mRNA. The cellular ATP content was measured to determine the extent that manganese altered mitochondrial function. Since mitochondria are regulators of Ca2+ homeostasis, and there are indications that manganese affects intracellular Ca2+ levels, [Ca2+]i was also tested. The effects of manganese on Leydig cell apoptosis and cell cycle distribution were studied to see whether these effects contribute to the reduction of steroidogenesis by manganese at later stage of manganese treatment. In the present study, we demonstrated that manganese could increase [Ca2+] i and reduced ATP contents in primary Leydig cells after 4 h treatment, while the effects on StAR mRNA level appeared later (24 h). Manganese could also induce arrest at the G(0)/G(1) phase cell cycle after 24 It manganese treatment and subsequently increased in the sub-G(1) phase DNA contents, indicating induction of apoptosis. Combined with our previous studies, the results indicate that inhibition of StAR protein expression and/or function, mitochondrial dysfunction and disturbance of calcium homeostasis contribute to the adverse effects of manganese on the Leydig cells at the early/immediate stage after treatment (2 and 4 h). However, at later stages (24 and 48 h) manganese could arrest the cell cycle and induce apoptosis of primary Leydig cells, StAR mRNA and enzyme activities of P450scc and 3 beta-HSD were also reduced, leading to reduced level of steroidogenesis in Cultured primary Leydig cells.

29. Choi C, Anantharam V, Kanthasamy A, Kanthasamy A. (2006) Effect of prion proteins on manganese-induced oxidative insult and mitochondrial dysfunction. Neurotoxicology 27(5):917-917.

30. Chukhlovin AB, Tokalov SV, Yagunov AS, Zharskaya VD. (1996) Acute effects of copper, chromium and manganese upon immature blood cells and macrophages. Trace Elements and Electrolytes 13(1):37-41.
BIOSIS COPYRIGHT: BIOL ABS. Cell survival and phagocytic capacity of rat thymocytes, bone marrow cells and bronchoalveolar macrophages have been tested after short-term incubations with different amounts of Cu(II), Cr(III) and Mn(II) ions (as chloride salts), and with aqueous farm soil extracts, containing excessive amounts of these metals. Copper ions (10-100 muM) exerted lethal effects upon all 3 cell populations tested. Cr caused apoptosis of thymocytes and marrow cells. Mn ions induced DNA autolysis of thymocytes and decrease in adherent macrophage numbers, though increasing relative amounts of phagocytes in the latter population. Copper and chromium ions caused loss of myeloid marrow cells in suspensions under study. Cytotoxic effects of metal-rich soil extracts included a variety of above mentioned cell alterations, several of them coinciding with effects obtained with pure metal salts, i.e. the loss of marrow myeloid cells expressed direct correlations with increased soil contents of copper

31. Chun HS, Lee H, Son JH. (2001) Manganese induces endoplasmic reticulum (ER) stress and activates multiple caspases in nigral dopaminergic neuronal cells, SN4741. Neuroscience Letters 316(1):5-8.
Chronic exposure to manganese causes Parkinson's disease (PD)-like clinical symptoms (Neurotoxicology 5 (1984) 13; Arch. Neurol. 46 (1989) 1104; Neurology 56 (2001) 4). Occupational exposure to manganese is proposed as a risk factor in specific cases of idiopathic PD (Neurology 56 (2001) 8). We have investigated the mechanism of manganese neurotoxicity in nigral dopaminergic (DA) neurons using the DA cell line, SN4741 (J. Neurosci. 19 (1999) 10). Manganese treatment elicited endoplasmic reticulum (ER) stress responses, such as an increased level of the ER chaperone BiP, and simultaneously activated the ER resident caspase-12. Peak activation of other major initiator caspases-like activities, such as caspase-1, -8 and -9, ensued, resulting in activation of caspase-3-like activity during manganese-induced DA cell death. The neurotoxic cell death induced by manganese was significantly reduced in the Bcl-2-overexpressing DA cell lines. Our findings suggest that manganese-induced neurotoxicity is mediated in part by ER stress and considerably ameliorated by Bcl-2 overexpression in DA cells. (C) 2001 Published by Elsevier Science Ireland Ltd.

32. Clegg MS, Donovan SM, Monaco MH, Baly DL, Ensunsa JL, Keen CL. (1996) Manganese deficiency effects circulating growth hormone (GH), IGF-I, and IGFBPS in the male rat. Faseb Journal 10(3):4539-4539.

33. Cox D, Bolin C, Cardozo-Pelaez F. (2003) Assessment of dopaminergic neurons, DNA damage, DNA repair, and antioxidants in a model for manganese (MN) neurotoxicity. Free Radical Biology and Medicine 35:S156-S156.

34. Crittenden PL, Filipov NM. (2004) Enhanced Proinflammatory Cytokine Production By Activated Microglial And Macrophage Cell Lines Exposed To Manganese In Vitro. Toxicologist 78(1-S):180.
Activated microglia and/or astrocytes have been proposed to play a role in the mechanism of manganese (Mn) neurotoxicity such that neurons adjacent to activated microglia could be injured by proinflammatory cytokines and reactive oxygen species elaborated from the microglia. Recently, we demonstrated that Mn greatly potentiated the LPS (lipopolysaccharide)-induced proinflammatory cytokine (IL- 1beta, IL-6, and TNF-alpha) production by the microglial cell line, N9. Because (i) Mn exposure may also potentiate proinflammatory cytokine production in the periphery, (ii) there are functional differences between brain microglia and peripheral macrophages, and (iii) peripheral inflammation contributes to/modulates the inflammatory response in the brain, our objective was to compare the influence of Mn on proinflammatory cytokine production by N9 microglia and J774 macrophage cell lines. Cells were exposed in vitro to increasing concentrations (up to 500 µM) of Mn (as MnCl2) in the presence or absence of LPS (up to 1000 ng/ml). Following 24 h incubation, supernatants were collected and IL-1beta, IL-6, and TNF-alpha concentrations were determined by ELISA. Similar to the effects already observed in N9 microglia, LPS-induced proinflammatory cytokine production was potentiated dose-dependently by Mn in the J774 macrophage cell line. This finding suggests that Mn augments proinflammatory cytokine production through a common mechanism which is now the subject of investigation. Considering that Mn exposure is not confined to the nervous system, increased inflammatory response in the periphery may be contributory to the mechanism of Mn neuro- and, possibly, systemic toxicity.

35. Crittenden PL, Filipov NM. (2005) Manganese-Induced Alterations In Nf-kappaB-related Gene Expression By Activated Microglia. Toxicol Sci 84(1-S):126.
The central nervous system is uniquely sensitive to inflammation and the brain microglia are a primary source of proinflammatory cytokines. In previous work we demonstrated that manganese and lipopolysaccharide in combination (Mn+LPS) potentiate microglial production of proinflammatory cytokines such as IL-1beta, IL- 6, and TNF-alpha. Microglial cells (N9) were exposed to up to 500µM MnCl2 either by itself or combined with LPS (100ng/ml). The Mn+LPS combination elicited dose-dependent cytokine production that was substantially greater than that induced by Mn or LPS alone. To determine the mechanism of Mn-induced potentiation of cytokine production, the early NF-kappaB-signaling pathway genes were examined by utilizing a pathway-specific gene array. N9 cells were exposed to Mn, LPS, or Mn+LPS for various time periods. At the end of exposure, RNA was isolated and cDNA synthesized to probe the gene array. In comparison to control cells, 1 hour exposure to Mn (250µM) and LPS (100 ng/ml) increased the mRNA expression for the TNF-receptor associated factor-1 (TRAF1) and GM-CSF. Both GM-CSF and TRAF-1 are known to promote cell growth while TRAF-1 may also induce proinflammatory cytokine synthesis by a NF-kappaB-dependent mechanism. Expression of the proinflammatory molecule complement component 3 (C3) was also increased following Mn+LPS exposure. By examining the time-dependent expression of these (and other) growth and inflammatory factors, we hope to elucidate the possible mechanism(s) for the Mn-induced proinflammatory cytokine production.

36. Davis CD, Feng Y. (1999) Dietary copper, manganese and iron affect the formation of aberrant crypts in colon of rats administered 3,2 '-dimethyl-4-aminobiphenyl. Journal of Nutrition 129(5):1060-1067.
Aberrant crypt foci (ACF) are preneoplastic lesions for colon cancer. Altered amounts of copper-zinc (CuZnSOD) and manganese (MnSOD) superoxide clismutases have been implicated in multistage carcinogesis of both rodents and humans. Dietary factors are potential modulators of both CuZnSOD and MnSOD activity. The purpose of this study was to investigate the interactive effects of dietary copper,manganese, and iron on 3,2'-dimethyl-4-aminobiphenyl (DMABP)-induced ACF and superoxide dismutase activities in weanling rats fed low or adequate copper (0.8 or 5.1 mu g Cu/g diet), low or adequate manganese (0.6 or 17 mu g Mn/g diet), and adequate or high iron (37 or 140 mu g Fe/g diet). Twelve rats were allowed free access to each of these eight diets for 3.5 wk prior to DMABP administration and for an additional 8 wk after the first: DMABP injection. Rats fed low dietary copper had 105% ($P < 0.0001$) higher formation of DMABP-induced ACF than those fed adequate dietary copper. Rats ingesting low rather than adequate dietary manganese had 23% higher formation of ACF, and rats ingesting high rather than adequate dietary iron had 18% higher formation of ACF. Heart total superoxide dismutase activity was significantly correlated with the number of ACF ($r = -0.43$, $P < 0.0001$) in rats administered DMABP. These results suggest that dietary alterations that affect superoxide dismutase activity may affect cancer susceptibility.

37. Dedizio MCC, Gomez G, Bonilla E, Suarezroca H. (1995) Autoreceptor Presynaptic Control of Dopamine Release from Striatum Is Lost at Early Stages of Manganese Poisoning. Life Sciences 56(22):1857-1864.
Manganese (Mn) poisoning in man produces an early psychotic disorder that is later followed by a Parkinson-like syndrome. Since alterations in the brain DA system are thought to be involved, we assessed the presynaptic autoreceptor regulation of K+-evoked H-3-DA release from superfused striatal slices of mice treated i.p. with 5 mg Mn/kg weight/day for 2 and 8 weeks. Mn poisoning did not change basal and evoked DA release. In controls, 1 mu M apomorphine (APO), a D-2-like DA receptor agonist, produced an inhibition of K+-evoked H-3-DA release that was blocked by the D-2-like DA receptor antagonist, S(-)-sulpiride (1 mu M). Yet, APO lost its capacity to inhibit the K+-evoked H-3-DA release after 2 weeks of Mn poisoning. After 8 weeks of Mn poisoning, APO was again able to reduce K+-evoked H-3-DA release. MK-801 (0.3 mu M), a NMDA-glutamate receptor antagonist, could restore APO inhibitory control on DA release lost at week 2 of Mn poisoning. These findings suggest a NMDA-glutamate-receptor-mediated loss of autoreceptor presynaptic control of striatal DA release at early Mn poisoning.

38. Defazio G, Soleo L, Zefferino R, Livrea P. (1996) Manganese toxicity in serumless dissociated mesencephalic and striatal primary culture. Brain Research Bulletin 40(4):257-262.
Exposure to elevated levels of Manganese (Mn) can result in an irreversible brain disease characterized by extrapyramidal signs and symptoms resembling Parkinson's disease, To identify the neuronal target of Mn neurotoxicity, MnCl2 was added to serumless dissociated mesencephalic-striatal cultures from rat embryo on day 4 in vitro. High affinity H-3-dopamine (DA) and C-14-GABA uptakes were assessed as specific functional markers of DAergic and GABAergic cell viability, respectively. After 60-min exposure, MnCl2 at 0-200 mu M did not modify the morphologic appearance of the cultures, specific DA and GABA uptakes, or the

number of DA neurons visualized by immuno-cytochemical staining with tyrosine hydroxylase, In contrast, culture exposure to 20 mu M MnCl2 for 24 h selectively reduced specific GABA uptake without affecting specific DA uptake or the number of DA neurons. The exposure to a higher MnCl2 concentration was accompanied by signs of general toxicity, Striatal GABA neurons seemed to be more susceptible to Mn toxicity than mesencephalic GABA neurons. Overall, our data suggest that striatal neurons rather than mesencephalic DA neurons may be the main target of Mn neurotoxicity.

39. Desjardins P, Bandeira P, Hazell AS, Buu NT, Ledoux S, Butterworth RF. (1997) Increased peripheral-type benzodiazepine receptor ptbr gene expression in brain and kidney in hepatic encephalopathy he results from exposure to ammonia or manganese. 48th Annual Meeting of the American Association for the Study of Liver Diseases, Chicago, Illinois, USA, November 7-11, 1997. Hepatology 26(4 PART 2):249A.
Biosis copyright: biol abs. rrm meeting abstract rat peripheral-type benzodiazepine receptor ptbr gene expression brain kidney hepatic encephalopathy ammonia manganese digestive system toxicology genetics nervous system excretory system nervous system disease digestive system disease

40. Desole MS, Sciola L, Delogu MR, Sircana S, Migheli R. (1996) Manganese and 1-methyl-4-(2'-ethylphenyl)-1,2,3,6-tetrahydropyridine induce apoptosis in PC12 cells. Neuroscience Letters 209(3):193-196.
Oxidative stress is thought to play a key role both in the neurotoxin MPTP- and manganese (Mn)-induced neurotoxicity and in apoptotic cell death. In the present study, we report that Mn and the MPTP analogue 1-methyl-4-(2'-ethylphenyl)-1,2,3,6-tetrahydropyridine (2'Et-MPTP), which is metabolized by MAO-A to 1-methyl-4-(2'-ethylphenyl)-pyridinium ion (at concentrations of 0.5 and 1.0 mM), induced apoptosis in PC12 cells. Apoptosis was tested by terminal deoxynucleotidyl transferase-mediated 2'-deoxyuridine-5'-triphosphate nick end labelling (TUNEL) technique, flow cytometry and fluorescence microscopy. Both Mn and 2'Et-MPTP induced also a time-dependent decrease in cell viability, as determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Only Mn-induced apoptosis and decrease in cell viability were inhibited by the antioxidant ascorbic acid. We conclude that apoptosis may be an important mechanism of cell death in MPTP- and Mn-induced parkinsonism. However, an oxidative stress mechanism may be recognized only in the Mn-induced apoptosis.

41. Desole MS, Sciola L, Delogu MR, Sircana S, Migheli R, Miele E. (1997) Role of oxidative stress in the manganese and 1-methyl-4-(2'-ethylphenyl)-1,2,3,6-tetrahydropyridine-induced apoptosis in PC12 cells. Neurochemistry International 31(2):169-176.
Oxidative stress is thought to play a key role in the apoptotic death of several cellular systems, including neurons. Oxidative stress is proposed also as a mechanism of the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)- and manganese (Mn)-induced neuronal death. We have recently shown that Mn and the MPTP analogue 1-methyl-4-(2'-ethylphenyl)-1,2,3,6-tetrahydropyridine (2'Et-MPTP), which is metabolized by MAO-A to 1-methyl-4-(2'-ethylphenyl)-pyridinium ion, induce apoptosis in PC12 cells. In the present study, we evaluated the effects of deprenyl and the antioxidant drugs N-acetylcysteine (NAC) and ascorbic acid (AA) on Mn- and 2'Et-MPTP-induced apoptosis in PC12 cells. Apoptosis was tested by terminal

deoxynucleotidyl transferase-mediated 2'-deoxy-uridine-5'-triphosphate nick end labelling (TUNEL) technique, flow cytometry and fluorescence microscopy. Cell viability was determined by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay. Mn-induced apoptosis and decrease in cell viability was inhibited by the antioxidants NAC and AA. Deprenyl failed to inhibit the above Mn effects. Neither NAC, AA nor deprenyl were able to inhibit both 2'Et-MPTP-induced apoptosis and decrease in cell viability. These results confirm that apoptosis may be an important mechanism of cell death in MPTP- and Mn-induced parkinsonism. However, an oxidative stress mechanism may be recognized, at least in vitro, only in the Mn-induced apoptosis. (C) 1997 Elsevier Science Ltd.

42. Desole MS, Serra PA, Esposito G, Delogu MR, Migheli R, Fresu L, Rocchitta G, Miele M. (2000) Glutathione deficiency potentiates manganese-induced increases in compounds associated with high-energy phosphate degradation in discrete brain areas of young and aged rats. Aging Clinical and Experimental Research 12(6):470-477.
Aging is a factor known to increase neuronal vulnerability to oxidative stress, which is widely accepted as a mechanism of manganese-induced neuronal damage. We previously showed that subchronic exposure to manganese induced greater energy impairment (as revealed by increases in hypoxanthine, xanthine and uric acid levels) in the striatum and brainstem of aged rats vs young rats. This study shows that inhibition of glutathione (GSH) synthesis, by means of buthionine (SR) sulfoximine, decreased GSH levels and increased the ascorbic acid oxidation status in the striatum and limbic forebrain of both young and aged rats. In addition, inhibition of GSH synthesis greatly potentiated the manganese-induced increase in inosine, hypoxanthine, xanthine and uric acid levels in both regions of aged rats; moreover, inhibition of GSH synthesis significantly increased inosine, hypoxanthine, xanthine and uric acid levels in both regions of young rats, compared with the manganese-treated group. These results suggest that an impairment in the neuronal antioxidant system renders young rats susceptible to manganese-induced energetic impairment, and further support the hypothesis that an impairment in this system plays a permissive role in the increase of neuronal vulnerability that occurs with aging.

43. DiLorenzo D, Ferrari F, Agrati P, deVos H, Apostoli P, Alessio L, Albertini A, Maggi A. (1996) Manganese effects on the human neuroblastoma cell line SK-ER3. Toxicology and Applied Pharmacology 140(1):51-57.
SK-ER3 cells were recently demonstrated to represent a valuable model for the study of estrogen-inducible differentiation of neural cells in culture. This system may constitute an important tool also for the analysis of the effects of neurotoxic drugs. The present study demonstrates that short term exposure to Mn causes increased proliferation rate of SK-ER3 cells regardless of their differentiation. Long term treatment causes cell death in undifferentiated cells at concentrations of the metal as low as 100 nM. When the cells are differentiated with estrogens, death is observed only with a Mn concentration two orders of magnitude higher. Measurement of neurite extension and quantitation of tyrosine hydroxylase content after long-term exposure to the metal allow the conclusion that Mn does not alter the state of differentiation of SK-ER3 cells induced by the treatment with the hormone. The study underlines the importance of studying the effect of Mn in proliferating neural cells and demonstrates the toxic role of micromolar concentrations of the metal in fully differentiated neural cells. Since other authors produced evidence of effects of the metal on cell death and proliferation only at

millimolar concentrations, and none described its proliferative activity, the model utilized in the present study seems to be of particular interest. (C) 1996 Academic Press, Inc.

44. Dodd CA, Ward DL, Klein BG. (2005) Basal ganglia accumulation and motor assessment following manganese chloride exposure in the C57BL/6 mouse. International Journal of Toxicology 24(6):389-397.
Equivocal clinical evidence for involvement of manganese in development of Parkinson's disease necessitates experimental studies on this issue. The aged, 1-methyl-4-phenyl-1,2,3,6-tetrahyropyridine-treated C57BL/6 mouse is one of the most common models for Parkinson's disease. However, there is little information on brain bioaccumulation of manganese, and little or no information on clinical/behavioral manifestations of manganese neurotoxicity, in this strain. Male C57BL/6 retired breeder mice were given a single subcutaneous injection of either 0, 50, or 100 mg/kg of MnCl2 (single-dose regimen) or three injections of either of these doses over 7 days (multiple-dose regimen). Behavioral assessment was performed 24 h after final injection, followed by sacrifice, and body weight was recorded each day. There was a 105% increase in striatal manganese concentration 1 day after a single 100 mg/kg injection, and 421% and 647% increases, respectively, 1 day after multiple doses of 50 or 100 mg/kg of MnCl2. One day after a single injection, there were respective 30.9% and 38.9% decreases in horizontal movement (grid crossing) for the 50 and 100 mg/kg doses and a 43.2% decrease for the multiple dose of 100 mg/kg. There was no significant main effect of dose level on rearing, swimming, grip strength, or grip fatigue. Unlike previous work with the C57BL/6 strain using smaller intraperitoneal doses, this study established dosing regimens that produced significant increases in basal ganglia manganese concentration reminiscent of brain increases in the CD-1 mouse following subcutaneous doses close to our lowest. A decrease in locomotor behavior, significant but not severe in this study, has been reported following manganese exposure in other mouse strains. These data, particularly the significant increase in basal ganglia manganese concentration, provide guidance for designing studies of the potential role of manganese in Parkinson's disease using the most common animal model for the disorder.

45. Dorman DC. (2000) An integrative approach to neurotoxicology. Toxicologic Pathology 28(1):37-42.
Exposure of human populations to a wide variety of chemicals has generated concern about the potential neurotoxicity of new and existing chemicals. Experimental studies conducted in laboratory animals remain critical to the study of neurotoxicity. An integrative approach using pharmacokinetic, neuropathological, neurochemical, electrophysiological, and behavioral methods is needed to determine whether a chemical is neurotoxic. There are a number of factors that can affect the outcome of a neurotoxicity study, including the choice of animal species, dose and dosage regimen, route of administration, and the intrinsic sensitivity of the nervous system to the test chemical. The neurotoxicity of a chemical can vary at different stages of brain development and maturity. Evidence of neurotoxicity may be highly subjective and species specific and can be complicated by the presence of systemic disease. The aim of this paper is to give an overview of these and other factors involved in the assessment of the neurotoxic potential for chemicals. This article discusses the neurotoxicity of several neurotoxicants (eg, acrylamide, trimethyltin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, manganese, and ivermectin), thereby highlighting a multidisciplinary approach to the assessment of chemically induced neurotoxicity in animals. These model chemicals produce a broad range of effects that

includes peripheral axonopathy, selective neuronal damage within the nervous system, and impaired neuronal-glial metabolism.

46. Dukhande VV, Malthankar-Phatak GH, Hugus JJ, Daniels CK, Lai JCK. (2006) Manganese-induced neurotoxicity is differentially enhanced by glutathione depletion in astrocytoma and neuroblastoma cells. Neurochemical Research 31(11):1349-1357.
Manganese (Mn) is neurotoxic: the underlying mechanisms have not been fully elucidated. L-Buthionine-(S,R)-sulfoximine (BSO) is an irreversible inhibitor of gamma-glutamylcysteine synthetase, an important enzyme in glutathione (GSH) synthesis. To test the hypothesis that BSO modulates Mn toxicity, we investigated the effects of treatment of U-87 or SK-N-SH cells with MnCl2, BSO, or MnCl2 plus BSO. We monitored cell viability using MTT assay, staining with HO-33342 to assess live and/or apoptotic cells, and staining with propidium iodide (PI) to assess necrotic cells; we also measured cellular glutathione. Our results indicate decreased viability in both cell types when treated with MnCl2 or BSO: Mn was more toxic to SK-N-SH cells, whereas BSO was more toxic to U-87 cells. Because BSO treatment accentuated Mn toxicity in both cell lines, GSH may act to combat Mn toxicity. Thus, further investigation in oxidative stress mediated by glutathione depletion will unravel new Mn toxicity mechanism(s).

47. Eder K, Kirchgessner M, Kralik A. (1996) The effect of trace element deficiency (iron, copper, zinc, manganese, and selenium) on hepatic fatty acid composition in the rat. Trace Elements and Electrolytes 13(1):1-6.
The present study has been performed to investigate comparatively the effect of iron-, copper-, manganese-, selenium-, and zinc deficiency on fatty acid metabolism in rats. The experiment included 7 groups of 12 rats each (control group, iron-deficient group, copper-deficient group, manganese-deficient group, selenium-deficient group, zinc-deficient group, and a control group pair-fed to zinc-deficient group). In order to asses the fatty acid metabolism, fatty acid composition of liver total lipids was determined. The most pronounced changes of fatty acid composition compared with control rats occurred in iron- and copper-deficient rats. The changes in iron-deficient rats indicate impaired desaturation of saturated fatty acids and linoleic acid by Delta 9, Delta 6 and Delta 5 desaturase. The changes in copper-deficient rats indicate impaired Delta 9 desaturation of saturated fatty acids. Manganese-deficient rats had slightly decreased levels of mono-unsaturated fatty acids indicating also decreased Delta 9 desaturation. Selenium deficiency did not influence the fatty acid composition of liver total lipids. The fatty acid composition of both zinc-deficient rats and pair-fed control rats was quite different from ad libitum control rats demonstrating the effect of low food intake. In comparison with pair-fed control rats, zinc-deficient rats had increased levels of (n - 3) poly-unsaturated fatty acids whereas neither Delta 5 and Delta 6 desaturation nor Delta 9 desaturation was influenced by zinc deficiency. In conclusion, the data of the study show that several trace elements influence fatty acid metabolism.

48. Ensunsa JL, Symons JD, Lanoue L, Schrader HR, Keen CL. (2004) Reducing arginase activity via dietary manganese deficiency enhances endothelium-dependent vasorelaxation of rat aorta. Experimental Biology and Medicine 229(11):1143-1153.
L-Arginine is a common substrate for the enzymes arginase and nitric oxide synthase (NOS). Acute inhibition of arginase enzyme activity improves endothelium-dependent vasorelaxation, presumably by increasing availability of substrate for NOS. Arginase is activated by manganese

(Mn), and the consumption of a Mn-deficient (Mn-) diet can result in low arginase activity. We hypothesize that endothelium-dependent vasorelaxation is greater in rats fed Mn- versus Mn sufficient (Mn+) diets. Newly weaned rats fed Mn- diets (0.5 mug Mn/g; n = 12) versus Mn+ diets (45 mug Mn/g; n = 12) for 44 +/- 3 days had (i) lower liver and kidney Mn and arginase activity (P less than or equal to 0.05), (ii) higher plasma L-arginine (P less than or equal to 0.05), (iii) similar plasma and urine nitrate + nitrite, and (iv) similar staining for endothelial nitric oxide synthase in thoracic aorta. Vascular reactivity of thoracic aorta (similar to720 mum i.d.) and small coronary arteries (similar to110 mum i.d.) was evaluated using wire myographs. Acetylcholine (ACh; 10(-8)-10(-4) M) produced greater (P less than or equal to 0.05) vasorelaxation in thoracic aorta from Mn- rats (e.g., maximal percent relaxation, 79 +/- 7%) versus Mn+ rats (e.g., maximal percent relaxation, 54 +/- 9%) at 5 of 7 evaluated doses. Tension produced by NOS inhibition using N-G monomethyl-L-arginine (L-NMMA; 10(-3) M) and vasorelaxation evoked by (i) arginase inhibition using difluoromethylornithine (DFMO; 10(-7) M), (ii) ACh (10(-8)-10(-4) M) in the presence of DFMO, and (iii) sodium nitroprusside (10(-9)-10(-4) M) were unaffected by diet. No differences existed between groups concerning these responses in small coronary arteries. These findings support our hypothesis that endothelium-dependent vasorelaxation is greater in aortic segments from rats that consume Mn- versus Mn+ diets; however, responses from small coronary arteries were unaffected.

49. Erikson K, Aschner M. (2002) Manganese causes differential regulation of glutamate transporter (GLAST) taurine transporter and metallothionein in cultured rat astrocytes. Neurotoxicology 23(4-5):595-602.
Neurotoxicity due to excessive brain manganese (Mn) can occur due to environmental (air pollution, soil, water) and/or metabolic aberrations (decreased biliary excretion). Manganese is associated with oxidative stress, as well as alterations in neurotransmitter metabolism with concurrent neurobehavioral deficits. Based on the few existing studies that have examined brain regional [Mn], it is likely that in pathological conditions it can reach 100-500 muM. Amino acid (e.g. aspartate, glutamate, taurine), as well as divalent metal (e.g. zinc, manganese) concentrations are regulated by astrocytes in the brain. Recently, it has been reported that cultured rat primary astrocytes exposed to Mn displayed decreased glutamate uptake, thereby, increasing the excitotoxic potential of glutamate. Since the neurotoxic mechanism(s) Mn employs in terms of glutamate metabolism is unknown, a primary goal of this study was to link altered glutamate uptake in Mn exposed astrocytes to alterations in glutamate transporter message. Further we wanted to examine the gene expression of metallothionein (MT) and taurine transporter (tau-T) as markers of Mn exposure. Glutamate uptake was decreased by nearly 40% in accordance with a 48% decrease in glutamate/aspartate transporter (GLAST) mRNA. Taurine uptake was unaffected by Mn exposure even though tdu-T mRNA increased by 123%. MT mRNA decreased in these Mn exposed astrocytes possibly due to altered metal metabolism, although this was not examined. These data show that glutamate and taurine transport in Mn exposed astrocytes are temporally different.

50. Erikson KM, Dorman DC, Fitsanakis V, Lash LH, Aschner M. (2006) Alterations of oxidative stress biomarkers due to in utero and neonatal exposures of airborne manganese. Biological Trace Element Research 111(1-3):199-215.
Neonatal rats were exposed to airborne manganese sulfate (MnSO4) (0, 0.05, 0.5, or 1.0 mg Mn/m(3)) during gestation (d 0-19) and postnatal days (PNDs) 1-18. On PND 19, rats were

killed, and we assessed biochemical end points indicative of oxidative stress in five brain regions: cerebellum, hippocampus, hypothalamus, olfactory bulb, and striatum. Glutamine synthetase (GS) and tyrosine hydroxylase (TH) protein levels, metallothionein (MT), TH and GS mRNA levels, and reduced and oxidized glutathione (GSH and GSSG, respectively) levels were determined for all five regions. Mn exposure (all three doses) significantly ($p = 0.0021$) decreased GS protein levels in the cerebellum, and GS mRNA levels were significantly ($p = 0.0008$) decreased in the striatum. Both the median and high dose of Mn significantly ($p = 0.0114$) decreased MT mRNA in the striatum. Mn exposure had no effect on TH protein levels, but it significantly lowered TH mRNA levels in the olfactory bulb ($p = 0.0402$) and in the striatum ($p = 0.0493$). Mn exposure significantly lowered GSH levels at the median dose in the olfactory bulb ($p = 0.0032$) and at the median and high dose in the striatum ($p = 0.0346$). Significantly elevated ($p = 0.0247$) GSSG, which can be indicative of oxidative stress, was observed in the cerebellum of pups exposed to the high dose of Mn. These data reveal that alterations of oxidative stress biomarkers resulting from in utero and neonatal exposures of airborne Mn exist. Coupled with our previous study in which similarly exposed rats were allowed to recover from Mn exposure for 3 wk, it appears that many of these changes are reversible. It is important to note that the doses of Mn utilized represent levels that are a hundred- to a thousand-fold higher than the inhalation reference concentration set by the United States Environmental Protection Agency.

51. Erikson KM, Dorman DC, Lash LH, Aschner M. (2005) Persistent alterations in biomarkers of oxidative stress resulting from combined in utero and neonatal manganese inhalation. Biological Trace Element Research 104(2):151-163.
Neonatal female and male rats were exposed to airborne manganese sulfate (MnSO4) during gestation and postnatal d 1-18. Three weeks post-exposure, rats were killed and we assessed biochemical end points indicative of oxidative stress in five brain regions: cerebellum, hippocampus, hypothalamus, olfactory bulb, and striatum. Glutamine synthetase (GS) protein levels, metallothionein (MT) and GS mRNA levels, and total glutathione (GSH) levels were determined for all five regions. Overall, there was a statistically significant effect of manganese exposure on decreasing brain GS protein levels ($p=0.0061$), although only the highest dose of manganese (1 mg Mn/m(3)) caused a significant increase in GS messenger RNA (mRNA) in both the hypothalamus and olfactory bulb of male rats and a significant decrease in GS mRNA in the striatum of female rats. This highest dose of manganese had no effect on MT mRNA in either males or females; however, the lowest dose (0.05 mg Mn/m(3)) decreased MT mRNA in the hippocampus, hypothalamus, and striatum in males. The median dose (0.5 mg Mn/m(3)) led to decreased MT mRNA in the hippocampus and hypothalamus of the males and olfactory bulb of the females. Overall, manganese exposure did not affect total GSH levels, a finding that is contrary to those in our previous studies. Only the cerebellum of manganese-exposed young male rats showed a significant reduction ($p < 0.05$) in total GSH levels compared to control levels. These data reveal that alterations in biomarkers of oxidative stress resulting from in utero and neonatal exposures of airborne manganese remain despite 3 wk of recovery; however, it is important to note that the doses of manganese utilized represent levels that are 100-fold to a 1000-fold higher than the inhalation reference concentration set by the US Environmental Protection Agency.

52. Erikson KM, Dorman DC, Lash LH, Dobson AW, Aschner M. (2004) Airborne manganese exposure differentially affects end points of oxidative stress in an age and sex-dependent manner. Biological Trace Element Research 100(1):49-62.
Juvenile female and male (young) and 16-mo-old male (old) rats inhaled manganese in the form of manganese sulfate (MnSO4) at 0, 0.01, 0.1, and 0.5 mg Mn/m(3) or manganese phosphate at 0.1 mg Mn/m(3) in exposures of 6 h/d, 5 d/wk for 13 wk. We assessed biochemical end points indicative of oxidative stress in five brain regions: cerebellum, hippocampus, hypothalamus, olfactory bulb, and striatum. Glutamine synthetase (GS) protein levels, metallothionein (MT) and GS mRNA levels, and total glutathione (GSH) levels were determined for all five regions. Although most brain regions in the three groups of animals were unaffected by manganese exposure in terms of GS protein levels, there was significantly increased protein ($p<0.05$) in the hippocampus and decreased protein in the hypothalamus of young male rats exposed to manganese phosphate as well as in the aged rats exposed to 0.1 mg/m(3) MnSO4. Conversely, GS protein was elevated in the olfactory bulb of females exposed to the high dose of MnSO4. Statistically significant decreases ($p<0.05$) in NIT and GS mRNA as a result of manganese exposure were observed in the cerebellum, olfactory bulb, and hippocampus in the young male rats, in the hypothalamus in the young female rats, and in the hippocampus in the senescent males. Total GSH levels significantly ($p<0.05$) decreased in the olfactory bulb of manganese exposed young male rats and increased in the olfactory bulb of female rats exposed to manganese. Both the aged and young female rats had significantly decreased ($p<0.05$) GSH in the striatum resulting from manganese inhalation. The old male rats also had depleted GSH levels in the cerebellum and hypothalamus as a result of the 0.1-mg/m(3) manganese phosphate exposure. These results demonstrate that age and sex are variables that must be considered when assessing the neurotoxicity of manganese.

53. Erikson KM, Suber RL, Aschner M. (2002) Glutamate/aspartate transporter (GLAST), taurine transporter and metallothionein mRNA levels are differentially altered in astrocytes exposed to manganese chloride, manganese phosphate or manganese sulfate. Neurotoxicology 23(3):281-288.
Manganese (Mn)-induced neurotoxicity can occur due to environmental exposure (air pollution, soil, water) and/or metabolic aberrations (decreased biliary excretion). High brain manganese levels lead to oxidative stress, as well as alterations in neurotransmitter metabolism with concurrent neurobehavioral deficits. Based on the few existing studies that have examined brain regional Mn concentration, it is likely that in pathological conditions, Mn concentration can reach between 100 and 500 muM. Environmental Mn exposure as a result of methylcyclopentadienyl manganese tricarbonyl (MMT) combustion is in the form of phosphate or sulfate (MnPO4, MnSO4, respectively). Pharmacokinetic studies have shown that the Mn salt will determine the rate of transport into the brain: MnCl2 > MnSO4 > MnPO4. The salt-specific neurotoxicity of these species is unknown. The primary goal of this study was to examine gene expression of glutamate/aspartate transporter (GLAST), taurine transporter (tau-T), and metallothionein-I (MT-I) in astrocytes exposed to manganese chloride (MnCl2) manganese sulfate (MnSO4), and manganese phosphate (MnPO4). We hypothesized that the effects of MnPO4 and MnSO4 exposure on GLAST expression in astrocytes would be similar to those induced by MnCl2, since irrespective of salt species exposure, once internalized by astrocytes, the Mn ion would be identically complexed. At the same time, we hypothesized that the magnitude of the effect would be salt-dependent, since the chemical speciation would determine

the rate of intracellular uptake of Mn. MnCl2 caused a significant overall decrease ($P < 0.0001$) in astrocytic GLAST mRNA levels with MnSO4 causing a moderate decrease. MnPO4 exposure did not alter GLAST mRNA in astrocytes. We also sought to examine astrocytic metallothionein and taurine transporter gene expression as markers of manganese exposure. Our findings suggest that manganese chloride significantly decreased ($P < 0.0001$) astrocytic metallothionein mRNA compared to both the sulfate and phosphate species. However astrocytic taurine transporter mRNA was not affected by Mn exposure, irrespective of the salt species. These data are consistent with the hypothesis that astrocytic neurotoxicity due to Mn exposure is dependent upon its species, with solubility, and by inference, intracellular concentration, representing a major determinant of its neurotoxicity.

54. Fernandes A, Ferreira JG, de Oliveira E, Ponzoni S. (2004) L-Deprenyl (selegiline) neuroprotective failure in a manganese neurotoxicity model. Movement Disorders 19:S41-S41.

55. Filipov NM, Seegal RF, Lawrence DA. (2005) Manganese potentiates in vitro production of proinflammatory cytokines and nitric oxide by microglia through a nuclear factor kappa B-dependent mechanism. Toxicological Sciences 84(1):139-148.
Recent evidence suggests that the mechanism of manganese (Mn) neurotoxicity involves activation of microglia and/or astrocytes; as a consequence, neurons adjacent to the activated microglia may be injured. Mn modulation of proinflammatory cytokine expression by microglia has not been investigated. Therefore, the objectives of this research were to (1) assess whether Mn induces proinflammatory cytokine expression and/or modulates lipopolysaccharide (LPS)-induced expression of proinflammatory cytokines and (2) investigate possible mechanisms for such an induction. N9 microglia were exposed in vitro to increasing concentrations (50-1000 muM) of Mn in the presence or absence of LPS (10, 100, or 500 ng/ml). After various incubation times (up to 48 h), media levels of several cytokines and nitric oxide (NO) were determined, as was the expression of the inducible form of NO synthase (iNOS). Lactate dehydrogenase (LDH) release into the medium and the cellular uptake of Neutral Red were used as general measures for cytotoxicity. In the absence of LPS, Mn moderately increased interleukin-6 and tumor necrosis factor alpha (TNF-a) production only at higher Mn concentrations, which were cytotoxic. At all LPS doses, however, proinflammatory cytokine production was dose-dependently increased by Mn. Similarly, LPS-induced NO production and iNOS expression were substantially enhanced by Mn. Pharmacological manipulations indicated that nuclear factor kappa B (NFkappaB) activation is critical for the observed enhancement of cytokine and NO production. Within the context of inflammation, increased production of proinflammatory cytokines and NO by Mn could be an important part of the mechanism by which Mn exerts its neurotoxicity.

56. Fitsanakis VA, Piccola G, Aschner JL, Aschner M. (2005) Manganese transport by rat brain endothelial (RBE4) cell-based transwell model in the presence of astrocyte conditioned media. Journal of Neuroscience Research 81(2):235-243.
Manganese (Mn), an essential nutrient, is neurotoxic at high levels and has been associated with the development of a parkinsonian syndrome termed manganism. Currently, the mechanisms responsible for transporting Mn across the blood-brain barrier (BBB) are unknown. By using rat brain endothelial 4 (RBE4) cell monolayers cultured in astrocyte-conditioned media (ACM), we examine the effects of temperature, energy, proton (pH), iron (Fe), and sodium (Na+)

dependence on Mn transport. Our results suggest that Mn transport is temperature, energy, and pH dependent, but not Fe or Na+-dependent. These data suggest that Mn transport across the BBB is an active process, but they also demonstrate that the presence of ACM in endothelial cell cultures decreases the permeability of these cells to Mn, reinforcing the use of ACM or astrocyte cocultures in studies examining metal transport across the BBB. (c) 2005 Wiley-Liss, Inc.

57. Fitsanakis VA, Piccola G, Aschner JL, Aschner M. (2006) Characteristics of manganese (Mn) transport in rat brain endothelial (RBE4) cells, an in vitro model of the blood-brain barrier. Neurotoxicology 27(1):60-70.
Manganese (Mn), an essential elemental nutrient, is known to be neurotoxic at high occupational levels. We examined the transport of Mn across a monolayer of rat brain endothelial cell (RBE4) to evaluate whether an electromotive permeability mechanism is responsible for Mn transport across the blood-brain barrier (BBB). The Mn-54(2+) apparent permeability and flux showed significant temperature-, energy- and pH-dependence, as well as partial sodium-dependence. Additionally, iron (Fe)-rich and Fe-deficient media significantly increased the apparent permeability of Mn-54(2+). Finally, Mn flux and permeability decreased when RBE4 cells were grown in astrocyte-conditioned media (ACM), compared to standard alpha-media. These data reinforce observations that transport of Mn across the BBB occurs in part through active transport process. (C) 2005 Elsevier Inc. All rights reserved.

58. Fitsanakis VA, Piccola G, dos Santos AP, Aschner JL, Aschner M. (2007) Putative proteins involved in manganese transport across the blood-brain barrier. Human & Experimental Toxicology 26(4):295-302.
Manganese (Mn) is an essential nutrient required for proper growth and maintenance of numerous biological systems. At high levels it is known to be neurotoxic. While focused research concerning the transport of Mn across the blood-brain barrier (BBB) is on-going, the exact identity of the transporter(s) responsible is still debated. The transferrin receptor (TfR) and the divalent metal transporter-1 (DMT-1) have long been thought to play a role in brain Mn deposition. However, evidence suggests that Mn may also be transported by other proteins. One model system of the BBB, rat brain endothelial (RBE4) cells, are known to express many proteins suspected to be involved in metal transport. This review will discuss the biological importance of Mn, and then briefly describe several proteins that may be involved in transport of this metal across the BBB. The latter section will examine the potential usefulness of RBE4 cells in characterizing various aspects of Mn transport, and basic culture techniques involved in working with these cells. It is hoped that ideas put forth in this article will stimulate further investigations into the complex nature of Mn transport, and address the importance as well as the limitation of in vitro models in answering these questions.

59. Fong CS, Wu RM, Shieh JC, Chao YT, Fu YP, Kuao CL, Cheng CW. (2007) Pesticide exposure on southwestern Taiwanese with MnSOD and NQO1 polymorphisms is associated with increased risk of Parkinson's disease. Clinica Chimica Acta 378(1-2):136-141.
Background: Hypothetic mechanism of the individual vulnerability to oxidative stress through metabolism of environmental xenobiotics and genotypic polymorphisms has been considered to promote the development of Parkinson's disease (PD). In this case-control study, we determined the role of manganese-containing superoxide dismutase (MnSOD) and NAD(P)H: quinone oxidoreductase I (NQO1) genes in PD risk in a population with high prevalence of pesticide

exposure. Methods: From southwestern region of Taiwan, we enrolled 153 patients with idiopathic PD and 155 healthy control subjects matched for age, sex and origin. Detailed questionnaires of face-to-face interviews among these subjects were collected. PCR-based restriction fragment length polymorphism (RFLP) assays were used to determine the genotypes of MnSOD (-9 T > C) and NQO1 (609 C > T) genes. Results: Exposure to pesticides associated with PD was significant among patients with an increased odds ratio (OR) of 1.69 (95%CI, 1.07-2.65), and this association remained significant after adjustment for age, sex, and cigarette smoking (aOR=1.68, 95%CI, 1.03-2.76, P=0.023). Considering genetic factors, there were no significant differences in frequencies of both genotypes of MnSOD and NQO1 polymorphisms between PD patients and the control subjects (P > 0.05). However, this difference in genotype distribution was significant among subjects who had been exposed to pesticide, with aOR of 2.49 (95%CI, 1.18-5.26, P=0.0072) for MnSOD C allele and aOR of 2.42 (95%Cl, 1.16-4.76, P=0.0089) for NQO1 T allele, respectively. Moreover, among subjects exposed to pesticide, the combined MnSOD/NQO1 variant genotype was significantly associated with a 4.09-fold increased risk of PD (95%Cl, 1.34-10.64, P=0.0052). Conclusion: Susceptible variants of MnSOD and NQO1 genes may interact with occupational pesticide exposure to increase PD risk in southwestem Taiwanese.

60. Galvani P, Fumagalli P, Santagostino A. (1995) Vulnerability of Mitochondrial Complex-I in Pc12 Cells Exposed to Manganese. European Journal of Pharmacology-Environmental Toxicology and Pharmacology Section 293(4):377-383.
The present findings provide experimental evidence for the hypothesis that an impairment of mitochondrial function may be involved in manganese neurotoxicity. Specifically, the treatment of dopaminergic neuronal-derived cell line (PC12) with MnCl2 produced a significant inhibition of some mitochondrial complexes of the respiratory chain, while in the glial-derived cell line (C6) this effect was not observed. In PC12 the decrease in complex I activity was more pronounced than in other mitochondrial complexes. However treatment of cells with ZnSO4 exerted no significant variations in enzymatic activities. A direct exposure of mitochondrial fraction to MnCl2 reduced enzymatic activities of mitochondria in both cell lines adding further support to the proposed theory that the different sensitivity of the cells to manganese may be explained by a difference in uptake or intracellular storage. These data indicate that manganese neurotoxicity could be the result of a direct effect just on complex I activity or due to a secondary effect of oxidative stress induced by an excess of this transition metal.

61. Gavin CE, Gunter KK, Gunter TE. (1999) Manganese and calcium transport in mitochondria: Implications for manganese toxicity. Neurotoxicology 20(2-3):445-453.
Mn2+ is sequestered by liver and brain mitochondria via the mitochondrial Ca2+ uniporter. The mitochondrial Ca2+ uniporter is a cooperative transport mechanism possessing an external activation site and a transport site. Ca2+ binding to the activation site greatly increases the velocity of uptake of both Ca2+ and Mn2+. Electron paramagnetic resonance (EPR) shows that over 97% of the Mn2+ in the mitochondrial matrix is normally bound to the membrane or to matrix proteins. EPR measurements of manganese within living isolated mitochondria can be repeat-ed for hours, and during this time most of the manganese remains in the Mn2+ state. Mn2+ is transported out of mitochondria via the very slow Na+-independent efflux mechanism, which is an active (energy-requiring) mechanism. Mn2+ is not significantly transported over the Na+-dependent efflux mechanism, which is the dominant efflux mechanism in heart and brain

mitochondria. Mn2+ inhibits the efflux of Ca2+ through both of these efflux mechanisms, having an apparent K-i of 7.9 nmol/mg protein on the Na+-independent efflux mechanism and an apparent K-i of 5.1 nmol/mg on the Na+-dependent efflux mechanism. Mn2+ inhibition of Ca2+ efflux may increase the probability of the mitochondria undergoing the mitochondrial permeability transition (MPT). Intramitochondrial Mn2+ also inhibits State 3 mitochondrial respiration using either succinate or malate plus glutamate as substrate. The data suggest that Mn2+ depletes cellular energy supplies by interfering with oxidative phosphorylation at the level of the F(1)ATPase and at much higher concentrations, at Complex I. Effects such as these could lead to apoptosis in active neurons. (C) 1999 Inter Press, Inc.

62. Gong HQ, Amemiya T. (1996) Ultrastructure of retina of manganese-deficient rats. Investigative Ophthalmology & Visual Science 37(10):1967-1974.
Purpose. To elucidate some biologic functions of manganese in the retina. Methods. Three-week-old weanling Wistar Kyoto rats were used. Manganese-deficient rats were fed a manganese-deficient solid diet containing 0.23 mg manganese/100 g diet and all other nutrients. Control rats were fed a solid diet with 2.9 mg manganese/100 g diet. The retinas were examined by electron microscopy in the 12th, 18th, and 30th months of experimentation. Results, There was a statistically significant decrease in the plasma manganese levels in manganese-deficient animals compared to controls. In rats fed a manganese-deficient diet for 12 months, photoreceptor cells showed karyopyknosis-like changes of nuclei and a decrease in size and number of outer segments. Rats fed a manganese-deficient diet for 18 months showed a complete loss of photoreceptor cells, and the inner nuclear layer nuclei came in direct contact with the retinal pigment epithelium. Rats with manganese deficiency of 30 months showed invasion by capillaries and processes of Muller-like cells from the sensory retina into the retinal pigment epithelium. In the sensory retina, Muller-like cells proliferated, and neural cells disappeared. Conclusions. Because manganese is related to Mn superoxide in the mitochondrial matrix and to protein and glycogen metabolism, manganese deficiency may disturb the renewal of photoreceptor outer segment discs, and the decrease in antioxidant action caused by a lower level of Mn superoxide dismutase may accelerate the damage to photoreceptor cells. After neural cell loss, Mailer-like cells may proliferate. Manganese appears to be essential for maintaining photoreceptor cells.

63. Gong HQ, Amemiya T. (1999) Corneal changes in manganese-deficient rats. Cornea 18(4):472-482.
Purpose. This study was undertaken to examine the changes in the cornea due to dietary manganese (Mn) deficiency in Wistar-Kyoto rats, because there is a lack of information on the significance of manganese in the cornea. Methods, Mature female Wistar-Kyoto albino rats were mated with males. All pregnant females were divided into Mn-deficient and control groups. The offspring were fed a Mn-deficient diet. When they reached age 3 months, Mn-deficient females were mated with Mn-deficient males. The offspring of this second generation of Mn-deficient rats continued to be fed on the Mn-deficient diet and were used for the experiment. The corneas were examined at age 2 months. After 3 months on a Mn-deficient diet, the rats were given a normal diet for a 3-month recovery experiment. The corneas were examined by transmission electron microscopy (TEM) and scanning electron microscopy (SEM). Results. TEM revealed very few microvilli and bundles of tonofibrils and abnormal mitochondria in the corneal epithelium of Mn-deficient rats. The stroma was thin, and collagen fibers were decreased

prominently in diameter. Descemet's membrane was thinner than in the control group. SEM showed many fewer microvilli in the Mn-deficient rats and more dark cells in the most superficial layer of epithelium. SEM also showed endothelial cells with a pentagonal instead of a hexagonal shape in Mn-deficient rats. Rats fed a normal diet for 3 months after Mn deficiency showed a normal serum Mn level and almost normal corneal structure. Conclusion. This study suggested that the cornea needs Mn for the maintenance of its cell structure.

64. Gong HQ, Amemiya T. (1999) Optic nerve changes in manganese-deficient rats. Experimental Eye Research 68(3):313-320.
In the present study the changes in the optic nerve due to dietary manganese (Mn) deficiency has examined in Wistar Kyoto rats, since there is a lack of information on the significance of manganese in the optic nerve. After 5 months on a Mn-deficient diet, the optic nerve was examined by light and transmission electron microscopy. The serum manganese level of the deficient rats was significantly lower than that of the controls. The light microscopic findings showed significantly fewer myelinated axons in the Mn-deficient rats and Mn-recovery rats than in the control group, and there were obviously more oligodendrocytes in the recovery rats. Ultrastructural findings were: significantly decreased diameters and lamellae of myelinated axons in the optic nerves of the Mn-deficient rats and abnormal mitochondria in the axons. Rats fed a normal diet for 3 months after 5 months on a Mn deficient diet had a normal serum manganese level, but no change in the abnormal morphology of the myelinated axons. Tt is concluded that the optic nerve needs manganese for the maintenance of its cell structure. (C) 1999 Academic Press.

65. Gunter TE, Gunter KK, Aschner M. (2006) Mn2+ interference with ca(2+) activation of ATP production by mitochondria: A novel hypothesis of Mn neurotoxicity. Neurotoxicology 27(5):901-902.

66. Halatek T, Opalska B, Rydzynski K, Bernard A. (2006) Pulmonary response to methylcyclopentadienyl manganese tricarbonyl treatment in rats: injury and repair evaluation. Histology and Histopathology 21(11):1181-1192.
Methylcyclopentadienyl manganese tricarbonyl (MMT), an organometallic compound, used as an antiknock additive in fuels, may produce alveolar inflammation and bronchiolar cell injury. The aim of the experimental study on female rats was to determine by morphological examination and sensitive biomarkers, the course of the injury and repair process following a single i.p. injection of 5 mg/kg MMT. The animals were sacrificed 12, 24, 48 hours or 7 days post-exposure (PE). The first biochemical changes 12 h PE showed an increase in GSH-S-transferase (GST) activity in the lung parallel to the earliest observed morphological changes-vacuolation and swollen cytoplasm in type I pneumocytes. Alterations in type I pneumocytes were most prevalent in rat lung 24 h PE. Clara cells with dilated smooth endoplasmic reticulum membranes and cytoplasmic vacuolation could be observed. Compared to the values found for controls, Clara cell protein (CC16) in the bronchoalveolar lavage fluid (BALF) at 24 and 48 h PE decreased by 58% and 55%, respectively. At the same time (at 24 and 48 h), the total protein concentration in BALF increased 5 and 7 times, respectively. A significant rise in hyaluronic acid (HA) level was observed 24 and 48 h PE. Divided type II pneumocyte cells and Clara cells in their mitotic phase were observed in immunocytochemistry (detecting BrdU binding into DNA) 48 h PE. Seven days after MMT administration, fibroblasts, macrophages, collagen and

elastin fibres could be seen in the alveolar walls as well as neutrophils, lymphocytes, and alveoli macrophages in the alveolar lumen. We conclude that injury and repair of bronchial epithelium cells, especially of Clara cells and type II pneumocyte cells, play an important part in MMT toxicity, probably depending on the antioxidant status of these cells. The sensitive biomarkers of CC16 and hyaluronic acid in BALF and serum reflect lung injury and indicate the time course of pulmonary damage and repair processes.

67. HaMai D, Campbell A, Bondy SC. (2001) Modulation of oxidative events by multivalent manganese complexes in brain tissue. Free Radical Biology and Medicine 31(6):763-768.
Manganese toxicity can evoke neuropsychiatric and neuromotor symptoms, which have frequently been attributed to profound oxidative stress in the dopaminergic system. However, the characterization of manganese as a pro-oxidant remains controversial because antioxidant properties also have been associated with this metal. The current study was designed to address these disparate findings concerning the oxidative properties of manganese. The apparent ability of manganese in its divalent form to promote formation of reactive oxygen species (ROS) within a cortical mitochondrial-synaptosomal (P2) fraction was completely abolished by the addition of one five hundredth of its molarity of desferroxamine (DFO), a trivalent metal chelator. This large ratio and the high specificity of DFO for trivalent metal ions discounted the possibility of inhibition of ROS generation by direct sequestration of divalent manganese, and implied the trace presence of a trivalent metal. Further analysis suggested that this trace metal was manganic rather than ferric ion. Ferric ion was able to dampen the reactive oxygen species-generating capacity of manganous chloride, whereas manganic ion markedly promoted this property attributed to manganous ion. Such findings of the potent effects of trace amounts of trivalent cations upon Mn2+-related free radical generation offer resolution of earlier disparate findings concerning the oxidative character of manganese. (C) 2001 Elsevier Science Inc.

68. HaMai D, Rinderknecht AL, Guo-Sharman K, Kleinman MT, Bondy SC. (2006) Decreased expression of inflammation-related genes following inhalation exposure to manganese. Neurotoxicology 27(3):395-401.
Excessive exposure to manganese (Mn) by inhalation can induce psychosis and Parkinsonism. The clinical manifestations of Mn neurotoxicity have been related to numerous physiological and cellular processes, most notably dopamine depletion. However, few studies have explored the molecular events that are triggered in response to exposure to Mn by inhalation. In this current study, the transcriptional patterns of genes related to oxidative stress or inflammation were examined in the brain rats of exposed to inhaled Mn during either gestation or early adulthood. The expression of genes encoding for proteins critical to an inflammatory response and/or possessing pro-oxidant properties, including TGF beta and nNOS, were slightly depressed by prenatal exposure, whereas inhalation exposure to Mn during adulthood markedly down-regulated their transcription. However, when exposures to manganese occurred during gestation, the extent of altered gene expression induced by subsequent exposure to Mn in adulthood was reduced. This suggests that prior exposure to Mn may have attenuated the effects of inhalation exposure to Mn in adulthood, in which the expression of inflammation-related genes were suppressed.

69. Hazell AS, Gros P, Normandin L, Yi JH. (2005) Focal accumulation of manganese is correlated with levels of the divalent metal transporter-1 in manganese neurotoxicity. Journal of Neurochemistry 94:100-100.

70. Hazell AS, Norenberg MD, Yi JH. (2004) Involvement of oxidative stress in astrocytic changes in experimental sub-acute manganese neurotoxicity. Journal of Neurochemistry 90:15-15.

71. Hazell AS, Normandin L. (2002) Up-regulation of 'peripheral-type' benzodiazepine receptors in the globus pallidus in manganese neurotoxicity. Journal of Neurochemistry 81:104-104.

72. Higashi Y, Asanuma M, Miyazaki I, Hattori N, Mizuno Y, Ogawa N. (2004) Parkin attenuates manganese-induced dopaminergic cell death. Journal of Neurochemistry 89(6):1490-1497.
Manganese as environmental factor is considered to cause parkinsonism and induce endoplasmic reticulum stress-mediated dopaminergic cell death. We examined the effects of manganese on parkin, identified as the gene responsible for familial Parkinson's disease, and the role of parkin in manganese-induced neuronal cell death. Manganese dose-dependently induced cell death of dopaminergic SH-SY5Y and CATH.a cells and cholinergic Neuro-2a cells, and that the former two cell types were more sensitive to manganese toxicity than Neuro-2a cells. Moreover, manganese increased the expression of endoplasmic reticulum stress-associated genes, including parkin, in SH-SY5Y cells and CATH.a cells, but not in Neuro-2a cells. Treatment with manganese resulted in accumulation of parkin protein in SH-SY5Y cells and its redistribution to the perinuclear region, especially aggregated Golgi complex, while in Neuro-2a cells neither expression nor redistribution of parkin was noted. Manganese showed no changes in proteasome activities in either cell. Transient transfection of parkin gene inhibited manganese- or manganese plus dopamine-induced cell death of SH-SY5Y cells, but not of Neuro-2a cells. Our results suggest that the attenuating effects of parkin against manganese- or manganese plus dopamine-induced cell death are dopaminergic cell-specific compensatory reactions associated with its accumulation and redistribution to perinuclear regions but not with proteasome system.

73. Hirata Y. (2002) Manganese-induced apoptosis in PC12 cells. Neurotoxicology and Teratology 24(5):639-653.
Manganese has been known to induce neurological disorders similar to parkinsonisms for a long time. Dopamine deficiency has been demonstrated in Parkinson's disease and in chronic manganese poisoning, suggesting that the mechanisms underlying the neurotoxic effects of the metal ion are related to dysfunction of the extrapyramidal system. However, the details of the mechanisms have yet to be elucidated. In an effort to learn more about the toxicity of manganese, we have employed an in vitro model that uses the PC12 catecholaminergic cell line. In this model, manganese induces apoptosis in PC12 cells. In this paper, experiments conducted with this model, the cellular biochemical changes, and the mechanism of the cell death are reviewed. (C) 2002 Elsevier Science Inc. All rights reserved.

74. Hirata Y, Adachi E, Kiuchi K. (1998) Activation of JNK pathway and induction of apoptosis by manganese in PC12 cells. Journal of Neurochemistry 71(4):1607-1615.

Manganese is known to induce neurological disorders similar to parkinsonisms. A dopamine deficiency has been demonstrated in Parkinson's disease and in chronic manganese poisoning, suggesting that the mechanisms underlying the neurotoxic effects of the metal ion are related to a functional abnormality of the extrapyramidal system. However, the details have yet to be elucidated. Here we report that manganese causes characteristic internucleosomal DNA fragmentation, a biochemical hallmark of apoptosis, in PC12 cells. It was transcription dependent, relatively specific for manganese, and blocked in Bcl-2-overexpressed PC12 cells, The results indicate that apoptosis may play a role in the dopaminergic neurotoxicity associated with manganese, the first metal to be reported to induce this form of cell death. The early biochemical events show the impairment of energy metabolism, and the process may require new synthesis of proteins such as c-Fos and c-Jun. In addition, manganese induces phosphorylation of c-Jun at Ser(63) and Ser(73) and SEK1/MKK4 (c-Jun N-terminal kinase kinase) at Thr(258) and tyrosine phosphorylation of several proteins. These results indicate that manganese activates specific signal cascades including the c-Jun N-terminal kinase pathway

75. Hirata Y, Furuta K, Miyazaki S, Suzuki M, Kiuchi K. (2004) Anti-apoptotic and pro-apoptotic effect of NEPP11 on manganese-induced apoptosis and JNK pathway activation in PC12 cells. Brain Research 1021(2):241-247.
Neurite outgrowth-promoting prostaglandins (NEPPs), cyclopentenone prostaglandin derivatives, are found to be neurotrophic. These small organic compounds promote neurite outgrowth of PC 12 cells and dorsal root ganglion explants in the presence of nerve growth factor, and prevent neuronal cell death of HT22 cells and cortical neurons induced by various stimuli. In this study, we examined whether NEPP11 prevents manganese-induced apoptosis of PC 12 cells. NEPP11 (5 muM) attenuated manganese-induced DNA fragmentation by approximately 50%. In addition, NEPP11 partially prevented manganese-induced c-Jun phosphorylation and c-Jun N-terminal kinase (JNK) phosphorylation determined by Western blotting. Inhibition of the JNK signaling pathway by NEPP11 appeared to be selective, because NEPP 11 did not inhibit manganese-induced activation of p38 mitogen-activated protein kinase (p38 MAPK), extracellular signal-regulated kinase1/2 (ERK1/2), MEK1/2 and p70 S6 kinase (p70S6K) in PC 12 cells. In contrast, NEPP11 alone was toxic at higher concentrations (>10 muM) producing DNA fragmentation and activation of the JNK pathway. Molecular modifications of NEPP11 may strengthen its inhibitory effects on the JNK pathway while preventing its cytotoxicity, and thus may become a useful small molecule reagent for the treatment of manganese toxicity and other similar neurodegenerative processes.

76. Hirata Y, Kiuchi K, Nagatsu T. (2001) Manganese mimics the action of 1-methyl-4-phenylpyridinium ion, a dopaminergic neurotoxin, in rat striatal tissue slices. Neuroscience Letters 311(1):53-56.
Manganese and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) are known to induce neurological pathologies similar to that of parkinsonism. Previous studies performed in rat striatal slices have shown that MPTP and related compounds inhibit tyrosine hydroxylation, a rate-limiting step of dopamine biosynthesis. Here, we reported that manganese inhibited tyrosine hydroxylation in rat striatal slices. In addition, manganese caused increase in the levels of lactate indicating that aerobic glycolysis was inhibited in striatal slices. This inhibition was unique to manganese since other divalent cations, such as magnesium and zinc, did not increase lactate

concentrations. These results suggest that the mechanisms by which manganese produces dysfunction of the nervous system are similar to those of MPTP. (C) 2001 Elsevier Science Ireland Ltd. All rights reserved.

77. Hojo Y, Asano Y, Tonan Y. (1999) Manganese(II)-induced brain toxicity and paramagnetic species. Japanese Journal of Toxicology and Environmental Health 45(1):P34-P34.

78. Hsiao WL, Mendosa G, Kothari NH, Fan H. (1996) Comparison of transformation by manganese sulfate and 5-azacytidine in rat 6 cells overexpressing the c-myc oncogene. Carcinogenesis 17(12):2771-2777

79. Huang CC, Weng YH, Lu CS, Chu NS, Yen TC. (2003) Dopamine transporter binding in chronic manganese intoxication. Journal of Neurology 250(11):1335-1339.
Chronic exposure to manganese may induce parkinsonism similar to idiopathic Parkinson's disease (PD). However, clinical manifestations of manganism also have some features different from PD. The mechanisms of manganese-induced parkinsonism remain not fully understood. Tc-99m-TRODAT-1 is a cocaine analogue that can bind to the dopamine transporter (DAT) site reflecting the function of presynaptic dopaminergic terminals. The purpose of this study was to evaluate DAT function using Tc-99m-TRODAT-1 to investigate the integrity of the presynaptic dopaminergic terminals in manganese-induced parkinsonism. Brain Tc-99m-TRODAT-1 single photon emission computed tomography was performed in 4 patients with chronic manganese intoxication in a ferromanganese smelting plant in Taiwan. Twelve PD patients and 12 healthy volunteers served as abnormal and normal controls, respectively. Clinically, all manganism patients had a bradykinetic-rigid syndrome. The scores of the Unified Parkinson's Disease Rating Scale ranged between 19 and 64. The uptake values of the Tc-99m-TRODAT-1 were 0.868+/-0.136 in the right corpus striatum and 0.865+/-0.118 in the left, as compared with 0.951+/-0.059 and 0.956+/-0.058, respectively for the normal controls. The data were significantly higher than 0.250+/-0.070 and 0.317+/-0.066 respectively for the PD patients. Interestingly, there was a mild decrease in the uptake of Tc-99m-TRODAT-1 in the putamen and the ratio of putamen and caudate when compared with the normal controls. Although the DAT shows a slight decrease in the putamen of manganism patients as compared with that of the normal controls, the data indicate that the presynaptic dopaminergic terminals are not the main target of chronic manganese intoxication. In addition Tc-99m-TRODAT-1 SPECT can provide a useful, convenient and inexpensive tool for differentiation between chronic manganism and PD.

80. Husain M, Khanna VK, Roy A, Tandon R, Pradeep S, Seth PK. (2001) Platelet dopamine receptors and oxidative stress parameters as markers of manganese toxicity. Human & Experimental Toxicology 20(12):631-636.
The present study has been undertaken to investigate whether neurotoxic effects of manganese (Mn) are reflected in platelets in rats to monitor the usefulness of platelet as peripheral model. Exposure of rats to Mn (10 or 15 mg/kg bw, i.p.) for 45 days caused a significant increase in membrane fluidity as evidenced by decrease in fluorescence polarisation in platelets (11% and 14%) and striatum (9% and 13%). These rats exhibited a significant increase in superoxide dismutase activity both in platelets (24% and 37%) and striatum (31% and 42%), respectively, in comparison to controls. Exposure of rats to Mn for 45 days (15 mg/kg bw, i.p.) caused a significant decrease in reduced glutathione content (platelets 20%, striatum 24%) and catalase

activity (platelets 35%, striatum 44%) compared to control rats. Rats exposed to Mn (10 or 15 mg/kg bw, i.p.) for 15 days exhibited a significant increase in dopamine receptors both in platelets (55% and 40%) and striatum (38% and 31%). The results suggest that exposure to Mn may alter the membrane functions and impair the anti-oxidant defense mechanism both in platelets and brain. The study also suggests that dopaminergic mechanisms are impaired following Mn exposure and such changes are reflected in platelets. Interestingly, parallel changes both in striatum and platelets, as observed in the present study, strengthen the usefulness of platelets as a peripheral neuronal model.

81. Isaac AO, Kawikova I, Bothwell ALM, Daniels CK, Lai JCK. (2006) Manganese treatment modulates the expression of peroxisome proliferator-activated receptors in astrocytoma and neuroblastoma cells. Neurochemical Research 31(11):1305-1316.
Peroxisome proliferator-activated receptors (PPARs) play roles in neural cells by regulating energy balance, cell proliferation and anti-oxidant responses although the molecular mechanisms underlying such roles are unclear. Chronic exposure to excess manganese (Mn) leads to neurotoxicity, although Mn-induced neurotoxic mechanisms have not been fully elucidated. We hypothesized Mn neurotoxicity differentially alters the expression of PPARs. We investigated the effects of manganese chloride treatment (0.01-4 mM) on protein expression of PPAR isoforms (alpha, beta, and gamma) in human astrocytoma (U87) and neuroblastoma (SK-NSH) cells. The two cell types expressed the 3 PPAR isoforms differentially: their expression of the PPARs was altered by Mn-treatment. Furthermore, nuclear and cytosolic fractions derived from the 2 cell types, with and without Mn-treatment, exhibited marked differences in the protein content of PPARs. Our results constitute the first demonstration that the PPAR signaling pathway may assume pathophysiological importance in Mn neurotoxicity.

82. Javorina A, Duhart H, Ali SF, Schlager JJ, Hussain SM. (2006) Assessment Of Manganese Nanoparticle (Mn-40nm) In PC12 Cells. Toxicol Sci 90(1-S):319.
This study was designed to investigate whether manganese nanosize 40nm particles induce dopamine (DA) depletion in PC12 cells. The cells were exposed to various (0-100 ug/ml) concentrations of Mn-40nm, Mn-acetate and Ag-15nm for 24 hours. After exposure, MTT and neurotransmitters such as DOPAC, HVA, 5HIAA, 5HT and DA were measured to examine the toxicity and changes in levels of neurotransmitters. The MTT assay results demonstrated that Ag-15nm displayed a significant toxicity at the 25 ug/ml dose, whereas Mn-40 nm displayed a more moderate toxicity. However, Mn-40nm induced potent dose-dependent depletion of dopamine. The dopamine depletion was compared with bulk manganese material that is known to induce dopamine depletion. Mn-acetate induced dopamine depletion but the level of Mn-40nm induced depletion was relatively higher. Ag-15nm did not show significant depletion of dopamine although significant toxicity was evident as per the MTT assay. The results clearly demonstrated that Mn-40nm induced dopamine depletion in a dose dependent manner when compared to other nanomaterials. To better characterize the effects of the Mn- 40nm particles, the cells were examined via an advanced optical illumination system, CytoViva. Mn-40nm particles were observed to be internalized by the cells as well as attach to the cell surface. Additionally, cells were grown in the presence of nerve growth factor (NGF) to determine the effects of Mn-40nm on cell differentiation. These results indicate qualitative changes in the NGF treated cells in response to Mn-40nm exposure.

83. Kalea AZ, Harris PD, Klimis-Zacas DJ. (2005) Dietary manganese suppresses alpha(1) adrenergic receptor-mediated vascular contraction. Journal of Nutritional Biochemistry 16(1):44-49.
We examined the effect of dietary manganese (Mn) on the vascular contractile machinery in rat thoracic aortas. Weanling male Sprague Dawley rats were fed either an Mn-deficient (MnD), Mn-adequate (MnA) or Mn-supplemented (MnS) diet (< 1, 10-15 and 45-50 ppm Mn, respectively). After 15 weeks on the diets the rats were sacrificed and 3-min aortic rings were contracted in six cumulative doses of the alpha(1), adrenergic receptor agonist L-phenylephrine (L-Phe, 10(-8) to 3 X 10(-6) M) under 1.5-g preload and relaxed with one dose of acetylcholine (3 x 10(-6) M) to assess intact endothelium. The maximal force (F-max) of contraction and relaxation, as well as the vessel sensitivity (pD(2)) were determined. Manganese deficiency, assessed by hepatic Mn content, significantly lowered the rate of animal growth. A two-way analysis of variance revealed that MnS animals developed lower F-max when contracted with L-Phe compared with the MnD and MnA animals (Pless than or equal to001). Thus, dietary Mn at levels of 45-50 ppm affects the contractile machinery by reducing maximal vessel contraction to an alpha(1) adrenergic agonist. The observed pD(2) was significantly greater in the MnD group compared with the MnA and MnS animals (Pless than or equal to.001). Thus, restriction of dietary Mn affects vascular sensitivity to the alpha(1) adrenergic receptor. Our results demonstrate for the first time that dietary Mn influences the receptor signaling pathways and contractile machinery of vascular smooth muscle cells in response to an a, adrenergic receptor.

84. Kalea AZ, Schuschke DA, Harris PD, Klimis-Zacas DJ. (2006) Cyclooxygenase inhibition restores endothelium-mediated vasodilation in manganese deficiency. Faseb Journal 20(4):A729-A729.

85. Kanthasamy A, Choi C, Anantharam V, Kanthasamy A. (2006) Manganese upregulates cellular prion proteins and inhibits the rate of proteinase-K dependent proteolysis in cell culture models of prion diseases. Neurotoxicology 27(6):1163-1164.

86. Keller J, Owens CT, Lai JCK, Devaud LL. (2005) The effects of 17 beta-estradiol and ethanol on zinc- or manganese-induced toxicity in SK-N-SH cells. Neurochemistry International 46(4):293-303.
Serious neurodegenerative disorders are increasingly prevalent in our society and excessive oxidative stress may be a key mediator of neuronal cell death in many of these conditions. A variety of metals, such as manganese and zinc, are essential trace elements but can reach localized toxic concentrations through various disease processes or environmental exposures and have been implicated as having a role in neurodegeneration. Both manganese and zinc exist as bivalent cations and are essential cofactors/activators for numerous enzymes. Evidence suggests one action of these metals, when concentrated beyond physiological levels, may be to inhibit cellular energy production, ultimately leading to increased radical formation. Our studies were undertaken to directly investigate the toxic effects of manganese and zinc in an immortalized neuronal-like cell line (SK-N-SH) by testing interactions with the antioxidant, 17beta-estradiol, and the neurotoxin, ethanol. Employing undifferentiated SK-N-SH cells, we found that these metals caused biphasic effects, enhancing cell proliferation at low doses and inducing cell death at higher doses. Zinc was both more efficacious and more potent than manganese in enhancing

growth and in causing cell death. 17beta-Estradiol and ethanol enhanced the proliferative actions of zinc and manganese across a wide concentration range. Furthermore, co-treatment with either 17beta-estradiol or ethanol afforded protection against manganese-, but not zinc-induced toxicity. Finally, combined administration of 17beta-estradiol and ethanol to SK-N-SH cells resulted in both a loss of growth enhancement and protective properties that were observed when these substances were administered individually. We also noted that the toxic effects occurred more rapidly from zinc than manganese exposure. Taken together, these data suggest that oxidative stress likely has a role in cell death resulting from toxic exposure to either zinc or manganese, but there is a difference in the precise mechanism of their effects.

87. Khan KN, Andress JM, Smith PF. (1997) Toxicity of subacute intravenous manganese chloride administration in beagle dogs. Toxicologic Pathology 25(4):344-350.
Manganese (Mn), a naturally occurring essential trace element, is currently being used as a metal complex for pharmaceutical and magnetic resonance imaging agents. Despite its popularity in these practices, minimal attention has focused on possible toxicity of released free Mn ions, which could occur if these agents decomplexed. There is especially limited information available regarding acute toxicity of Mn in dogs. In this study, we performed an in-depth evaluation of acute toxicologic potential of manganese chloride (MnCl2) when administered as a 4-hr/day intravenous infusion to male beagle dogs. The dose of MnCl2 used (16 mg/kg/day) was equivalent to approximately 3-5 times the daily dose of Mn typically administered in some of the Mn-complexed agents. All routine toxicologic endpoints were evaluated, including cardiovascular parameters. This dosing regimen resulted in the death or moribund sacrifice of all the animals within 4 days of initiation of treatment. Clinical evidence of toxicity included loss of appetite, reduction in blood pressure with reflex tachycardia, and a marked increase in liver enzymes, beginning with the first dose and increasing in severity with successive doses. Gross and histopathologic evaluations confirmed severe hepatotoxicity. which was characterized by massive hepatocellular necrosis, periportal hemorrhages, and mild biliary epithelial hyperplasia. These results indicate that acute treatment of beagle dogs with MnCl2 causes severe hepatotoxicity and hypotension with reflex tachycardia and suggest that dogs are very sensitive to toxic effects of Mn.

88. Kim Y, Park JK, Choi Y, Yoo CI, Lee CR, Lee H, Lee JH, Kim SR, Jeong TH, Yoon CS and others. (2005) Blood manganese concentration is elevated in iron deficiency anemia patients, whereas globus pallidus signal intensity is minimally affected. Neurotoxicology 26(1):107-111.
Objectives: To determine whether blood manganese (Mn) concentration is elevated in patients with iron deficiency anemia (IDA), and whether this affects signal intensities in the globus pallidus. Methods: Twenty-seven patients with IDA and 10 control subjects were tested for blood Mn, and brain magnetic resonance images (MRI) were also examined. Seventeen of the 27 patients were followed-up after iron therapy. Results: IDA patients had a mean blood Mn concentration of 2.05 +/- 0.44 mug/dl, which was higher than controls. The mean pallidal index (PI) of anemic patients was not different from that of controls. There was a correlation between log blood Mn and PI ($p = 0.384$, $P = 0.048$; $n = 27$) in IDA patients. None of the patients showed increased signals in the globus pallidus in TI-weighted MRI Blood Mn levels decreased and hemoglobin levels increased after iron therapy ($P < 0.05$). Conclusion: Although blood Mn is elevated in IDA patients, there is no increase in globus pallidus MRI signal intensity. These

findings stand in contrast to those of our other studies showing patients with chronic liver disease or occupational Mn exposure have elevated signal intensities remarkably. (C) 2004 Elsevier Inc. All rights reserved.

89. Kralik A, Kirchgessner M, Eder K. (1995) The Effect of Manganese Deficiency on Parameters of Thyroid-Hormone Metabolism in Rats. Journal of Animal Physiology and Animal Nutrition-Zeitschrift Fur Tierphysiologie Tierernahrung Und Futtermittelkunde 73(5):269-275.
The effect of manganese deficiency on parameters of thyroid-hormone metabolism in rats The effect of manganese deficiency on parameters of thyroid-hormone metabolism was examined in two experiments with 24 male, weanling, Sprague Dawley rats per experiment. The animals were fed a semisynthetic casein-based diet containing either 0.2 mg Mn/kg (manganese deficient diet) or 40 mg Mn/kg (control diet). The activity of arginase in liver was chosen as the criterion for determining the manganese status of the rats, and was clearly lowered in both experiments by manganese deficiency. While being unchanged in experiment 1, the live weight of the manganese-deficient animals at the end of experiment 2 was significantly reduced in contrast to control. The concentration of T-3 in the serum of the deficient animals was decreased in experiment 1, while tending to be increased in experiment 2. The concentration of T-4 in the serum of the manganese-deficient rats was significantly decreased in both experiments (experiment 1: -18 %; experiment 2: -31 %). The concentration of free T-4 in serum was not changed by manganese deficiency. The activity of hepatic deiodinase was increased in both experiments in manganese-deficient rats (experiment 1: 35 %, ns; experiment 2: 48 %). The results of this investigation show a potential role for manganese in thyroid-hormone metabolism.

90. Krieger D, Krieger S, Jansen O, Gass P, Theilmann L, Lichtnecker H. (1995) Manganese and Chronic Hepatic-Encephalopathy. Lancet 346(8970):270-274.
Clinical observations and animal studies have raised the hypothesis that increased concentrations of manganese (Mn) in whole blood might lead to accumulation of this metal within the basal ganglia in patients with end-stage liver disease. We studied ten patients with liver failure (and ten controls) by magnetic resonance imaging (MRI) and measurement of Mn in brain tissue of three patients who died of progressive liver failure (and three controls) was also done. Whole blood Mn concentrations in patients with liver cirrhosis were significantly increased (median 34.4 mu g/L vs 10.3 mu g/L in controls; p=0.0004) and pallidal signal intensity indices correlated with blood Mn (R(s)=0.8, p=0.0058). Brain tissue samples reveal highest Mn concentrations in the caudate nucleus, followed by the quadrigeminal plate and globus pallidus. Mn accumulates within the basal ganglia in liver cirrhosis. Similarities between Mn neurotoxicity and chronic hepatic encephalopathy suggest that this metal may have a role in the pathogenesis of chronic hepatic encephalopathy. Further studies are warranted because the use of chelating agents could prove to be a new therapeutic option to prevent or reverse this neuropsychiatric syndrome.

91. KulkarniNarla A, Getchell TV, Schmitt FA, Getchell ML. (1996) Manganese and copper-zinc superoxide dismutases in the human olfactory mucosa: Increased immunoreactivity in Alzheimer's disease. Experimental Neurology 140(2):115-125.
Superoxide dismutases are the cell's major enzymatic defenses against cytotoxic reactive oxygen species and oxidative stress. Reactive oxygen species, which induce the expression of these enzymes, leave been implicated in the neurodegeneration associated with Alzheimer's disease

(AD), and individuals with AD exhibit early, severe deficits in olfactory ability. We used immunohistochemistry to examine the cellular localization of manganese and copper-zinc superoxide dismutases in the olfactory mucosae of nondemented young/middle-aged and old subjects as well as age- and postmortem-interval matched nondemented elderly individuals and those with AD. Tissues were obtained at autopsy from individuals ranging in age from 19 to 98 years old. Immunoreactivity for both enzymes was localized in olfactory receptor neurons, sustentacular and basal cells in the olfactory epithelium, and in olfactory and extrinsic nerves, Bowman's glands, and vascular endothelium in the lamina propria. Computer-assisted quantitative analysis demonstrated that very intense immunoreactivity for both manganese and copper-zinc superoxide dismutases occupied significantly more area, particularly near the surface and in the basal region, of the olfactory epithelium from subjects with AD than from the age- and postmortem interval-matched nondemented elderly subjects. The pronounced increase in superoxide dismutase immunoreactivity in the olfactory epithelium of AD subjects suggests that oxidative stress may be responsible, at least in part, for the olfactory deficits in subjects with AD. (C) 1996 Academic Press, Inc.

92. Kumar R, Srivastava S, Agrawal AK, Seth PK. (1996) Alteration in some membrane properties in rat brain following exposure to manganese. Pharmacology & Toxicology 79(1):47-48.
Biosis copyright: biol abs. rrm research article rat toxicology manganese neurotoxins brain membrane alteration manganese-induced central nervous system dysfunction membranes toxicity nervous system disease

93. Lai JCK, Chan AWK, Minski MJ, Lim L. (1995) Trace-Metals in Brain Mitochondria and Synaptosomes - Modulation by Manganese Toxicity. Faseb Journal 9(3):A446-A446.

94. Laurant P, Chanut E, Bobillier-Chaumont S, Gaillard E, Jacquot C, Trouvin JH, Berthelot A. (2003) Attenuation of the development of DOCA salt hypertension by a high Mn intake in the rat. Trace Elements and Electrolytes 20(3):172-180.
The effects of a high Mn intake on blood pressure, vascular reactivity and central catecholamine levels were studied in DOCA salt-hypertensive rats. High Mn intake inhibited blood pressure elevation in DOCA salt rats but did not modify it in normotensive rats. The blood pressure-lowering effect of Mn was associated with inhibited cardiac hypertrophy and increased natriuresis. Pharmacological studies in blood vessels showed that high Mn intake normalized vasoconstriction and sensitivity to norepinephrine of isolated and perfused mesenteric vascular beds from DOCA salt rats. Furthermore, high Mn intake improved the endothelium- and NO-dependent relaxation in isolated aortae from DOCA salt-hypertensive rats but not in those from normotensive rats. Norepinephrine levels were higher in the hypothalamus of DOCA salt-hypertensive rats than in those of normotensive rats, and high Mn intake decreased norepinephrine levels in hypothalamus of DOCA salt rats. In conclusion, a high Mn intake attenuated the development of hypertension with beneficial vascular and central effects. Mechanisms related to the pathophysiological development of DOCA salt hypertension may be involved.

95. Layrargues GP, Rose C, Spahr L, Zayed J, Normandin L, Butterworth RF. (1998) Role of manganese in the pathogenesis of portal-systemic encephalopathy. Metabolic Brain Disease 13(4):311-317.
Amongst the potential neurotoxins implicated in the pathogenesis of hepatic encephalopathy, manganese emerges as a new candidate. In patients with chronic liver diseases, manganese accumulates in blood and brain leading to pallidal signal hyperintensity on T-1-weighted Magnetic Resonance (MR) Imaging. Direct measurements in globus pallidus obtained at autopsy from cirrhotic patients who died in hepatic coma reveal 2 to 7-fold increases of manganese concentration. The intensity of pallidal MR images correlates with blood manganese and with the presence of extrapyramidal symptoms occurring in a majority of cirrhotic patients. Liver transplantation results in normalization of pallidal MR signals and disappearance of extrapyramidal symptoms whereas transjugular intrahepatic portosystemic shunting induces an increase in pallidal hyperintensity with a concomitant deterioration of neurological dysfunction. These findings suggest that the toxic effects of manganese contribute to extrapyramidal symptoms in patients with chronic liver disease. The mechanisms of manganese neurotoxicity are still speculative, but there is evidence to suggest that manganese deposition in the pallidum may lead to dopaminergic dysfunction. Future studies should be aimed at evaluating the effects of manganese chelation and/or of treatment of the dopaminergic deficit on neurological symptomatology in these patients.

96. Ledig M, Copin JC, Tholey G, Leroy M, Rastegar F, Wedler F. (1995) Effect of manganese on the development of glial cells cultured from prenatally alcohol exposed rats. Neurochemical Research 20(4):435-441.
BIOSIS COPYRIGHT: BIOL ABS. Maternal alcohol abuse is known to produce retardation in brain maturation and brain functions. Using cultured glial cells as a model system to study these effects of alcohol we found an alcohol antagonizing property for manganese (Mn). Mn was added to the alcohol diet (MnCl2, 25 mg/l of 20% v/v ethanol) of pregnant rats. Glial cells were cultured during 4 weeks from cortical brain cells of pups born to these mothers. Several biochemical parameters were examined: protein levels, enzymatic markers of glial cell maturation (enolase and glutamine synthetase), superoxide dismutase a scavenger of free radicals produced during alcohol degradation. The results were compared to appropriate controls. A beneficent effect of Mn was observed for the pups weight which was no more significantly different from the control values. Protein levels, enolase and glutamine synthetase activities were increased mainly during the proliferative period when Mn was added to the alcohol diet compa

97. Lee B, Hiney JK, Pine MD, Srivastava VK, Dees WL. (2007) Manganese stimulates luteinizing hormone releasing hormone secretion in prepubertal female rats: hypothalamic site and mechanism of action. Journal of Physiology-London 578(3):765-772.
We have shown recently that Mn2+ stimulates gonadotropin secretion via an action at the hypothalamic level, and a diet supplemented with a low dose of the element is capable of advancing the time of female puberty. In this study, we used an in vitro approach to investigate the mechanism by which Mn2+ induces luteinizing hormone-releasing hormone (LHRH) secretion from prepubertal female rats. Themedial basal hypothalamus from 30-day-old rats was incubated in Locke solution for 30 min to assess basal LHRH secretion, then incubated with buffer alone or buffer plus either a nitric oxide synthase (NOS) inhibitor (N-monomethyl-L-arginine (NMMA); 300 or 500 mu M) or a soluble guanylyl cyclase (sGC) inhibitor (1H-[1,2,4]

oxadiazolo[4,3- a] quinoxalin-1-one(ODQ); 100 or 250 mu M) for another 30 min. Finally, the incubation continued for a further 30 min, but in the presence of MnCl2 (50 or 250 mu M) to assess the effect of the blockers on stimulated LHRH secretion. Both 50 and 250 mu M MnCl2 stimulated LHRH release ($P < 0.05$ and $P < 0.01$, respectively). The addition of 300-500 mu M NMMA to the medium did not block Mn2+-stimulated release of LHRH, even with the higher dose of MnCl2. Furthermore, while 50, 100 and 250 mu M MnCl2 all significantly induced LHRH release, the two lowest doses did not stimulate total nitrite released from the same tissue, an effect only observed with the highest dose. Taken together, these data suggest that Mn2+ is not an effective stimulator of NO. Conversely, inhibiting sGC with ODQ blocked the Mn2+-stimulated secretion of LHRH in a dose-dependent manner, indicating that GC is the site of action of Mn2+. Additionally, we showed that Mn2+ stimulated cGMP and LHRH from the same tissues, and that downstream blocking of protein kinase G formation with KT5823 (10 mu M) inhibited Mn2+-induced LHRH release. These data demonstrate that the principal action of Mn2+ within the hypothalamus is to activate sGC directly and/or as a cofactor with available NO, hence generating cGMP and resulting in prepubertal LHRH release.

98. Lison D, Lardot C, Huaux F, Zanetti G, Fubini B. (1997) Influence of particle surface area on the toxicity of insoluble manganese dioxide dusts. Archives of Toxicology 71(12):725-729.
The objective of this study was to examine the influence of specific surface area on the biological activity of insoluble manganese dioxide (MnO2) particles. The biological responses to various MnO2 dusts with different specific surface area (0.16, 0.5, 17 and 62 m(2)/g) were compared in vitro and in vivo. A mouse peritoneal macrophage model was used to evaluate the in vitro cytotoxic potential of the particles via lactate dehydrogenase (LDH) release. In vivo, the lung inflammatory response was assessed by analysis of bronchoalveolar lavage after intratracheal instillation in mice (LDH activity, protein concentration and cellular recruitment). In both systems, the results show that the amplitude of the response is dependent on the total surface area which is in contact with the biological system, indicating that surface chemistry phenomena are involved in the biological reactivity. Freshly ground particles with a specific surface area of 5 m(2)/g were also examined in vitro. These particles exhibited an enhanced cytotoxic activity, which was almost equivalent to that of 62 m(2)/g particles, indicating that undefined reactive sites produced at the particle surface by mechanical cleavage may also con tribute to the toxicity of insoluble particles. We conclude that, when conducting studies to elucidate the effect of particles on the lung, it is important for insoluble particles such as manganese dioxide to consider the administered dose in terms of surface area (e.g. m(2)/kg) rather than in gravimetric terms (e.g. mg/kg).

99. Liu XH, Buffington JA, Tjalkens RB. (2005) NF-kappa B-dependent production of nitric oxide by astrocytes mediates apoptosis in differentiated PC12 neurons following exposure to manganese and cytokines. Molecular Brain Research 141(1):39-47.
Neuronal injury in manganisin is accompanied by activation of astroglia within the basal ganglia that is thought to increase production of inflammatory mediators such as nitric oxide (NO). The present studies Postulated that astroglial-derived NO mediates neuronal apoptosis induced by manganese (Mn) and pro-inflammatory cytokines. Pheochromocytoma (PC12) cells differentiated with nerve growth factor (NGF) were co-cultured with primary astrocytes and exposed to Mn and tumor necrosis factor-alpha (TNF-alpha.) plus interferon-gamma (IFN-gamma). Mn enhanced cytokine-indu[ced expression of inducible nitric oxide synthase (NOS2,

EC 1.14.13.39) and production of NO in astrocytes that correlated with apoptosis in co-cultured neurons, as determined by caspase activity, terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick-end labeling (TUNEL), and nuclear morphology. Apoptosis in PC12 neurons required the presence of astrocytes and was blocked by overexpression of a phosphorylation-deficient mutant Of I kappa B alpha (S32/36A) in astrocytes that prevented induction of NOS2. Pharmacologic inhibition of NOS2 with (+/-)-2-amino-5,6-dihydro-6-methyl-4H-1,3-thiazine (AMT) significantly reduced neuronal apoptosis, and the addition of low concentrations of the NO donor, S-nitroso-N-acetylpenicillamine (SNAP), to neurons Cultured without astrocytes was sufficient to recover the apoptotic phenotype following exposure to Mn and TNF-alpha/IFN-gamma. It is concluded that Mn- and cytokine-dependent apoptosis in PC12 neurons requires astroglial-derived NO and NF-kappa B-dependent expression of NOS2.

100. Malecki EA. (2001) Manganese toxicity is associated with mitochondrial dysfunction and DNA fragmentation in rat primary striatal neurons. Brain Research Bulletin 55(2):225-228.
Manganese (Mn) in excess is toxic to neurons of the globus pallidus, leading to a Parkinsonian-like syndrome. We used rat primary neuron cultures to examine the cellular events following manganese exposure. Following exposure to Mn2+ for 48 h, striatal neurons showed dose-dependent losses of mitochondrial membrane potential and complex II activity. The Mn exposure effect on mitochondrial membrane potential was significant at every concentration measured (5, 50, and 500 muM), and the manganese exposure effect on complex II activity was significant at 50 and 500 muM. Exposure of striatal neurons to both Mn2+ and the complex II inhibitor 3-nitropropionic acid resulted in additive toxicity. Striatal neurons exposed to 5 muM Mn2+ for 48 h exhibited DNA fragmentation and decreases in the immunohistochemically detectable microtubule-associated protein MAP-2. These results indicate that manganese may trigger apoptotic-like neuronal death secondary to mitochondrial dysfunction. Rescue of neurons by apoptosis inhibitors may be helpful in treating manganese toxicity and similar neurodegenerative processes.

101. Malecki EA, Connor JR. (2000) Manganese (Mn) is toxic to rat striatal neurons in primary culture. Journal of Neurochemistry 74:S76-S76.

102. Malecki EA, Devenyi AG, Barron TF, Mosher TJ, Eslinger P, Flaherty-Craig CV, Rossaro L. (1999) Iron and manganese homeostasis in chronic liver disease: Relationship to pallidal T1-weighted magnetic resonance signal hyperintensity. Neurotoxicology 20(4):647-652.
The hyperintense signal in the globus pallidus of cirrhotic patients on T1-weighted magnetic resonance (MR) imaging has been postulated to arise from deposition of paramagnetic manganese(2+) (Mn). Intestinal absorption of both iron and Mn are increased in iron deficiency; iron deficiency may therefore increase susceptibility to Mn neurotoxicity. To investigate the relationships between MR signal abnormalities and Mn and Fe status, 21 patients with chronic liver disease were enrolled (alcoholic liver disease, 5; primary biliary cirrhosis, 9; primary sclerosing cholangitis, 3; hepatitis B virus, 2; hepatitis C virus, 1; alpha 1-antitrypsin deficiency 1). Signal hyperintensity in the pallidum on axial T1 weighted images repetition time/evolution time: 500 ms/15ms was observed in 13 of 21 subjects: four patients had mild hyperintensity, three moderate, and six exhibited marked hyperintensity. Erythrocyte Mn concentrations were positively correlated with the degree of the MR hyperintensity (Kendall's tau-b=0.52, $P<0.005$).

The log of erythrocyte Mn concentration was also inversely correlated with all measures of iron status: hemoglobin (Pearson's R=-0.73, P<0.0005); hematocrit (R=-0.62, P<0.005); serum Fe concentrations (R=-0.65, P<0.005); and TIBC saturation (R=-0.62, P<0.005). These findings confirm the association of Mn with the development of pallidal hyperintensity in patients with liver disease. We further found that iron deficiency is an exacerbating factor probably because of increased intestinal absorption of Mn. We therefore recommend that patients with chronic liver disease avoid Mn supplements without concurrent iron supplementation. (C)1999 Intox Press, Inc.

103. Malecki EA, Greger JL. (1996) Manganese protects against heart mitochondrial lipid peroxidation in rats fed high levels of polyunsaturated fatty acids. Journal of Nutrition 126(1):27-33.
We demonstrated previously that dietary manganese (Mn) deficiency depressed Mn concentrations in most tissues and consistently depressed Mn superoxide dismutase (MnSOD) levels in heart. To examine the functional consequences of these effects, we fed weanling male Sprague-Dawley rats (n = 12/diet) diets containing 20% (wt/wt) corn oil or 19% menhaden oil + 1% corn oil by weight and 0.75 or 82 mg Mn/kg diet for 2 mo (the fish oil mixture was supplemented with +-(mixed)-alpha-tocopherol to the level in corn oil). Heart and liver Mn concentrations in the Mn-deficient rats were 56% of those in Mn-adequate rats (P < 0.0001), confirming Mn deficiency. The Mn-deficient rats had more conjugated dienes in heart mitochondria than Mn-adequate rats (P < 0.001); rats fed fish oil had more conjugated dienes than those fed corn oil (P < 0.001). The MnSOD activity was inversely correlated with conjugated dienes (r = -0.71, P < 0.005), and Mn-deficient rats had 37% less MnSOD activity in the heart than did Mn-adequate rats (P < 0.0001). The dietary treatments did not affect heart microsomal conjugated diene formation, possibly because of compensation by copper-zinc (CuZn) SOD activity; CuZnSOD activities were 35% greater in the hearts of Mn-deficient animals (P < 0.01). Liver was less sensitive to Mn deficiency than was the heart as judged by MnSOD activity and conjugated diene formation. This work is the first to demonstrate that dietary Mn protects against in vivo oxidation of heart mitochondrial membranes.

104. Malecki EA, Lo HC, Yang H, Davis CD, Ney DM, Greger JL. (1995) Tissue Manganese Concentrations and Antioxidant Enzyme-Activities in Rats Given Total Parenteral-Nutrition with and without Supplemental Manganese. Journal of Parenteral and Enteral Nutrition 19(3):222-226.
Background: Manganese is an essential but potentially toxic mineral. Parenteral administration of manganese via total parenteral nutrition (TPN) bypasses homeostatic mechanisms (intestinal absorption and presystemic hepatic elimination). Our objective in this study was to determine the effect of supplemental manganese in TPN solutions on manganese status in a rat model. Methods: Male Sprague-Dawley rats underwent jugular catheterization and were given 61.0 +/- 0.4 g/d TPN solution providing 0.5 +/- 0.2 nmol manganese/g (Mn-; n = 6) or 16 +/- 3 nmol manganese/g (Mn+; n = 7) for 7 days. Reference rats (RF; n = 8) were fed a purified diet containing 1.3 mmol manganese/g. Results: Liver manganese decreased in both TPN groups, but tibia, spleen, and pancreas manganese concentrations were greater in Mn+ rats than in Mn- or RF rats. Although no treatment differences were seen in heart or liver manganese superoxide dismutase activity, heart copper-zinc superoxide dismutase activity was lower in the Mn+ rats than in Mn- or RF rats (p < .05). Glutathione peroxidase activity was depressed in livers of both

Mn- and Mn+ rats relative to RF rats ($p < .001$), which was not due to selenium deficiency. Conclusions: Supplemental parenteral manganese is taken up to a greater extent by peripheral tissues than the liver. In this first report of antioxidant enzyme activities in animals maintained with TPN, we found that TPN as well as supplemental manganese can influence antioxidant enzyme activities. We conclude that it is generally unnecessary and potentially toxic to supplement TPN solutions with manganese during short-term usage.

105. Malthankar GV, White BK, Bhushan A, Daniels CK, Rodnick KJ, Lai JCK. (2004) Differential lowering by manganese treatment of activities of glycolytic and tricarboxylic acid (TCA) cycle enzymes investigated in neuroblastoma and astrocytoma cells is associated with manganese-induced cell death. Neurochemical Research 29(4):709-717.
Manganese (Mn) is a trace metal required for normal growth and development. Manganese neurotoxicity is rare and usually associated with occupational exposures. However, the cellular and molecular mechanisms underlying Mn toxicity are still elusive. In rats chronically exposed to Mn, their brain regional Mn levels increase in a dose-related manner. Brain Mn preferentially accumulates in mitochondria; this accumulation is further enhanced with Mn treatment in vivo. Exposure of mitochondria to Mn in vitro leads to uncoupling of oxidative phosphorylation. These observations prompted us to investigate the hypothesis that Mn induces alterations in energy metabolism in neural cells by interfering with the activities of various glycolytic and TCA cycle enzymes using human neuroblastoma (SK-N-SH) and astrocytoma (U87) cells. Treatments of SK-N-SH and U87 cells with MnCl2 induced cell death in these cells, in a concentration- and time-dependent manner, as determined by MTT assays. In parallel with the Mn-induced, dose-dependent decrease in cell survival, treatment of these cells with 0.01 to 4.0 mM MnCl2 for 48 h also induced dose-related decreases in their activities of hexokinase, pyruvate kinase, lactate dehydrogenase, citrate synthase, and malate dehydrogenase. Hexokinase in SK-N-SH cells was the most affected by Mn treatments, even at the lower range of concentrations. Mn treatment of SK-N-SH cells affected pyruvate kinase and citrate synthase to a lesser extent as compared to its effect on other enzymes investigated. However, citrate synthase and pyruvate kinase in U87 cells were more vulnerable than other enzymes investigated to the effects of Mn. The results suggest the two cell types exhibited differential susceptibility toward the Mn-induced effects. Additionally, the results may have significant implications in flux control because HK is the first and highly regulated enzyme in brain glycolysis. Thus these results are consistent with our hypothesis and may have pathophysiological implications in the mechanisms underlying Mn neurotoxicity.

106. Migheli R, Godani C, Sciola L, Delogu MR, Serra PA, Zangani D, De Natale G, Miele E, Desole MS. (1999) Enhancing effect of manganese on L-DOPA-induced apoptosis in PC12 cells: Role of oxidative stress. Journal of Neurochemistry 73(3):1155-1163.
L-DOPA and manganese both induce oxidative stress-mediated apoptosis in catecholaminergic PC12 cells, in this study, exposure of PC12 cells to 0.2 mM MnCl2 or 10-20 mu M L-DOPA neither affected cell viability, determined by the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, nor induced apoptosis, tested by flow cytometry, fluorescence microscopy, and the TUNEL technique. L-DOPA (50 mu M) induced decreases in both cell viability and apoptosis. When 0.2 mM MnCl2 was associated with 10, 20, or 50 mu M L-DOPA, a concentration-dependent decrease in cell viability was observed, Apoptotic cell death also occurred. In addition, manganese inhibited L-DOPA effects on dopamine (DA)

metabolism (i.e., increases in DA and its acidic metabolite levels in both cell lysate and incubation medium). The antioxidant N-acetyl-L-cysteine significantly inhibited decreases in cell viability, apoptosis, and changes in DA metabolism induced by the manganese association with L-DOPA, An increase in autoxidation of L-DOPA and of newly formed DA is suggested as a mechanism of manganese action. These data show that agents that induce oxidative stress-mediated apoptosis in catecholaminergic cells may act synergistically.

107. Miller KB, Caton JS, Finley JW. (2006) Manganese depresses rat heart muscle respiration. Biofactors 28(1):33-46.
It has previously been reported that moderately high dietary manganese (Mn) in combination with marginal magnesium (Mg) resulted in ultrastructural damage to heart mitochondria. Manganese may replace Mg in biological functions, including the role of enzyme cofactor. Manganese may accumulate and substitute for Mg during the condition of Mg-deficiency. The objective of the current study was to determine whether high Mn alters heart muscle respiration and Mg-enzyme activity as well as whole body Mn retention under marginal Mg. An additional objective was to determine whether high Mn results in increased oxidative stress. In experiment 1: forty-eight rats were fed a 2 x 3 factorial arrangement of Mn (10, 100, or 1000 mg/kg) and Mg (200 or 500 mg/kg). In experiment 2: thirty-two rats were fed one of four diets in a 2 x 2 factorial arrangement of Mn (10 or 250 mg/kg) and Mg (200 or 500 mg/kg). In experiment 3: thirty-two rats were fed one of four diets in a 2 x 2 factorial arrangement of Mn (10 or 650 mg/kg) and Mg (200 or 500 mg/kg). In experiment 2, high Mn and marginal Mg reduced ($P < 0.05$) oxygen consumption of left ventricle muscle. Marginal Mg, but not Mn, reduced ($P < 0.05$) activity of sarcoplasmic reticulum calcium-ATPase enzyme. Dietary Mg had no affect on Mn-54 kinetics, but high dietary Mn decreased ($P < 0.01$) absorption, retention, and rate of excretion of Mn-54. Neither cellular stress, measured by Comet assay, nor antioxidant activities were increased by high Mn. A strong interaction ($P < 0.001$) between increasing Mn and adequate Mg on hematology was observed. These results confirm previous research in swine that high Mn alters myocardial integrity as well as function, but not as a result of altered calcium transport or oxidative stress.

108. Molina JA, Jimenez-Jimenez FJ, Aguilar MV, Meseguer I, Mateos-Vega CJ, Gonzalez-Munoz MJ, de Bustos F, Porta J, Orti-Pareja M, Zurdo M and others. (1998) Cerebrospinal fluid levels of transition metals in patients with Alzheimer's disease. Journal of Neural Transmission 105(4-5):479-488.
We compared CSF and serum levels of iron, copper, manganese, and zinc, measured by atomic absorption spectrophotometry, in 26 patients patients with Alzheimer's disease (AD) without major clinical signs of undernutrition, and 28 matched controls. CSF zinc levels were significantly decreased in AD patients as compared with controls ($p < 0.05$). The serum levels of zinc, and the CSF and serum levels of iron, copper, and manganese, did not differ significantly between AD-patient and control groups. These values were not correlated with age, age at onset, duration of the disease, and scores of the MiniMental State Examination in the AD group. Weight and body mass index were significantly lower in AD patients than in controls. Because serum zinc levels were normal, the possibility that low CSF zinc levels were due to a deficiency of dietary intake seems unlikely. However, it is possible that they might be related to the interaction of beta-amyloid and/or amyloid precursor protein with zinc, that could result in a depletion of zinc levels.

109. Montes S, Alcaraz-Zubeldia M, Muriel P, Rios C. (2001) Striatal manganese accumulation induces changes in dopamine metabolism in the cirrhotic rat. Brain Research 891(1-2):123-129.
Manganese (Mn) is an essential metal that, in excess, causes an extrapyramidal syndrome consisting in tremor, rigidity and akinesia. Recently, Mn was found to accumulate in brains of cirrhotic patients who also present motor abnormalities. Manganese alters dopaminegic transmission promoting an increase in the turnover of dopamine (DA). In this study, we studied the changes in dopamine and its main metabolite homovanillic acid (HVA) to evaluate DA turnover following administration of manganese to bile-duct obstructed rats. Some groups of rats were treated with manganese chloride in two concentrations: 0.5 and 1 mg/ml of Mn2+ in their drinking water. Four weeks after surgery and treatment with manganese, striatal Mn, DA and HVA were assessed. Marked increases ($P<0.05$) of striatal manganese content were observed in cirrhotic rats treated and untreated with manganese, these augments were dependent on the Mn concentration in water. Striatal contents of DA in cirrhotic rats diminished by 30% ($P<0.05$), administration of 0.5 mg/ml of manganese in drinking water to these rats returned dopamine to the basal level and 1 mg/ml of manganese increased dopamine content by 27%. The relationship of Mn content and DA turnover (HVA:DA) in the same animal showed a positive and statically significant correlation ($P<0.05$), with differences in slope for sham ($b(1) = 0.1528$) and cirrhotic rats ($b(1) = 0.0174$). These results suggest that manganese brain accumulation observed in liver failure could be a key element to understand dopamine metabolism in cirrhotic condition of humans.

110. Mutkus L, Aschner JL, Fitsanakis V, Aschner M. (2005) The in vitro uptake of glutamate in GLAST and GLT-1 transfected mutant CHO-K1 cells is inhibited by manganese. Biological Trace Element Research 107(3):221-230.
In the central nervous system (CNS), extracellular concentrations of amino acids (e.g., aspartate, glutamate) and divalent metals (e.g., zinc, copper, manganese) are primarily regulated by astrocytes. Adequate glutamate homeostasis and control over extracellular concentrations of these excitotoxic amino acids are essential for the normal functioning of the brain. Not only is glutamate of central importance for nitrogen metabolism but, along with aspartate, it is the primary mediator of excitatory pathways in the brain. Similarly, the maintenance of proper Mn levels is important for normal brain function. Brain glutamate is removed from the extracellular fluid mainly by astrocytes via high affinity astroglial Na+-dependent excitatory amino acid transporters, glutamate/aspartate transporter (GLAST) and glutamate transporter-1 (GLT-1). The effects of Mn on specific glutamate transporters have yet to be determined. As a first step in this process, we examined the effects of Mn on the transport of [D-2, 3-H-3]D-aspartate, a non-metabolizable glutamate analog, in Chinese hamster ovary cells (CHO) transfected with two glutamate transporter subtypes, GLAST (EAAT1) or GLT-1 (EAAT2). Mn-mediated inhibition of glutamate transport in the CHO-K1 cell line DdB7 was pronounced in both the GLT-1 and GLAST transfected cells. This resulted in a statistically significant inhibition ($p < 0.05$) of glutamate uptake compared with transfected control in the absence of Mn treatment. These studies suggest that Mn accumulation in the CNS might contribute to dysregulation of glutamate homeostasis.

111. Oikawa S, Hirosawa I, Tada-Oikawa S, Furukawa A, Nishiura K, Kawanishi S. (2006) Mechanism for manganese enhancement of dopamine-induced oxidative DNA damage and neuronal cell death. Free Radical Biology and Medicine 41(5):748-756.
Although the cause of dopammergic cell death in Parkinson's disease is still poorly understood, there is accumulating evidence suggesting that metal ions can be involved in the processes. We investigated the effect of manganese on cell death and DNA damage in Pd12 ells treated with dopamine. Mn(II) enhanced cell death induced by dopamine. Mn(II) also increased the 8-oxo-7,8-dihydro-2-deoxyguanosine (8-oxodG) contents of DNA in PC12 cells treated with dopamine. To clarify the mechanism of cellular DNA damage, we investigated DNA damage induced by dopamine and Mn(II) using (32)p-labeled DNA fragments. Mn(II) enhanced Cu(II)-dependent DNA damage by dopamine. The Mn(II)-enhanced DNA damage was greatly increased by NADH. Piperidine and fornamidopyrimidine-DNA glycosylase treatment induced cleavage sites mainly at T and G of the 5'-TG-3' sequence, respectively. Bathocuproine, a Cu(I) chelator, and catalase inhibited the DNA damage. Oxygen consumption and UV-visible spectroscopic measurements showed that Mn(II) enhanced autoxidation of dopamine with H2O2 formation. These results suggest that reactive species derived from the reaction of H2O2 with Cu(I) participates in Mn(II)-enhanced DNA damage by dopamine plus Cu(II). Therefore, it is concluded that oxidative DNA damage induced by dopamine in the presence of Mn(II), NADH, and Cu(II) is possibly linked to the degeneration of dopaminergic neurons.

112. Oner G, Senturk UK. (1995) Reversibility of Manganese-Induced Learning Defect in Rats. Food and Chemical Toxicology 33(7):559-563.
In this study the mechanism by which manganese (Mn) induces learning defect and its reversibility has been investigated in rats. Female albino rats were dosed orally with 357 mu g Mn/kg body weight for 15 or 30 days. Attempts were made to correct the Mn-induced learning defect by (1) co-administration of mevinolin and Mn for 30 days;(2) administration of mevinolin for 15 days after 15 days of dosing with Mn, and (3) by withdrawal of Mn treatment (15 days dosing with Mn followed by 15 days without Mn). Mevinolin was given orally at 235.7 mu g/kg body weight. Significant increases in the Mn and cholesterol levels in the hippocampus were accompanied by an obvious slowness in learning of rats exposed to Mn. After one training period (day 29) the time required to reach the exit of a T-maze was 104.5 +/- 13.8 sec for rats dosed with Mn for 30 days, whereas that of the controls was 28.7 +/- 11.4 sec on day 30. This delay was completely corrected (to 30.7 +/- 6.0 sec) in rats co-administered mevinolin (an inhibitor of cholesterol biosynthesis) with Mn. Withdrawal of Mn, with or without inhibiting the cholesterol biosynthesis, also corrected the Mn-induced learning defect. These results suggest that Mn toxicity produces learning disability by increasing cholesterol biosynthesis and this reversible disability in learning can be corrected by withdrawal of Mn exposure.

113. Papp A, Pecze L, Szabo A, Vezer T. (2006) Effects on the central and peripheral nervous activity in rats elicited by acute administration of lead, mercury and manganese, and their combinations. Journal of Applied Toxicology 26(4):374-380.
Adult male Wistar rats were treated with inorganic lead, mercury and manganese, and their double combinations, in acute application. The aim was to study the effects on spontaneous and stimulus-evoked cortical, and evoked peripheral, nervous activity, to detect any interaction of the metals and any correlation between the changes caused in the spontaneous and stimulus-evoked

electrical activity of the primary somatosensory cortical area, and the compound action potential of the tail nerve. In the frequency distribution of the spontaneous cortical activity, a shift to lower frequencies was seen. The cortical responses evoked by whisker or tail stimulation showed an increase of the peak-to-peak amplitude and peak latency on administration of the metals and metal combinations. With the metal combinations, synergism was observed. Correlations found between alterations of the spontaneous and evoked, or between cortical and peripheral, activity were evaluated in terms of mechanism. According to the results, combined exposure to the three heavy metals studied might lead to synergistic action, indicating an increased health risk in settings with exposure to several heavy metals. Copyright (c) 2006 John Wiley & Sons, Ltd.

114. Pascal LE, Tessier DM. (2004) Cytotoxicity of chromium and manganese to lung epithelial cells in vitro. Toxicology Letters 147(2):143-151.
Chromium, nickel and manganese are the predominant metals in welding fumes and are associated through epidemiological studies with an increased risk for developing occupational asthma due to welding activities. Here, we show that chromium(VI) and manganese, but not nickel, are cytotoxic to normal human lung epithelial cells in vitro (SAEC and BEAS-2B), at concentration ranges of 0.2-200 muM. The toxic effect was associated with increased levels of intracellular phosphoprotein and subsequent release of inflammatory cytokines IL-6 and IL-8, while no release of TNF-alpha was observed. Changes in intracellular phosphoprotein levels occurred at concentrations below the cytotoxic effect. IL-6 and IL-8 production increased up to 4.4-fold relative to controls. IL-6 and IL-8 are released from lung epithelium to recruit cells of the immune system to sites of tissue damage. Therefore, the observed effects of chromium(VI) and manganese in lung epithelial cells demonstrate a mechanism through which the toxicity of these metals to epithelial cells can result in recruitment of cells of the immune system. (C) 2003 Elsevier Ireland Ltd. All rights reserved.

115. Pecze L, Papp A, Nagymajtenyi L. (2004) Changes in the spontaneous and stimulus-evoked activity in the somatosensory cortex of rats on acute manganese administration. Toxicology Letters 148(1-2):125-131.
In this work, acute effects of inorganic manganese exposure on nervous electrical activity of rats were investigated. Young adult male Wistar rats were prepared for recording in anaesthesia and spontaneous cortical as well as stimulus-evoked cortical and peripheral nervous activity was recorded before and after i.p. administration of 25 and 50 mg/kg Mn2+. The alterations found resulted possibly from several known neuronal effects of manganese. The frequency shift of spontaneous cortical activity, and increased latency and decreased amplitude of the peripheral nerve action potential, were probably due to the Mn2+-induced impairment of the mitochondria, whereas the increased amplitude of the evoked cortical response, to the effect on glutamatergic transmission. (C) 2004 Elsevier Ireland Ltd. All rights reserved.

116. Puli S, Lai JCK, Edgley KL, Daniels CK, Bhushan A. (2006) Signaling pathways mediating manganese-induced toxicity in human glioblastoma cells (U87). Neurochemical Research 31(10):1211-1218.
Although essential, manganese (Mn) intake in excess leads to neurotoxicity. Mn neurotoxicity induces impairment of energy metabolism and ultimately cell death. Nevertheless, the signaling mechanisms underlying Mn toxicity are unknown. Employing human glioblastoma (U87) cells, we investigated several signaling pathways (ones promoting cellular proliferation and invasion)

underlying Mn toxicity. Mn-treatment of U87 cells induced a down-regulation of MAPK pathway but the AKT pathway was not markedly affected. Mn-treatment of these cells induced decreases in their levels of c-Jun and c-Fos transcription factors and extracellular matrix degrading enzymes like MMP-2, which are associated with glioblastoma invasiveness. Mn-treatment also induced apoptosis in U87 cells. Thus, our results indicate that other than inducing apoptosis in U87 cells, Mn exerts differential effects on several signaling pathways promoting glioblastoma proliferation and invasion. Consequently, Mn may have pathophysiological roles in inducing apoptosis and in blocking glioblastoma invasion. Our results may thus have therapeutic implications.

117. Ramesh GT, Ghosh D, Gunasekar PG. (2002) Activation of early signaling transcription factor, NF-kappa B following low-level manganese exposure. Toxicology Letters 136(2):151-158.
Occupational and environmental exposure to manganese (Mn2+) is an increasing problem. It manifests neuronal degeneration characterized by dyskinesia resembling Parkinson's disease. The study was performed to test the hypotheses whether exposure to Mn2+ alters cellular physiology and promotes intracellular signaling mechanism in dopaminergic neuronal cell line. Since transcription factors have been shown to play an essential role in the control of cellular proliferation and survival, catecholaminergic rich pheochromocytoma (PC12) cells were used to measure changes in the DNA binding activities of nuclear factor kappa B (NF-kappaB) by electrophoretic mobility shift assay (EMSA) following Mn2+ (0.1-10 muM) exposure. Cells that were exposed to Mn2+ produced five-fold-activation of transcription factor NF-kappaB DNA binding activity. This remarkable increase was seen within 30-60 min period of Mn2+ exposure. Activation of NF-kappaB DNA binding activity by Mn2+ at 1.0 muM correlated with proteolytic degradation of the inhibitory subunit IkappaBalpha as evidenced in cytosol. Additional experiments on NF-kappaB reporter gene assay also showed increased NF-kappaB gene expression at 1.0 and 5.0 muM Mn2+ and this was completely blocked in the presence of NF-kappaB translocation inhibitor, IkappaBalpha-DN supporting that NF-kappaB induction occurred during Mn2+ exposure. In addition, Mn2+ exposure to PC 12 cells led to activation of signal responsive mitogen activated proteinexposure. In addition, Mn2+ exposure to PC 12 cells led to activation of signal responsive mitogen activated protein kinase kinase (MAPKK). These results suggest that Mn2+ at a low dose appears to induce the expression of immediate early gene, NF-kappaB through MAPKK by a mechanism in which IKBoc phosphorylation may be involved.)

118. Rao KVR, Norenberg MD. (2004) Manganese induces the mitochondrial permeability transition in cultured astrocytes. Journal of Biological Chemistry 279(31):32333-32338.
Manganese is known to cause central nervous system injury leading to parkinsonism and to contribute to the pathogenesis of hepatic encephalopathy. Although mechanisms of manganese neurotoxicity are not completely understood, chronic exposure of various cell types to manganese has shown oxidative stress and mitochondrial energy failure, factors that are often implicated in the induction of the mitochondrial permeability transition (MPT). In this study, we examined whether exposure of cultured neurons and astrocytes to manganese induces the MPT. Cells were treated with manganese acetate (10-100 muM), and the MPT was assessed by changes in the mitochondrial membrane potential and in mitochondrial calcein fluorescence. In astrocytes, manganese caused a dissipation of the mitochondrial membrane potential and

decreased the mitochondrial calcein fluorescence in a concentration- and time-dependent manner. These changes were completely blocked by pretreatment with cyclosporin A, consistent with induction of the MPT. On the other hand, similarly treated cultured cortical neurons had a delayed or reduced MPT as compared with astrocytes. The manganese-induced MPT in astrocytes was blocked by pretreatment with antioxidants, suggesting the potential involvement of oxidative stress in this process. Induction of the MPT by manganese and associated mitochondrial dysfunction in astrocytes may represent key mechanisms in manganese neurotoxicity.

119. Rao KVR, Pichili VB, Bellam N, Norenberg MD. (2006) Manganese upregulates aquaporin-4 in cultured astrocytes: role of oxidative stress. Journal of Neurochemistry 96:129-129.

120. Reaney SH, Kwik-Uribe CL, Smith DR. (2002) Manganese oxidation state and its implications for toxicity. Chemical Research in Toxicology 15(9):1119-1126.
Manganese (Mn) is ubiquitous in mammalian systems and is essential for proper development and function, though it can also be toxic at elevated exposures. While essential biologic functions of Mn depend on its oxidation state [e.g., Mn(II), Mn(III)], little is known about how the oxidation state of elevated Mn exposures affect cellular uptake, and function/toxicity. Here we report the dynamics of EPR measurable Mn(II) in fresh human plasma and cultured PC12 cell lysates as a function of exposure to either manganese(II) chloride or manganese(III) pyrophosphate, and the effects of exposure to Mn(II) versus Mn(III) on total cellular aconitase activity and cellular Mn uptake. The results indicate that Mn(II) or Mn(III) added in vitro to fresh human plasma or cell lysates yielded similar amounts of EPR measurable Mn(II). In contrast, Mn added as Mn(III) was significantly more effective in inhibiting total cellular aconitase activity, and intact PC 12 cells accumulated significantly more Mn when exposures occurred as Mn(III)., Collectively, these data reflect the dynamic nature of Mn speciation in simple biological systems, and the importance of Mn oxidation/speciation state in mediating potential cellular toxicity. This study supports concern over increased environmental exposures to Mn in different oxidation states [Mn(II), Mn(III), and Mn(IV)] that may arise from combustion products of. the gasoline antiknock additive methycyclopentadienyl manganese tricarbonyl (MMT).

121. Rico H, Gomez-Raso N, Revilla M, Hernandez ER, Seco C, Paez E, Crespo E. (2000) Effects on bone loss of manganese alone or with copper supplement in ovariectomized rats - A morphometric and densitomeric study. European Journal of Obstetrics Gynecology and Reproductive Biology 90(1):97-101.
Objective: The aim of this study was to examine the effect of manganese (Mn) alone and with the addition of copper (Cu) in the inhibition of osteopenia induced by ovariectomy (OVX) in rats. Study conditions: Four lots of 100-day-old female Wistar rats were divided into experimental groups of 15 each. One group received a diet supplemented with 40 mg/kg of Mn per kilogram of feed (OVX+Mn). The second group received the same diet as the first, but with an additional 15 mg/kg of copper (OVX+Mn+Cu). The third group of 15 OVX and the fourth group of 15 Sham-OVX received no supplements. At the conclusion of the 30-day experiment, the rats were slaughtered and their femurs and fifth lumbar vertebrae were dissected. Femoral and vertebral length were measured with caliper and bones were weighed on a precision balance.

The bone mineral content (BMC) and bone density (BMD) of the femur (F-BMC, mg and F-BMD, mg/cm(2)) and the fifth lumbar vertebra (V-BMC, mg and V-BMD, mg/cm(2)) were measured separately with dual energy X-ray absorptiometry. Results: The F-BMD, mg/cm(2) was lower in the OVX than in the Sham-OVX group (P<0.0001) and in the other two groups receiving mineral supplements (P<0.005 in both). F-BMC, mg was significantly lower in the OVX group than in the other three (P<0.0001 in all cases), Calculations for V-BMC, mg and V-BMD, mg/cm(2) are similar to findings in the femur. Conclusions: These data show that a Mn supplement is an effective inhibitor of loss of bone mass after OVX, both on the axial and the peripheral levels, although this effect is not enhanced with the addition of Cu. (C) 2000 Elsevier Science Ireland Ltd. All rights reserved.

122. Rojas P, Rios C. (1995) Short-term manganese pretreatment partially protects against 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine neurotoxicity. Neurochemical Research 20(10):1217-1223.
1-Methyl-4-phenyl-1,2,3,6-tetrahydropyrine (MPTP) is a neurotoxin that induces parkinsonism in human and non-human primates. Its mechanism of action is not fully elucidated. Recently, the participation of trace metals, such as manganese, on its neurotoxic action has been postulated. In this work, we studied the effect of manganese administration on the neurochemical consequences of MPTP neurotoxic action. Male Swiss albino mice were treated with manganese chloride (MnCl2 . 4H(2)O; 0.5 mg/ml or 1.0 mg/ml of drinking water) for 7 days, followed by three MPTP administrations (30 mg/Kg, intraperitoneally). Seven days after the last MPTP administration, mice were sacrificed and dopamine and homovanillic acid contents in corpus striatum were analyzed. Striatal concentration of dopamine was found increased by 60% in mice pretreated with 0.5 mg/ml and 52% in the group treated of 1.0 mg/ml as compared versus animals treated with MPTP only. Homovanillic acid content in both groups treated with manganese was the same as those in control animals. The results indicate that manganese may interact with MPTP, producing an enhancement of striatal dopamine turnover as the protective effect of manganese was more pronounced in the metabolite than in the neurotransmitter.

123. Roth JA, Horbinski C, Higgins D, Lein P, Garrick MD. (2002) Mechanisms of manganese-induced rat pheochromocytoma (PC12) cell death and cell differentiation. Neurotoxicology 23(2):147-157.
Mn is a neurotoxin that leads to a syndrome resembling Parkinson's disease after prolonged exposure to high concentrations. Our laboratory has been investigating the mechanism by which Mn induces neuronal cell death. To accomplish this, ire have utilized rat pheochromocytoma (PC12) cells as a model since they possess much of the biochemical machinery associated with dopaminergic neurons. Mn, like nerve growth factor (NGF), can induce neuronal differentiation of PC12 cells but Mn-induced cell differentiation is dependent on its interaction with the cell surface integrin receptors and basement membrane proteins, vitronectin or fibronectin. Similar to NGF Mn-induced neurtite outgrowth is dependent on the phosphorylation and activation of the MAP kinases, ERKI and 2 (p44/42). Unlike NGF, Mn is also cytotoxic having an IC50 value of similar to600 muM. Although many apoptotic signals are turned on by Mn, cell death is caused ultimately by disruption of mitochondrial function leading to loss of ATP. RT-PCR and immunoblotting studies suggest that some uptake of Mn into PC12 cells depends on the divalent metal transporter 1 (DMTI). DMTI exists in trio isoforms resulting from alternate splicing of a single gene product with one of the two mRNA species containing an iron response clement

(IRE) motif downstream from the stop codon. The presence of the IRE provides a binding site for the iron response proteins (IRPI and 2); binding of either of these proteins could stabilize DMTI mRNA and would increase expression of the +IRE form of the transporter. Iron and Mn compete for transport into PC12 cells via DMTl, so removal of iron from the culture media enhances Mn toxicity. The two isoforms of DMTI (IRE) are distributed in different subcellular compartments with the (+/-IRE) species selectively present in the nucleus of neuronal and neuronal-like cells. (C) 2002 Elsevier Science Inc. All rights reserved.

124. Roth JA, Walowitz J. (1999) Mechanism of manganese-induced neurotoxicity and neurite outgrowth in rat PC12 cells. Faseb Journal 13(4):A237-A237.

125. Seth K, Agrawal AK, Date I, Seth PK. (2002) The role of dopamine in manganese-induced oxidative injury in rat pheochromocytoma cells. Human & Experimental Toxicology 21(3):165-170.
Reactive dopamine (DA) metabolites have been implicated in both Parkinson's disease and manganese (Mn) neurotoxicity. Rat PC12 and genetically modified PC12 (PC12M) cells capable of producing higher DA content, on exposure to MnCl2 (10(-6) M) for 72 hours, exhibited a significant decrease in glutathione content. Activity of antioxidant enzyme catalase was also inhibited following 24- and 72-hour MnCl2 exposure. MnCl2 caused a concentration-dependent (10(-7) to 10(-3) M) loss in mitochondrial activity after 24 and 72 hours and an impaired DNA synthesis after 72 hours with changes being more marked in PC12M cells. The results indicate that the free-radical-mediated toxicity of Mn at cellular level involves down-regulation of antioxidants in normal and DA-rich PC12 cells. PC12M cells appeared to be more sensitive than PC12 cells.

126. Seth P, Husain MM, Gupta P, Schoneboom BA, Grieder FB, Mani H, Maheshwari RK. (2003) Early onset of virus infection and up-regulation of cytokines in mice treated with cadmium and manganese. Biometals 16(2):359-368.
A substantial database indicates that a large number of environmental pollutants, chemicals and therapeutic agents to which organisms are exposed cause immunotoxicity. The suppression of immune functions may cause increased susceptibility of the host to a variety of microbial pathogens potentially resulting in a life-threatening state. Evaluation of the immunotoxic potential of chemical xenobiotics is of great concern and, therefore, we have investigated the impact of exposure of inorganic metals, specifically cadmium (Cd) and manganese (Mn) on Encephalomyocarditis virus (EMCV), Semliki Forest virus (SFV), and Venezuelan Equine Encephalitis virus (VEEV) infection. Pretreatment with a single, oral dose of Cd or Mn increased the susceptibility of mice to a sub-lethal infection of these viruses as observed by increased severity of symptoms and mortality compared to untreated controls. An early onset of virus infection was found in brains of Cd and Mn treated animals. Histopathological observations of the brain indicate evidence of inflammation and greater tissue pathology in Cd- or Mn-exposed mice compared to control animals. Meningitis and vascular congestion was seen in virus infected mice in all the metal treated groups, and further, the perivascular inflammation appeared earlier in treated mice compared to control. Encephalitis was maximum in Cd pretreated mice. Widespread environmental contamination of metals and the potential for their exposure and subsequent infection of humans or animals is indicative that further studies of these and all other metals are important to understand the effect of environmental pollution on human health.

127. Smith DR, Whitman S, Reaney S, Kwik-Uribe C, Arnold C, Gwiazda R, Holman T. (2003) 2-D DIGE proteomic analsyes of mn exposure in dopamine and GABA producing cell lines: Implications for Mn neurotoxicity. Toxicological Sciences 72:20-21.

128. Soliman EF, Slikker W, Ali SF. (1995) Manganese-Induced Oxidative Stress as Measured by a Fluorescent-Probe - an in-Vitro Study. Neuroscience Research Communications 17(3):185-193.
The fluorescent probe, 2',7'dichlorofluorescein-diacetate (DCFH-DA) was used to quantitate the formation of reactive oxygen species (ROS) in brain tissue. Sprague-Dawley rats were sacrificed at different ages, postnatal day (PND) 1, 24, 41 and 4 and 18 months, and brains were dissected into caudate nucleus (CN) and cerebellum (CE). In vitro exposure to Mn (0.2-2.0 mM) increased the formation of ROS in brain synaptosomes at all ages. Age-related differences were found in the formation of ROS between CN and CE. In PND 1 brain synaptosomes, Mn induced dose dependent (0.2-2.0 mM) increases in the formation of ROS. This effect was also observed at other ages in CN and CE, but at higher concentrations (0.8-2.0 mM). It may be concluded that oxidative stress, as measured by ROS, may be a potential mechanism underlying the neurotoxicity induced by Mn and that the neonatal rat brain may be more susceptible than the adult rat brain.

129. Spranger M, Schwab S, Desiderato S, Bonmann E, Krieger D, Fandrey J. (1998) Manganese augments nitric oxide synthesis in murine astrocytes: A new pathogenetic mechanism in manganism? Experimental Neurology 149(1):277-283.
Since manganese (Mn2+) is known to be sequestered in glial cells, we investigated possible neurotoxic mechanisms involving astrocytes in vitro. Low concentrations of Mn2+ were toxic only in astrocyte-neuronal cocultures but not in pure astrocyte or neuronal cultures. As a possible mediator of manganese-derived neurotoxicity, we measured the production of nitric oxide in astrocytes. Manganese, but not other transition metals, dose dependently increased iNOS mRNA and protein levels and the release of nitric oxide in activated astrocytes. This effect was specific for astrocytes, since we observed no stimulation in microglial cells. The observations suggest that besides the known inhibition of mitochondrial function the neurotoxic effect of manganese in low concentrations might be mediated by the increased production of nitric oxide in astrocytes. (C) 1998 Academic Press.

130. Stredrick DL, Stokes AH, Worst TJ, Freeman WM, Johnson EA, Lash LH, Aschner M, Vrana KE. (2004) Manganese-induced cytotoxicity in dopamine-producing cells. Neurotoxicology 25(4):543-553.
Manganese (Mn) is an essential metal that, at excessive levels in the brain, produces extrapyramidal symptoms similar to those in patients with Parkinson's disease (PD). In the present study, Mn toxicity was characterized in a human neuroblastoma (SK-N-SH) cell line and in a mouse catecholaminergic (CATH.a) cell line. Mn was demonstrated to be more toxic in the catecholamine-producing CATH.a cells (EC50 = 60 muM) than in non-catecholaminergic SK-N-SH cells (EC50 = 200 muM). To test the hypothesis that the sensitivity of CATH.a cells to Mn is associated with their dopamine (DA) content, DA concentrations were suppressed in these cells by pretreatment with a-methyl-para-tyrosine (AMPT). Treatment for 24 h with 100 muM AMPT decreased intracellular DA, but offered no significant protection from Mn exposure (EC50 = 60

muM). Additional studies were carried out to assess if Mn toxicity was dependent on glutathione (GSH) levels. CATH.a cells were significantly protected by the addition of 5 mM GSH (Mn EC50 = 200 muM) and 10 mM N-acetyl cysteine (NAC) (Mn EC50 = 300 muM), therefore, indirectly identifying intracellular ROS formation as a mechanism for Mn neurotoxicity. Finally, apoptotic markers of Mn-induced cell death were investigated. DNA fragmentation, caspase-3 activation, and apoptosis-related gene expression were studied in CATH.a cells. No internucleosomal fragmentation or caspase activation was evident, even in the presence of supraphysiological Mn concentrations. cDNA hydridization array analysis with two differing Mn concentrations and time points, identified no noteworthy mRAA inductions of genes associated with programmed cell death. In conclusion, DA content was not responsible for the enhanced sensitivity of CATH.a cells to Mn toxicity, but oxidative stress was implicated as a probable mechanism of cytotoxicity. (C) 2003 Published by Elsevier Inc.

131. Suarez N, Walum E, Eriksson H. (1995) Cellular Neurotoxicity of Trivalent Manganese Bound to Transferrin or Pyrophosphate Studied in Human Neuroblastoma (Sh-Sy5y) Cell-Cultures. Toxicology in Vitro 9(5):717-721.
Previous studies have shown that cellular uptake of manganese is related to its binding to transferrin. However, it is not known how transferrin binding influences manganese toxicity. Therefore, the cytotoxic activity of manganese bound as manganic ion to either transferrin or pyrophosphate was investigated in the cloned human neuroblastoma cell line SH-SY5Y. The toxicity of the two compounds was studied as changes in cell growth and survival by lipid and protein determinations. There was a significant difference in the toxicity between the two complexes after 72 hr of exposure. The toxicity of the manganic-pyrophosphate (MnPPi) complex differed from that of the manganic-transferrin (MnTf) complex by a factor of 2(IC50: 26 +/- 2.6 and 65 +/- 2.4 mu M, respectively). After 3 days of exposure to MnPPi and MnTf, the mitochondrial integrity was monitored by the mitochondrial dehydrogenase activity. The two manganese complexes reduced the enzyme activity to the same extent. Measurements of membrane integrity, using (3)[H]-2-deoxy-D-glucose as a probe, showed an increase in the membrane permeability of cells exposed to MnPPi for 60 min. Exposure to MnTf did not result in any significant change in membrane permeability. These findings suggest that transferrin not only mediates manganese transport into the neurone, but also protects the cell from damage caused by the manganic ion. The increase in cell membrane permeability after MnPPi exposure indicates that this complex may enter the cell. Furthermore, the results show that inhibited mitochondrial function is part of the mechanism of manganese neurotoxicity.

132. Tomas-Camardiel M, Herrera AJ, Venero JL, Sanchez-Hidalgo MC, Cano J, Machado A. (2002) Differential regulation of glutamic acid decarboxylase mRNA and tyrosine hydroxylase mRNA expression in the aged manganese-treated rats. Molecular Brain Research 103(1-2):116-129.
Recent studies have implicated chronic elevated exposures to environmental agents, such as metals (e.g. manganese, Mn) and pesticides, as contributors to neurological disease. Eighteen-month-old rats received intraperitoneal injections of manganese chloride (6 mg Mn/kg/day) or equal volume of saline for 30 days in order to study the effect of manganese on the dopamine- and GABA-neurons. The structures studied were substantia nigra, striatum, ventral tegmental area, nucleus accumbens and globus pallidus. First, we studied the enzymatic activity of mitochondrial complex 11 succinate dehydrogenase (SDH). We found an overall decrease of

SDH in the different brain areas analyzed. We then studied the mRNA levels for tyrosine hydroxylase (TH) and the dopamine transporter (DAT) by in situ hybridization. TH mRNA but not DAT mRNA was significantly induced in substantia nigra and ventral tegmental area following Mn treatment. Correspondingly, TH immunoreactivity was increased in substantia nigra and ventral tegmental area. Manganese treatment significantly decreased GAD mRNA levels in individual GABAergic neurons in globus pallidus but not in striatum. We also quantified the density of glial fibrillary acidic protein (GFAP)-labeled astrocytes and OX-42 positive cells. Reactive gliosis in response to Mn treatment occurred only in striatum and substantia nigra and the morphology of the astrocytes was different than in control animals. These results suggest that the nigrostriatal system could be specifically damaged by manganese toxicity. Thus, changes produced by manganese treatment on 18-month-old rats could play a role in the etiology of Parkinson's disease.

133. Vettori MV, Gatti R, Orlandini G, Belletti S, Alinovi R, Smargiassi A, Mutti A. (1999) An in vitro model for the assessment of manganese neurotoxicity. Toxicology in Vitro 13(6):931-938.
PC12 (undifferentiated and differentiated) and C6 cells have been used to investigate kinetics, morphological and functional endpoints following exposure to MnCl2 and manganic transferrin (Mn-Tf). [Mn](i) in undifferentiated (non-differentiated cells) exposed to both free (MnCl2) and bound Mn (Mn-Tf), was three- to fivefold lower as compared to differentiated (differentiated) PC12 cells and higher by one order of magnitude as compared to glial C6 cells. Exposure to both MnCl2 and Mn-Tf was followed by time- and dose-dependent morphological changes characteristic of apoptosis, which was never observed in Mn-exposed C6 glial cells. Results from cell viability assays were consistent with apoptotic response rates quantified by cell count. Threshold concentrations for undifferentiated and differentiated PC12 cells were 10(-6) and 10(-5) M, respectively. Thus, despite their greater ability to accumulate Mn, differentiated PC12 cells are less sensitive to Mn-induced apoptosis. This model might be relevant to neuronal degeneration induced by Mn occurring in the developing brain and possibly in clinical manganism. Such critical doses at the cellular level seem to be consistent with Mn levels (5 x 10(-6) M) recorded in the basal ganglia of monkeys chronically exposed to Mn and developing clinical signs of manganism.

134. Vidal L, Alfonso M, Campos F, Faro LRF, Cervantes RC, Duran R. (2005) Effects of manganese on extracellular levels of dopamine in rat striatum: An analysis in vivo by brain microdialysis. Neurochemical Research 30(9):1147-1154.
The aim of this study is to determine the effects of intrastriatal administration of MnCl2, on the extracellular levels of dopamine (DA) and metabolites dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA) in basal conditions and stimulated by depolarization with KCl and pargyline administration. Also, we studied the effect of MnCl2 on extracellular levels of l-Dopa in the presence of aromatic amino acid decarboxylase (AADC) inhibitor 3-hydroxybencilhydracine-HCl (NSD 1015). This study concluded that MnCl2, reduced the basal and K+-stimulated DA-release in striatum, without notably affecting the DOPAC and HVA levels. Intraperitoneal injection of pargyline increased striatal DA levels, decreasing DOPAC and HVA levels. The infusion of MnCl2 removed the increase in DA levels, without affecting DOPAC and HVA levels. Perfusion of NSD 1015 increased the extracellular levels of L-DOPA in striatum, and MnCl2 increased the effect of NSD1015 on L-Dopa.

135. Wang RG, Zhu XZ. (2003) Subtoxic concentration of manganese synergistically potentiates 1-methyl-4-phenylpyridinium-induced neurotoxicity in PC12 cells. Brain Research 961(1):131-138.
Endogenous or exogenous substances that are toxic to dopaminergic cells have been proposed as possible cause of idiopathic Parkinson's disease (PD). 1-Methyl-4-phenylpyridinium (MPP+) and manganese are dopaminergic neurotoxins causing a parkinsonism-like syndrome. Here, we studied the possible synergistic reaction between these two neurotoxins using rat PC12 pheochromocytoma cells. MPP+ induced a delayed neurotoxicity in PC12 cells. Although low concentration of manganese did not cause cell damage, it markedly enhanced MPP+-induced neurotoxicity with characteristics of apoptosis, such as DNA laddering and activation of caspase-3. To understand the mechanism of enhancement of subtoxic concentration of manganese on MPP+-induced neurotoxicity, we investigated the reactive oxygen species (ROS) generation using a molecular probe, 2',7'-dichlorofluorescein diacetate. Although subtoxic concentration of manganese alone did not induce ROS increase, it significantly enhanced the ROS generation induced by MPP+. We also determined the intracellular MPP, content. A time- and concentration-dependent increase of MPP+ levels was found in PC12 cells treated with MPP+. The accumulation of MPP+ by PC12 cells was not affected by manganese. Taken together, these studies suggest that co-treatment with MPP+ and manganese may induce synergistic neurotoxicity in PC12 cells and that subtoxic concentration of manganese may potentiate the effect of MPP+ by an ROS-dependent pathway. (C) 2002 Elsevier Science B.V. All rights reserved.

136. Yang HJ, Wang TN, Li JY, Gu L, Zheng XX. (2006) Decreasing expression of alpha(1c) calcium L-type channel subunit mRNA in rat ventricular myocytes upon manganese exposure. Journal of Biochemical and Molecular Toxicology 20(4):159-166.
Manganese is an essential trace element found in many enzymes. As it is the case of many essential trace elements, excessive level of manganese is toxic. It has been proven that excessive manganese could cause heart problems. In order to understand the mechanism of manganese toxicity in the heart, the effects of manganese on isolated rat ventricular myocytes were studied. The L-type calcium channel current was measured by whole-cell patch clamp recording mode. In the electrophysiology experiments, both 50 mu M Mn2+ and 100 mu M Mn2+ could effectively decrease the channel current amplitude density by 35.7% and 68.2%, respectively. Moreover, Mn2+ shifted the steady-state activation curve toward more positive potential and the steady-state inactivation curve toward more negative potential. Investigation by RT-PCR showed that the mRNA expression of alpha(1C)/Cav1.2 treated with manganese was decreased depending on its concentration, while the mRNA expression of alpha(1D)/Cav1.3 was almost unchanged. Fluo-3/AM was utilized for real-time free calcium scanning with laser scanning confocal microscopy (LSCM), and the results showed that Mn2+ could elicit a slow and continuous increase of [Ca2+](i) in a concentration-dependent manner. These results have suggested that manganese could interfere with the function of the L-type calcium channel, downregulate the mRNA expression of alpha(1C)/Cav1.2, and thus causing long-lasting molecular changes of L-type calcium channel which have probably been triggered by overloading of calcium in myocytes. (c) 2006 Wiley Periodicals, Inc.

137. Yazbeck C, Moreau T, Sahuquillo J, Takser L, Huel G. (2006) Effect of maternal manganese blood levels on erythrocyte calcium-pump activity in newborns. Science of the Total Environment 354(1):28-34.
Manganese (Mn) is widely distributed in the biosphere but occurs in only trace amounts in animal tissues. Although Mn deficiency and toxicity both have pathological consequences, the underlying biochemical lesions have not been well defined. In vitro studies suggest that transport proteins are affected by Mn, lead (Pb), and selenium (Se). Among these transport proteins, the calmodulin-regulated calcium pump (Ca(2+)Mg(2+)ATPase) could be inhibited by Mn. In order to understand Mn biochemical pathways, we examined the relationships between Mn blood levels and red blood cell Ca-pump activity among 248 mothers and newborns, environmentally exposed to Mn, Pb, and Se. Population and methods: 248 mother-newborn pairs were recruited at Robert Debre University Hospital (Paris). Blood Mn and Pb concentrations were measured by absorption spectrophotometry. Se was measured by fluorometric method. Red blood cell membrane suspensions were obtained for Ca-pump activity measurements. Linear and quadratic regression models and Pearson correlation were performed. Results: A non-linear parabolic relationship between maternal Mn blood levels and newborn Ca-pump activity was discovered from the analysis of the observed data. The peak level of maternal Mn that corresponded to a maximal activity of the newborn Ca-pump was estimated at 23.9 mu g/l with a 95% confidence interval of 17.6 to 32.4 mu g/l. An inhibition of this enzyme was observed at low and high levels of maternal Mn. The relationships between the newborn Ca-pump activity and maternal Se and Pb levels became non-significant after adjustment on all the co-factors included in the final model. Conclusion: Maternal environmental exposure to Mn, as reflected by maternal blood levels of this metal, is associated with a reduced activity of newborn erythrocyte Ca-pump in a non-linear pattern. Mn levels between 17.6 and 32.4 mu g/l in maternal blood probably correspond to the optimal physiological concentration for the metabolism of this enzyme in newborns. (c) 2004 Elsevier B.V. All rights reserved.

138. Yoritaka A, Hattori N, Mori H, Kato K, Mizuno Y. (1997) An immunohistochemical study on manganese superoxide dismutase in Parkinson's disease. Journal of the Neurological Sciences 148(2):181-186.
We report an immunohistochemical study on manganese superoxide dismutase (Mn SOD) in Parkinson's disease (PD) patients and age-matched control subjects. Overall appearance of immunostaining intensity of nigral neurons did not differ significantly between the PD patients and the control subjects. However, when the immunostaining intensity of each neuron was semiquantitatively analyzed, both very intensely stained (more than normal) neurons as well as neurons stained only weakly were more frequently detected in the lateral part than in the medial and the central parts of the substantia nigra in PD patients. As a result, the proportion of normally stained neurons was significantly smaller in the lateral part of the substantia nigra in PD patients; however, the overall distribution of the neurons among the three rating grades for immunostaining did not differ significantly. The immunostaining intensity of the neuropils in the medial and the central part of the substantia nigra tended to be more intense in PD patients than in the control subjects. Our results suggest up-regulation of Mn SOD mainly in the dendritic processes of the less involved nigral neurons. (C) 1997 Elsevier Science B.V.

139. Zaidi S, Patel A, Mehta N, Patel K, Takiar R, Saiyed H. (2005) Early biochemical alterations in manganese toxicity: Ameliorating effects of magnesium nitrate and vitamins. Industrial Health 43(4):663-668.
Manganese-induced early biochemical changes and effects of supplementation of magnesium nitrate (Mg(NO3)(2)) and antioxidant vitamins (A, C, D and E) were studied in rats intoxicated with manganese. Significant elevation in the level of chlorides in plasma, erythrocytes, liver and cerebellum, and a decrease in plasma inorganic phosphate (pi) with an increase in liver pi were observed in animals exposed to manganese as compared to controls. The level of erythrocyte-acid labile phosphate (ALP), nicotinamide adeninedinucleotide (NAD(+)) and plasma sialic acid (N-acetyneuraminic acid, NANA) also increased significantly. Elevated levels of chlorides in plasma, erythrocytes and cerebellum reversed to normal control values whereas liver chlorides restored partially by the supplementation of Mg(NO3)(2). Vitamins supplementation was effective to reverse chlorides level in erythrocytes, liver and cerebellum. Decreased level of pi in plasma and the highly elevated level of erythrocyte ALP were also recovered in animals received Mg(NO3)(2) in addition to MnSO4. However, such effect of Mg(NO3)(2) was not seen in lowering the elevated level of NANA that restored by the administration of vitamins. Thus, the early alterations in plasma levels of chlorides, pi, and NANA and erythrocyte-ALP seem to be an indicative of early manganese toxicity while Mg(NO3)(2) and vitamins supplementation appear to provide, at least in part, protection against manganese toxicity.

140. Zaloglu N, Koc E, Yildirim G, Bastug M, Ficicilar H. (2003) How does chronic manganese chloride application affect the rat isolated ileal contractility? Trace Elements and Electrolytes 20(3):154-159.
In this study, we investigated the effects of chronic manganese chloride (MnCl2) application at high dosage on the mechanical responses evoked by acetylcholine (2.7 x 10(-7) M) on isolated rat ileum in standard and calcium-free tyrode perfusion solutions with diltiazem (5.5 x 10(-7) M) and non-diltiazem mediums. In the experimental group (n = 10), MnCl2 (50 mg/kg/day) was injected for 50 days intraperitoneally. Acetylcholine-induced contraction amplitude increased significantly with respect to that of the control in standard tyrode perfusion medium. When ileal segments were pre-incubated with diltiazem, the amplitude of acetylcholine-induced contractions decreased in experimental and control groups with respect to those of the standard mediums. In calcium-free medium, pretreatment with diltiazem did not cause any change in acetylcholine-induced contractions. Our data suggested that manganese (Mn2+) might have penetrated through cell membrane and accumulated in the cell when. manganese was applied chronically and overdose. Increase in plasma manganese level might have induced the increase in manganese influx whereas calcium influx might have been induced by manganese itself The increase in contraction amplitude maybe attributed to this phenomenon.

141. Zhang SR, Fu JL, Zhou ZC. (2004) In vitro effect of manganese chloride exposure on reactive oxygen species generation and respiratory chain complexes activities of mitochondria isolated from rat brain. Toxicology in Vitro 18(1):71-77.
Manganese (Mn) is known to induce mitochondrial dysfunction in excessive dose; however the mechanisms underlying its action are not elucidated clearly. To determine if Mn2+ can act directly on mitochondria or indirectly by producing reactive oxygen species (ROS), isolated mitochondria were exposed to different concentration of Mn 21 (5, 50, 500, 1000 muM). ROS generation, respiratory control ratio (RCR), mitochondrial membrane potential (MMP) and

respiratory chain complexes activities were investigated. Dose-dependent inhibition of respiratory chain complexes and induction of ROS were observed; these changes were paralleled by decreasing of respiratory control ratio (RCR) both with succinate or glutamate + malate. Further investigation indicated that the membrane potential determined by Rhodamine123 release decreased after MnCl2 exposure at 1000 muM. In addition, effects of the antioxidants NAC (500 muM), GSH (500 muM) and Vitamin C (500 muM) were studied at 500 muM Mn2+. The results indicate that the effect of Mn2+ exposure on respiratory chain is not site-specific, and antioxidants can protect the mitochondria function by reducing the formation of free radicals.

142. Zhang SR, Zhou ZC, Fu JL. (2003) Effect of manganese chloride exposure on liver and brain mitochondria function in rats. Environmental Research 93(2):149-157.
Manganese (Mn) is an essential trace element found in many enzymes. As is the case for many essential trace elements, excessive Mn is toxic. Individuals suffering from manganese toxicity exhibit several symptoms, which are similar to those frequently observed in cases of Parkinson's disease. In this investigation, we studied the effect of manganese chloride (7.5, 15.0, and 30.0 mg/kg body weight) on mitochondrial function and attempted to ascertain the mechanism of manganese-induced mitochondrial dysfunction. The production of reactive oxygen species in mitochondria of rat liver and brain was assayed using 2,7'-dichlorofluorescin diacetate, and the activities of respiratory chain enzymes were examined spectrophotometrically. Monoamine oxidase (MAO) activity was assayed by measuring reduction of benzylamine. Manganese and calcium content in mitochondria were determined by atomic absorption spectrophotometry. These results indicate that manganese chloride (MnCl2) can decrease MAO activity and inhibit the respiratory chain. Manganese can accumulate in mitochondria and inhibit efflux of calcium. There is a significant inverse correlation between the amount of superoxide radicals and the specific activities of the mitochondria enzymes. Mitochondrial function was significantly affected in both males and females.

143. Zheng W, Zhao QQ. (2001) Iron overload following manganese exposure in cultured neuronal, but not neuroglial cells. Brain Research 897(1-2):175-179.
Our previous studies show that manganese (Mn) exposure inhibits aconitase, an enzyme regulating the proteins responsible for cellular iron (Fe) equilibrium. This study was performed to investigate whether Mn intoxication leads to an altered cellular Fe homeostasis in cultured neuronal or neuroglial cells as a result of disrupted Fe regulation. Our results reveal a significant increase in the expression of transferrin receptor (TfR) mRNAs and a corresponding increase in cellular Fe-59 net uptake by PC12 cells, but not astrocytes, following Mn exposure. These findings suggest that alteration by Mn of cellular Fe homeostasis may contribute to Mn-induced neuronal cytotoxicity.

144. Zhong WX, Yan T, Webber MM, Oberley TD. (2004) Alteration of cellular phenotype and responses to oxidative stress by manganese superoxide dismutase and a superoxide dismutase mimic in RWPE-2 human prostate adenocarcinoma cells. Antioxidants & Redox Signaling 6(3):513-522.
To study biologic effects of increased manganese superoxide dismutase (MnSOD) on cell behavior, we overexpressed MnSOD in a human prostate cancer cell line RWPE-2 by cDNA transfection. Stable transfectants of MnSOD showed a two- to threefold increase in MnSOD

protein and enzymatic activity and a decrease in growth rate with prolonged cell population doubling times. Western blot analysis showed a 1.5- to twofold increase in the cyclin-dependent kinase inhibitor p21(Waf1) in MnSOD transfectants. Overexpression of MnSOD resulted in a seven- to eightfold increase in reduced glutathione (GSH), 18- to 26-fold increase in oxidized glutathione (GSSG), and a two- to threefold decrease in the ratio of GSH to GSSG. MnSOD-overexpressing cells showed an increase in sensitivity to the cytotoxicity of buthionine sulfoximine, a glutathione-depleting agent, and vitamin C, but a decrease in sensitivity to sodium selenite. Treatment with a superoxide dismutase (SOD) mimic MnTMPyP resulted in similar effects of MnSOD overexpression on cell responses to vitamin C and selenium. These data demonstrate that overexpression of MnSOD or treatment with SOD mimics can result in antioxidant or prooxidant effects in cells, depending on the presence of other antioxidants and prooxidants. MnSOD also has redox regulatory effects on cell growth and gene expression. These findings suggest that MnSOD and SOD mimics have the potential for cancer prevention or treatment.

145. Zwingmann C, Leibfritz D, Hazell AS. (2003) Altered metabolic trafficking via glutamine-glutamate-cycle between astrocytes and neurons in manganese neurotoxicity. Journal of Neurochemistry 87:142-142.

146. Zwingmann C, Leibfritz D, Hazell AS. (2003) Energy metabolism in astrocytes and neurons treated with manganese: Relation among cell-specific energy failure, glucose metabolism, and intercellular trafficking using multinuclear NMR-spectroscopic analysis. Journal of Cerebral Blood Flow and Metabolism 23(6):756-771.
A central question in manganese neurotoxicity concerns mitochondrial dysfunction leading to cerebral energy failure. To obtain insight into the underlying mechanism(s), the authors investigated cell-specific pathways of [1-C-13] glucose metabolism by high-resolution multinuclear NMR-spectroscopy. Five-day treatment of neurons with 100-mumol/L MnCl2 led to 50% and 70% decreases of ATP/ADP and phosphocreatine-creatine ratios, respectively. An impaired flux of [1_13 C]glucose through pyruvate dehydrogenase, which was associated with Krebs cycle inhibition and hence depletion of [1-C-13]glutamate, [2-C-13]GABA, and [C-13]glutathione, hindered the ability of neurons to compensate for mitochondrial dysfunction by oxidative glucose metabolism and further aggravated neuronal energy failure. Stimulated glycolysis and oxidative glucose metabolism protected astrocytes against energy failure and oxidative stress, leading to twofold increased de novo synthesis of [3-C-13] lactate and fourfold elevated [4-C-13] glutamate and [C-13] glutathione levels. Manganese, however, inhibited the synthesis and release of glutamine. Comparative NMR data obtained from cocultures showed disturbed astrocytic function and a failure of astrocytes to provide neurons with substrates for energy and neurotransmitter metabolism, leading to deterioration of neuronal antioxidant capacity (decreased glutathione levels) and energy metabolism. The results suggest that, concomitant to impaired neuronal glucose oxidation, changes in astrocytic metabolism may cause a loss of intercellular homeostatic equilibrium, contributing to neuronal dysfunction in manganese neurotoxicity.

4.6 REVIEW ARTICLES

Key References (18)

1. Anonymous. (1997) Manganese. RAIS Toxicity Profiles (1997).
Manganese is an essential trace element in humans that can elicit a variety of serious toxic responses upon prolonged exposure to elevated concentrations either orally or by inhalation. The central nervous system is the primary target. Initial symptoms are headache, insomnia, disorientation, anxiety, lethargy, and memory loss. These symptoms progress with continued exposure and eventually include motor disturbances, tremors, and difficulty in walking, symptoms similar to those seen with Parkinsonism. These motor difficulties are often irreversible. Based on human epidemiological studies, 0.8 mg/kg/day for drinking water exposure and 0.34 mg/m3 in air for inhalation exposure have been estimated as lowest-observed-adverse-effect levels (LOAELs) for central nervous system effects. Effects on reproduction (decreased fertility, impotence) have been observed in humans with inhalation exposure and in animals with oral exposure at the same or similar doses that initiate the central nervous system effects. An increased incidence of coughs, colds, dyspnea during exercise, bronchitis, and altered lung ventilatory parameters have also been seen in humans and animals with inhalation exposure. A possible effect on the immune system may account for some of these respiratory symptoms. Because of the greater bioavailability of manganese from water, separate reference doses (RfD) for water and diet were calculated. A chronic (EPA 1995) and subchronic RfD (EPA 1994) for drinking water of 0.005 mg/kg/day has been calculated by EPA from a human noobservedadverse-effect level (NOAEL) of 0.005 mg/kg/day; the NOAEL was determined from an epidemiological study of human populations exposed for a lifetime to manganese concentrations in drinking water ranging from 3.6-2300 µg/L (Kondakis et al. 1989). A chronic (EPA 1995) and subchronic RfD (EPA 1994) of 0.14 mg/kg/day for dietary exposure has been calculated by EPA from a human NOAEL of 0.14 mg/kg/day, which was determined from a series of epidemiological studies (Schroeder et al. 1966, WHO 1973, NRC 1989). Large populations with different concentrations of manganese in their diets were examined. No adverse effects that were attributable to manganese were seen in any of these groups. For both the drinking water and dietary values, the RfD was derived from these studies without uncertainty factors since manganese is essential in human nutrition and the exposure of the most sensitive groups was included in the populations examined. EPA (1995) indicates that the chronic RfD values are pending change. A reference concentration (RfC) of 0.05 µg/m3 (EPA 1995) for chronic inhalation exposure was calculated from a human LOAEL of 0.05 mg/m3 for impairment of neurobehavioral function from an epidemiological study by Roels et al. (1992). The study population was occupationally exposed to airborne manganese dust with a median concentration of 0.948 mg/m3 for 0.2 to 17.7 years with a mean duration of 5.3 years. Neurological examinations, psychomotor tests, lung function tests, blood tests, and urine tests were used to determine the possible effects of exposure. The LOAEL was derived from an occupational-lifetime integrated respirable dust concentration of manganese dioxide expressed as mg manganese/m3 x years. Confidence in the inhalation RfC is rated medium by the EPA. Some conflicting data exist on possible carcinogenesis following injections of manganese chloride and manganese sulfate in mice. However, the EPA weight-of-evidence classification is: D, not classifiable as to human carcinogenicity based on no evidence in humans and inadequate evidence in animals (EPA 1995).

2. Anonymous. (2001) Manganese and inorganic compounds. ACGIH. Documentation of the threshold limit values and biological exposure indices Vol:7th Ed (2001) 6 p.
A TLV-TWA of 0.2 mg/m3, as Mn, is recommended for occupational exposure to elemental manganese and its inorganic compounds. This value is intended to minimize the potential for pre-clinical adverse effects in the lungs and CNS and adverse effects on the fertility of male workers exposed to manganese. The lowest exposure concentration of manganese at which early effects on the CNS and the lungs may occur is still unknown. However, once neurological signs are present, they tend to continue and worsen after exposure ends. Additional data are needed to more accurately determine the exposure doses necessary to protect nearly all workers. Sufficient data were not available to recommend Skin, SEN, or carcinogenicity notations or a TLV-STEL.

3. Anonymous. (2001) Manganese Cyclopentadienyl Tricarbonyl. ACGIH. Documentation of the threshold limit values and biological exposure indices Vol:7th Ed (2001) 2 p.
A TLV-TWA of 0.1 mg/m3, measured as manganese, is recommended for occupational exposure to manganese cyclopentadienyl tricarbonyl (MCT). This value is intended to minimize the potential for skin irritation, neuropathic effects that include tremor and convulsion, and pulmonary edema reported from studies with experimental animals. Systemic toxicity, including mortality, in rats treated by tail immersion in MCT warrants assignment of the Skin notation. The toxicity of MCT appears to be twice as potent as that of the organomanganese compound 2-methylcyclopentadienyl manganese tricarbonyl (see the current TLV Documentation for 2-methylcyclopentadienyl manganese tricarbonyl). Sufficient data were not available to recommend SEN or carcinogenicity notations or a TLV-STEL.

4. Anonymous. (2003) Methylcyclopentadienyl Manganese Tricarbonyl (MMT). NICNAS: Priority existing chemical assessment report Vol:24 (2003) 149 p.
Health hazards. In fuel, MMT is combusted and converted to a mixture of Mn oxides such as Mn3O4 and salts including Mn phosphate (Mn3[PO4]2) and Mn sulphate (MnS04). A proportion of those inorganic derivatives are released in association with particulate material in vehicle exhaust. The balance (around 80%) is accumulated in engines or exhaust systems. Therefore, the health hazards associated with the use of MMT also include those associated with inorganic Mn compounds. MMT is acutely toxic by all routes of exposure. The critical effects from acute exposure to MMT are neurological and pulmonary dysfunction. In humans, giddiness, headache, nausea, chest tightness, dyspnea and paresthesia are reported in anecdotal cases of acute occupational exposure. Acute lethal exposure to MMT in animals is associated with lomage to the lungs, kidney, liver and spleen effects, tremors, convulsions, dyspnea and weakness. In both animals and humans, slight skin and eye irritation results from dermal and ocular exposure respectively. Limited data show that repeated inhalation exposure to MMT in animals results in degenerative changes in liver and kidneys. A NOAEL of 0.0062 mg/L for inhalation exposure was reported. Manganese has been the subject of several extensive reviews and the summary of Mn toxicity for this present report is based predominantly on the WHO Concise International Chemical Assessment Document - Manganese and Its Compounds. In humans, Mn is an essential element. In animal studies, the critical effect following acute exposure to inorganic Mn compounds is neurological dysfunction. Decreased activity, alertness, muscle tone, touch response and respiration have been reported with oral administration. Pulmonary effects are also reported in inhalation studies, but these may at least in part reflect an inflammatory effect following inhalation of particulate matter rather than a result of pulmonary

toxicity of Mn. In repeated dose animal studies of Mn toxicity, the critical effect is also neurological dysfunction, and effects range from decreased motor activity to increased activity, aggression and movement tremors. In humans, chronic occupational exposure to respirable Mn dusts is associated with subclinical nervous system toxicity through to overt manganism, a progressive neurological disorder. Reproductive effects including impotence and loss of libido in male workers have also been associated with high Mn exposures. It is generally agreed that the critical study for neurological effects due to Mn exposure is Roels et al., (1992). This principal neuroepidemiological study of occupational inhalation exposure to Mn was used by WHO (1999) to determine a dose-response relationship for neurological effects. A lower 95% confidence limit was estimated for the level of Mn exposure expected to result in a 5% response rate. This value (30 [ug/M3) was considered a surrogate for a NOAEL for neurological effects in the present assessment. MMT (as Mn) is currently listed in the NOHSC List of Designated Hazardous Substances (NOHSC, 1999b) with no classification. In accordance with the NOHSC Approved Criteria for Classifying Hazardous Substances (NOHSC, 1999a), It is recommended that MMT is classified "Hazardous" with the following risk phrases: R26 - Very Toxic by Inhalation; R28 - Very Toxic if Swallowed; R24 - Toxic in Contact with Skin; R48/23 - Toxic: Danger of Serious Damage to Health by Prolonged Exposure Through Inhalation. As a result of this classification, the following additional safety phrases are also recommended: S36 - Wear Suitable Protective Clothing; There is currently no environmental hazard classification system in Australia. In accordance with the OECD Globally Harmonized System of Classification and Labelling of Chemicals, MMT would be classified Chronic 1 Very Toxic to Aquatic Life with Long-Jasting Effects (OECD, 2002). Occupational health and safety risks. Occupational exposure to MMT mainly via the dermal route may be envisaged for refinery and formulater workers during blending of LRP or aftermarket fuel additives. Occupational exposure to MMT is possible also for those workers in downstream processes that handle fuel, fuel additives and automotive fuel system components e.g. petrol station and automotive maintenance workers. In addition, occupational exposure to Mn, mainly via inhalation, is possible for these and other workers associated with or in the vicinity of automotive usage e.g, service station attendants, professional drivers, car park and road maintenance personnel. Although MMT is toxic by oral, dermal and inhalation routes, the enclosed processes used predominantly for blending of fuel or fuel additives where concentrates are handled renders the possibility of exposure low. Mild irritation is possible upon contact with fuels or fuel additives containing MMT but given the significant dilution of MMT with petroleum distillates, irritation is likely due to the irritant properties of the petroleum distillates more tian the MMT itself. Exposure to MMT is possible during handling of additived fuels, fuel additives and automotive fuel system components but is expected to be infrequent, minor and of short duration and limited due to its dilution with solvents and other additives in the fuel and fuel additives. Overall, the risks to workers posed by MMT during formulation and during handling of fuels, fuel additives containing MMT and automotive fuel system components contaminated with MMT is low. The main route of exposure to Mn particulates is inhalation and in occupations where automotive usage is ubiquitous, Chonic inhalation of inorganic Mn species may result. A worst-case scenario was considered for Mn exposure of Australian auto mechanics from the use of MMT. Using overseas personal inhalational exposure estimates, a Margin of Exposure of 203 for local mechanics was derived. This is considered a sufficient Margin of Exposure given the conservative exposure estimates derived from data from Canada where MMT is used widely as an octane enhancer in fuels and ambient air levels of Mn are higher and calculations assuming 100% market share for MMT.

Therefore, the occupational health risks associated with Mn exposure from MMT combustion are assessed as low. MSDS and labels for imported MMT concentrates and formulated aftermarket additives were assessed qualitatively against the NOHSC MSDS and Labelling Codes. In general, labels were lacking ingredient information and although sonve relevant hazard warnings were present, the recommended risk and safety phrases from this assessment were missing. Signal words and disclosure of the presence of MMT were also missing from sonve labels. Local contact details were absent from labels of imported concentrates. MSDS in general contained relevant health effect information but also did not include recommended risk and safety phrases. Most also had other important elements missing such as correct hazard statements and emergency telephone numbers. A sample MSDS for MMT is included in Appendix 3. S38 - In Case of Insufficient Ventilation Wear Suitable Respiratory Equipment. Based on a toxicity profile from animal experiments, MMT meets the criteria of the ADG Code (FORS, 1998) for classification as a toxic substance Class 6.1, Packing Group I. MMT can be ascribed a Proper Shipping Name using the General Entry "Toxic Liquid, Organic, NOS" or Specific Entry "Metal Carbonyls, NOS". MMT is currently not listed in the SUSDP. However, according to the Guidelines for the National Drugs and Poisons Schedule Cbmmittee, its domestic use and toxicity profile are allo consistent with a Schedule 7 entry in the SUSDP. Consequently, this report will be referred for consideration of scheduling by the NDPSC. Environmental hazards and risks. MMT is highly toxic to aquatic organisms and spill incidents and leaks to water bodies and land should be managed through existing Federal, State and Territory legislative frameworks and protocols to mitigate adverse effects to the aquatic envirownent. Such incidents may potentially occur during shipment into Australia, bulk handling and storage and leakage of underground storage tanks. All States and Territories have general environment protection legislativn pertaining to pollution and contaminated land. However, there are currently no existing leak prevention or leak detection requirements for operators of underground fuel storage tanks in NSW, and probably other States and Territories, to detect and control leakages from UST facilities. UST leak detection systems are implemented on a voluntary basis by industry, particularly by major petroleum suppliers. Use of MMT in internal combustion engines as a fuel additive and subsequent degradation through combustion, and its short persistence in the environment, indicate that aquatic and terrestrial organisms are unlikely to be exposed to MMT at or above levels of concern through existing use as an AVSR. A low environmental risk is predicted. Manganese, the principle degradation by-product from combustion of MMT, is naturally occurring and ubiquitous in the environment. It is an essential nutrient of plants and animals. Environmental exposure to Mn compounds will mostly anse through the gaseous phase. Eventually, these will deposit to land and waters. The emission of Mn into the environment from use of fuels containing MMT is unlikely to develop to levels of concern and therefore poses a low risk for terrestrial or aquatic environments. The findings of this assessment highlight the potential for leaking USTs to pose an unacceptable risk to the environment. Such leakages represent localised, point source discharge, but have the potential to detrimentally affect significant areas of the environment. Although a large number of USTs have been replaced or have bad leak detection systems or other measures installed, most USTs do not have leak detection systems, and many that are currently in service are old and have the potential to leak in the future if not decommissioned or replaced. Although there is potential for risk to the environment from leakage of fuel (which may or may not contain MMT) from USTs, the risk would be site Specific. MMT (as Mn) is listed in the NOHSC Exposure Standards for Atmospheric Contaminants in the Occupational Environment with an exposure standard of 0.2

mg/m~, (8 h TWA), skin notation (NOHSC 1995b). Public health risks. Direct public exposure to MMT is likely to occur primarily via the dermal route as a result of spills and splashes of LRP and aftermarket products. In LRP, MMT is not expected to be a skin irritant at present concentrations. Estimated dermal doses of MMT to be received under a worst case scenario of LRP spillage were several orders of magnitude below comparable animal dermal LD50s. Therefore, there is a low risk of acute health effects for the general public as a result of dermal exposure to MMT in LRP. Similarly, in aftermarket products, MMT at concentrations presently reported is not expected to be a skin irritant. A comparison of dermal LD50 values with exposure estimates suggests some potential for acute toxicity resulting from dermal exposure to MMT in aftermarket products. However, LD50 values in rats were obtained after a constant 24-hour exposure to MMT and in contrast, much shorter exposures are expected following spillage. Overall, the risk of acute dermal effects in consumers is low given the small amounts of additive to which people are likely to be exposed, the low concentration of MMT present with the fuel additive and that any spill on the skin is unlikely to reside untreated for long periods. The risk of acute health effects as a result of accidental ocular exposure to MMT in LRP and aftermarket products is also considered to be low since exposure to very small amounts of product is expected to occur only infrequently and MMT is not expected to cause eye irritation at low concentrations present in these products. Acute health effects could occur as a result of accidental ingestion of MMT by a child or by adults when siphoning fuel. The health risk to adults from accidental ingestion of LRP containing MMT during siphoning or to children following ingestion of LRP stored inappropriately around the home is considered low, given the low level of MMT (< 0.01% w/w) in LRP. However, assuming comparable toxicokinetics of MMT in rats and humans after oral exposure and using the lowest rat LD50 for MMT of approximately 10 mg/kg bw, a child (IOkg) ingesting about one mL of an aftermarket product containing 10% w/w MMT could receive a potentially lethal dose. Children between one and a quarter and three and a half years of age can swallow approximately 4.5 mL of liquid, giving a potential dose several times higher than the lowest oral LD50 observed in laboratory animals. The potential risk associated with accidental ingestion of aftermarket products containing MMT is lessened by the likely storage of aftermarket products in garages, products being generally not "attractive" for ingestion by a child and products as assessed packaged with child resistant closures. However, since very small volumes provide a potentially lethal dose, products containing MMT represent a significant acute health risk for children. Manganese is a ubiquitous element and chronic Mn exposures (from all sources combined) are unlikely to be significantly changed by the use of MMT. Exposure via food and water forms, by far, the greatest proportion of the total human Mn dose, and are not expected to change significantly as a result of the estimated use of MMT. However, MMT used according to the Present Use scenario of maintained LRP inarket share or the 2004 scenario of diminished LRP inarket share will potentially significantly increase the Mn dose received by inhalation (excluding smoking). Based on the study of Roels et al (1992), the NOAEL for neurological effects in humans was established at 30 ug/m3 and Margins of Exposure were calculated in this report converting intermittent Mn exposures (5 days/week, 24 hours/day) to continuous exposures. For the Present Use scenario, where current LRP inarket share is maintained with a calculated ambient air concentration for Mn of 4.9 ng/m3, the Margin of Exposure was calculated at 1458. For the 2004 scenario, where the LRP market share declines with a calculated ambient air concentration for Mn of 20 ng/m3, the Margin of Exposure was calculated at 3571. These Margins of Exposure are considered sufficient, taking into account the conservative exposure estimates used. It is noted

that the estimated ambient air concentration of Mn due to MMT combustion is at the lower end of a range of overseas inhalation health standards and guidance values. However, a number of conservative assumptions were used in this present exposure assessment. Consequently, the risk to public health as a result of the use of MMT as an AVSR is expected to be low. However, there are uncertainties associated with this risk assessment and there are likely to be sub-populations that have higher exposures and hence are at greater risk than the general population. For example, although the measured ambient air concentration of respirable Mn is probably unrelated to the use of MMT, exposure of people in Launceston is of potential concern since the ambient air concentration of total (but not respirable) Mn in that city is higher than some of the ambient air standards developed overseas. The use of MMT would add potentially to environmental Mn levels in this region.

5. ATSDR. 2000. Public Health Statement Manganese. In: CDC, editor: ATSDR.

6. Clewell HJ, Lawrence GA, Calne DB, Crump KS. (2003) Determination of an occupational exposure guideline for manganese using the benchmark method. Risk Analysis 23(5):1031-1046. An occupational risk assessment for manganese (Mn) was performed based on benchmark dose analysis of data from two epidemiological studies providing dose-response information regarding the potential neurological effects of exposure to airborne Mn below the current Occupational Safety and Health Administration (OSHA) Permissible Exposure Level (PEL) of 5 mg Mn/m(3). Based on a review of the scientific evidence regarding the toxicity of Mn, it was determined that the most appropriate measure of exposure to airborne Mn for the subclinical effects measured in these studies is recent (rather than historical or cumulative) concentration of Mn in respirable (rather than total) particulate. For each of the studies analyzed, the individual exposure and response data from the original study had been made available by the investigators. From these two studies benchmark concentrations calculated for eight endpoints ranged from 0.09 to 0.27 mg Mn/m(3). From our evaluation of these results, and considering the fact that the subtle, subclinical effects represented by the neurological endpoints tested in these studies do not represent material impairment, we believe an appropriate occupational exposure guideline for manganese would be in the range of 0.1 to 0.3 mg Mn/m(3), based on the respirable particulate fraction only, and expressed as an 8-hour time-weighted average.

7. EPA. 2003. Health Effects Support Document for Manganese. Supersedes PB2002-108377. Sponsored by Environmental Protection Agency, Washington, DC. Health and Ecological Criteria Div.
The U.S. Environmental Protection Agency (EPA) has prepared this Health Effects Support Document to assist in determining whether to establish a National Primary Drinking Water Regulation (NPDWR) for manganese. At high doses by inhalation, manganese is very toxic, as seen by occupational exposure in miners. On the other hand, manganese is essential for normal physiological function of animals and humans. The Food and Nutrition Board of the National Academy of Science (NAS) sets an adequate intake for manganese at 2.3 mg/day for men and 1.8 mg/day for women, and an upper limit for daily intake at 11 mg for adults (IOM, 2002). Manganese has a low aesthetic threshold in water. Based on staining and taste, EPA has set a secondary level for manganese at 0.05 mg/L which is below the level that may present a health concern. Available data suggest that regulation of manganese in public water does not present a

meaningful basis for health risk reduction. EPA will present a determination and further analysis in the Federal Register Notice covering the Contaminant Candidate List proposals.

8. Gerber GB, Leonard A, Hantson P. (2002) Carcinogenicity, mutagenicity and teratogenicity of manganese compounds. Critical Reviews in Oncology Hematology 42(1):25-34.
Manganese, an essential trace element, is one of the most used metals in the industry. Recently, several new manganese compounds have been introduced as fungicide, as antiknock agent in petrol and as contrasting agent in nuclear magnetic resonance tomography. Manganese displays a somewhat unique behaviour with regard to its toxicity. It is relatively non-toxic to the adult organism except to the brain where it causes Parkinson-like symptoms when inhaled even at moderate amounts over longer periods of time. Relatively high doses of manganese affect DNA replication and repair in bacteria and causes mutations in microorganism and mammalian cells although the Ames test does not appear to be particularly responsive to manganese. In mammalian cells, manganese causes DNA damage and chromosome aberrations. Information on organic manganese derivatives is still insufficient. Large amounts of manganese affect fertility in mammals and are toxic to the embryo and foetus. The fungicide MANEB and the contrasting agent MnDPDP also can be embryotoxic, but the latter only at doses much higher than those clinically employed, Information on the anti-knock agent MMT is inadequate. On the other hand, manganese deficiency can also affect fertility and be teratogenic. Information on cancer due to manganese is scanty but the results available do not indicate that inorganic manganese is carcinogenic. More information is desirable with regard to the organic manganese derivatives. It may surprise that an agent that causes mutations is not also carcinogenic. The experience with manganese shows that conclusions with regard to carcinogenicity of an agent based on the observation of mutations are subject to uncertainties. Altogether, it appears that, because of the very high doses at which positive effects hake been found, manganese would not represent a significant carcinogenic risk to the population and workers. Care must, however, be exercised with respect to central-nervous symptoms after chronic exposure and with respect to effects on the embryo. Pregnant women should not be exposed to manganese at the work place.

9. Goldhaber SB. (2003) Trace element risk assessment: essentiality vs. toxicity. Regulatory Toxicology and Pharmacology 38(2):232-242.
Risk assessment of essential trace elements examines high intakes resulting in toxicity and low intakes resulting in nutritional deficiencies. This paper analyzes the risk assessments carried out by several U.S. governmental and private organizations for eight essential trace elements: chromium, copper, iodine, iron, manganese, molybdenum, selenium, and zinc. The compatibility of the toxicity values with the nutritionally essential values is examined, in light of recently derived values, termed Dietary Reference Intakes, set by the U.S. Food and Nutrition Board of the Institute of Medicine. The results show that although there are differences in the values set by the different organizations, increased coordination has resulted in values that are more compatible than revealed in past evaluations.

10. Greger JL. (1998) Dietary standards for manganese: Overlap between nutritional and toxicological studies. Journal of Nutrition 128(2):368S-371S.
The Estimated Safe and Adequate Daily Dietary Intake (ESADDI) for adults for manganese is 2-5 mg Mn/d, The LOAEL (lowest-observable-adverse-effect level) for manganese in water is 0.06

mg Mn/(kg.d) or 4.2 mg Mn/d for a 70-kg individual. The inconsistency in these standards reflects limitations in the available data as well as differences in the way in which the standards are calculated, Manganese balance and excretion data are not useful biomarkers of manganese exposure but do demonstrate that the body is protected against manganese toxicity primarily by low absorption and/or rapid presystemic elimination of manganese by the liver. Serum manganese concentrations in combination with lymphocyte manganese-dependent superoxide dismutase (MnSOD) activity, and perhaps blood arginase activity, seem to be the best way to monitor ingestion of insufficient manganese, Serum manganese concentrations in combination with brain magnetic resonance imaging (MRI) scans, and perhaps a battery of neurofunctional tests, seem to be the best way to monitor excessive exposure to manganese.

11. Greger JL. (1999) Nutrition versus toxicology of manganese in humans: Evaluation of potential biomarkers. Neurotoxicology 20(2-3):205-212.
Manganese intake can vary greatly with food choices, water composition, and supplement use. Thus, individuals consuming Western diets consume from <1 to >10 mg Mn/d. The levels of manganese intake associated with adverse effects (both deficient and toxic) are debatable. Moreover, many of the symptoms of manganese deficiency (growth retardation, changes in circulating HDL cholesterol and glucose levels, reproductive failure) and manganese toxicity (growth depression, anemia) are nonspecific. The bone deformities observed in manganese-deficient animals and neurological symptoms of individuals who have inhaled excess manganese are permanent and illustrate the need to identify sensitive biomarkers of manganese status that appear before these symptoms. Manganese balance and excretion data are not useful biomarkers of manganese exposure but demonstrate that the body is protected against manganese toxicity primarily by low absorption and/or rapid presystemic elimination of manganese by the liver. Serum manganese concentrations in combination with lymphocyte manganese-dependent superoxide dismutase (MnSOD) activity and perhaps blood arginase activity, appear to be the best ways to monitor ingestion of insufficient manganese. Serum manganese concentrations in combination with brain MRI (magnetic resonance imaging) scans, and perhaps a battery of neurofunctional tests, appear to be the best ways to monitor excessive exposure to manganese. (C) 1999 Inter Press, Inc.

12. Gwiazda R, Lucchini R, Smith D. (2007) Adequacy and consistency of animal studies to evaluate the neurotoxicity of chronic low-level manganese exposure in humans. Journal of Toxicology and Environmental Health-Part a-Current Issues 70(7):594-605.
The adequacy of existing animal studies to understand the effects of chronic low- level manganese exposures in humans is unclear. Here, a collection of subchronic to chronic rodent and nonhuman primate studies was evaluated to determine whether there is a consistent dose-response relationship among studies, whether there is a progression of effects with increasing dose, and whether these studies are adequate for evaluating the neurotoxicity of chronic low-level manganese exposures in humans. Neurochemical and behavioral effects were compared along the axis of estimated internal cumulative manganese dose, independent of the route of exposure. In rodents, motor effects emerged at cumulative doses below those where occupationally exposed humans start to show motor deficits. The main neurochemical effects in rodents were an increase in striatal gamma- aminobutyric acid (GABA) concentration throughout the internal cumulative dose range of 18 to 5300 mg Mn/ kg but a variable effect on striatal dopamine concentration emerging at internal cumulative doses above similar to 200 mg

Mn/ kg. Monkey studies showed motor deficits and effects on the globus pallidus at relatively low doses and consistent harmful effects on both the globus pallidus and the caudate and putamen at higher doses (> 260 mg Mn/ kg). Internal cumulative manganese doses of animal studies extend more than two orders of magnitude (< 1 to 5300 mg Mn/ kg) above the doses at which occupationally exposed humans show neurological dysfunction (10 - 15 mg Mn/ kg). Since the animal data indicate that manganese neurotoxicity may be different at low compared to elevated exposures, most existing animal model studies might be of limited relevance for the risk assessment of chronic low- level manganese exposure to humans.

13. Jankovic J. (2005) Searching for a relationship between manganese and welding and Parkinson's disease. Neurology 64(12):2021-2028.
Research into the causes of Parkinson disease (PD) has accelerated recently with the discovery of novel gene mutations. The majority of PD cases, however, remain idiopathic and in those cases environmental causes should be considered. Several recent reports have focused on welding and manganese toxicity as potential risk factors for parkinsonism and some have even proposed that welding is a risk factor for PD. The controversy has stimulated this review, the primary aim of which is to critically and objectively examine the evidence or lack of evidence for a relationship among welding, manganese, parkinsonism, and PD.

14. Newland MC. (1999) Animal models of manganese's neurotoxicity. Neurotoxicology 20(2-3):415-432.
Manganese's neurotoxicity continues to present a puzzling array of differences across individuals and across published reports in the profile of effects seen in humans and nonhuman species, but some of the sources of individual variability are becoming clear from studies of animals. The kinetics of manganese is a critical component of any assessment of risk associated with exposure. After inhalation, the uptake of manganese into and elimination from the central nervous system are slow and same manganese remains in the nervous system a year after inhalation. Comparison with other parenteral routes suggests that manganese depots in lung prolongs exposure even after environmental exposure has ended. Manganese's neurotoxicity is associated with its appearance in basal ganglia structures, especially the globus pallidus. Manganese a Iso appears in the pituitary gland but the functional consequences of this are not well understood. Other critical components in characterizing manganese's neurotoxicity appear to be the behavioral endpoints used, the species studied, and the exposure rate. Overt neurological signs and excitability are associated with high exposure rates and the appearance of manganese throughout basal ganglia and basal forebrain regions. More focused behavioral endpoints are required to detect the subtle signs associated with slow exposure rates low exposure levels, but when such designs are used the effect is unequivocal. At lower exposure levels, doses of 5 mg/kg and greater, deficits in a task in which a monkey executed a rowing type motion against a spring approximating its body weight were clearly related to manganese exposure while other traditional measures of response patterns under schedules of reinforcement remained intact. Excitability and other signs of emotionality have not been reported at low exposure rates. In rodents, manganese accumulation and alterations in the function or concentration of neurotransmitters have been reported. Investigations of behavioral effects in these species, which usually involved locomotor activity, have resulted in less consistent results. Manganese produces a constellation of neurotoxic signs whose appearance and detection are influenced by dose and exposure rate. Despite investigations of manganese's neurotoxicity in

animals over a wide range of exposure levels, a NOAEL has not been identified. (C) 1998 Inter Press, Inc.

15. OEHHA. 2004. Chronic Toxicity Summary Managenese and Compounds. In: Assessment OoEHH, editor: California Environmental Protection Agency (Cal/EPA).
CHRONIC TOXICITY SUMMARY MANGANESE AND COMPOUNDS Molecular Formula Synonyms Molecular Weight CAS Reg. No. Mn elemental manganese; colloidal manganese; cutaval 54.94 g/mol 7439-96-5 MnO manganese oxide; manganese monoxide; manganosite 70.

16. Olanow CW. (2004) Manganese-induced parkinsonism and Parkinson's disease. Redox-Active Metals in Neurological Disorders. NEW YORK: NEW YORK ACAD SCIENCES. pp 209-223.
It has long been appreciated that manganese exposure can cause neurotoxicity and a neurologic syndrome that resembles Parkinson's disease (PD). Current evidence indicates that manganese-induced parkinsonism can be differentiated from PD because of its predilection to accumulate in and damage the pallidum and striatum rather than the SNc. The clinical syndrome, response to levodopa, imaging studies with MRI and PET, and pathologic features all help to distinguish these two conditions and permit the correct diagnosis to be established. This is of particular relevance in differentiating patients with parkinsonism due to manganese intoxication from patients with idiopathic PD who have incidental manganese exposure.

17. Roth JA, Garrick MD. (2003) Iron interactions and other biological reactions mediating the physiological and toxic actions of manganese. Biochemical Pharmacology 66(1):1-13.
Chronic exposure to the divalent heavy metals, such as iron, lead, manganese (Mn), and chromium, has been linked to the development of severe, often irreversible neurological disorders and increased vulnerability to developing Parkinson's disease. Although the mechanisms by which these metals elicit or facilitate neuronal cell death are not well defined, neurotoxicity is limited by the extent to which they are transported across the blood-brain barrier and their subsequent uptake within targeted neurons. Once inside the neuron, these heavy metals provoke a series of biochemical and molecular events leading to cell death induced by either apoptosis and/or necrosis. The toxicological properties of Mn have been studied extensively in recent years because of the potential health risk created by increased atmospheric levels owing to the impending use of the gas additive methylcyclopentadienyl manganese tricarbonyl. Individuals exposed to high environmental levels of Mn, which include miners, welders, and those living near ferroalloy processing plants, display a syndrome known as manganism, best characterized by debilitating symptoms resembling those of Parkinson's disease. Mn disposition in vivo is influenced by dietary iron intake and stores within the body since the two metals compete for the same binding protein in serum (transferrin) and subsequent transport systems (divalent metal transporter, DMTI). There appear to be two distinct carrier-mediated transport systems for Mn and ferrous ion: a transferrin-dependent and a transferrin-independent pathway, both of which utilize DMT1 as the transport protein. Accordingly, this commentary focuses on the biochemical and molecular processes responsible for the cytotoxic actions of Mn and the role that cellular transport plays in mediating the physiological as well as the toxicological actions of this metal.

18. Santamaria A, Cushing C, Antonini J, Finley B, Mowat F. (2007) State-of-the-Science Review: Does Manganese Exposure During Welding Pose a Neurological Risk? Journal of Toxicology and Environmental Health Part B: Critical Reviews 10(6):416-475(449).
Recent studies report that exposure to manganese (Mn), an essential component of welding electrodes and some steels, results in neurotoxicity and/or Parkinson's disease (PD) in welders. This "state-of-the-science" review presents a critical analysis of the published studies that were conducted on a variety of Mn-exposed occupational cohorts during the last 100 yr, as well as the regulatory history of Mn and welding fumes. Welders often perform a variety of different tasks with varying degrees of duration and ventilation, and hence, to accurately assess Mn exposures that occurred in occupational settings, some specific information on the historical work patterns of welders is desirable. This review includes a discussion of the types of exposures that occur during the welding process - for which limited information relating airborne Mn levels with specific welding activities exists - and the human health studies evaluating neurological effects in welders and other Mn-exposed cohorts, including miners, millers, and battery workers. Findings and implications of studies specifically conducted to evaluate neurobehavioral effects and the prevalence of PD in welders are also discussed. Existing exposure data indicate that, in general, Mn exposures in welders are less than those associated with the reports of clinical neurotoxicity (e.g., "manganism") in miners and smelter workers. It was also found that although manganism was observed in highly exposed workers, the scant exposure-response data available for welders do not support a conclusion that welding is associated with clinical neurotoxicity. The available data might support the development of reasonable "worst-case" exposure estimates for most welding activities, and suggest that exposure simulation studies would significantly refine such estimates. Our review ends with a discussion of the data gaps and areas for future research.

Supporting References (71)

1. (1998) Is airborne manganese a hazard? Environmental Health Perspectives 106(2):A57-A58.

2. anon. (1997) Manganese toxicity: hazard of intravenous food. Drugs Q. 1(1):31-32. IPA COPYRIGHT: ASHP.
A high incidence of toxic blood manganese levels in children receiving prolonged intravenous (IV) nutrition is discussed. Precautionary annual imaging of the basal ganglia is recommended for children who need IV feeding indefinitely, and immediate reduction of some 50 fold in the manganese content of some proprietary trace element solutions are suggested.

3. Antonini JM, Taylor MD, Zimmer AT, Roberts JR. (2004) Pulmonary responses to welding fumes: Role of metal constituents. Journal of Toxicology and Environmental Health-Part a-Current Issues 67(3):233-249.
It is estimated that more than 1 million workers worldwide perform some type of welding as part of their work duties. Epidemiology studies have shown that a large number of welders experience some type of respiratory illness. Respiratory effects seen in full-time welders have included bronchitis, siderosis, asthma, and a possible increase in the incidence of lung cancer. Pulmonary infections are increased in terms of severity, duration, and frequency among welders. Inhalation exposure to welding fumes may vary due to differences in the materials used and methods employed. The chemical properties of welding fumes can be quite complex. Most

welding materials are alloy mixtures of metals characterized by different steels that may contain iron, manganese, chromium, and nickel. Animal studies have indicated that the presence and combination of different metal constituents is an important determinant in the potential pneumotoxic responses associated with welding fumes. Animal models have demonstrated that stainless steel (SS) welding fumes, which contain significant levels of nickel and chromium, induce more lung injury and inflammation, and are retained in the longs longer than mild steel (MS) welding fumes, which contain mostly iron. In addition, SS fumes generated from welding processes using fluxes to protect the resulting weld contain elevated levels of soluble metals, which may affect respiratory health. Recent animal studies have indicated that the lung injury and inflammation induced by SS welding fumes that contain water-soluble metals are dependent on both the soluble and insoluble fractions of the fume. This article reviews the role that metals play in the pulmonary effects associated with welding fume exposure in workers and laboratory animals.

4. Aschner M, Erikson KM. (2003) Manganese and iron deficiency in neurodegeneration. Journal of Neurochemistry 87:129-129.

5. Aschner M, Lukey B, Tremblay A. (2006) The manganese health research program (MHRP): Status report and future research needs and directions. Neurotoxicology 27(5):733-736.
The manganese (Mn) research health program (MHRP) symposium was a full day session at the 22nd International Neurotoxicology Conference. Mn is a critical metal in many defense and defense-related private sector applications including steel making and fabrication, improved fuel efficiency, and welding, and a vital and large component in portable power sources (batteries). At the current time, there is much debate concerning the potential adverse health effects of the use of manganese in these and other applications. Due to the significant use of manganese by the Department of Defense, its contractors and its suppliers, the Manganese Health Research Program (MHRP) seeks to use the resources of the federal government, in tandem with manganese researchers, as well as those industries that are involved with manganese, to determine the exact health effects of manganese, as well as to devise proper safeguard measures for both public and private sector workers. Humans require manganese as an essential element; however, exposure to high levels of this metal is sometimes associated with adverse health effects, most notably within the central nervous system. Exposure scenarios vary extensively in relation to geographical location, urban versus rural environment, lifestyles, diet, and occupational setting. Furthermore, exposure may be brief or chronic, it may be to different types of manganese compounds (aerosols or salts of manganese with different physical and/or chemical properties), and it may occur at different life-stages (e.g., in utero, neonatal life, puberty, adult life, or senescence). These factors along with diverse genetic composition that imposes both a background and disease occurrence likely reflect on differential sensitivity of individuals to manganese exposure. Unraveling these complexities requires a multipronged research approach to address multiple questions about the role of manganese as an essential metal as well as its modulation of disease processes and dysfunction. A symposium on the Health Effects of Manganese (Mn) was held on Wednesday, September 14, 1005, to discuss advances in the understanding on role of Mn both in health and disease. The symposium was sponsored by the Manganese Health Research Program (MHRP). This summary provides background on the MHRP, identifies the speakers and topics discussed at the symposium, and

identifies research needs and anticipated progress in understanding Mn health- and disease-related issues. (C)2005 Elsevier Inc. All rights reserved.

6. ATSDR. 2001. ATSDR - ToxFAQs": Manganese.
Manganese is a trace element and eating a small amount from food or water is needed to stay healthy. Exposure to excess levels of manganese may occur from breathing air, particularly where manganese is used in manufacturing, and from drinking water and eating food. At high levels, it can cause

7. ATSDR. 2004. Interaction Profile: Lead, Manganese, Zinc, and Copper.
Agency for Toxic Substances and Disease Registry (ATSDR). 2004. Interaction profile for lead, manganese, zinc, copper. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service. Disclaimer

8. Barceloux DG. (1999) Manganese. Journal of Toxicology-Clinical Toxicology 37(2):293-307.
Manganese is a very hard, brittle metal, which is used to increase the strength of steel alloys, Absorption from the gastrointestinal tract occurs in the divalent and tetravalent forms. Permanganates, which are strong oxidizing agents, have a +7 valence. The principal organomanganese compound is the anti-knock additive, methylcyclopentadienyl manganese tricarbonyl. Manganese is a ubiquitous constituent of the environment comprising about 0.1% of the earth's crust. For the general population, food is the most important source of manganese with daily intake ranging from 2-9 mg Mn. Combustion of gasoline containing methylcyclopentadienyl manganese tricarbonyl releases submicron particles of Mn3O4 that are potentially respirable. Biomagnification of manganese in the food chain probably does not occur. The lungs and gastrointestinal tract absorb some manganese, but the relative amounts absorbed from each site are not known. Homeostatic mechanisms limit the absorption of manganese from the gastrointestinal tract. Elimination of manganese occurs primarily by excretion into the bile. Animal studies indicate that manganese is an essential co-factor for enzymes, such as hexokinase, superoxide dismutase, and xanthine oxidase. However, no case of manganese deficiency in humans has been identified, Manganism is a central nervous system disease first described in the 1800s following exposure to high concentrations of manganese oxides. Manganese madness was the term used to describe the initial psychiatric syndrome (compulsive behavior, emotional lability, hallucinations). More commonly, these workers developed a Parkinson's-like syndrome. Currently, the risks of exposure to low concentrations of manganese in the industrial and in the environmental settings (e.g., methylcyclopentadienyl manganese tricarbonyl in gasoline) are being evaluated with regards to the development of subclinical neuropsychological changes. The American Conference of Governmental and Industrial Hygienists recently lowered the TLV-TWA for manganese compounds and inorganic manganese compounds to 0.2 mg Mn/m(3).

9. Bizarro P, Sanchez I, Lopez I, Pasos F, Delgado V, Gonzalez-Villalva A, Colin-Barenque L, Acevedo S, Nino-Cabrera G, Mussali-Galante P and others. (2004) Morphological Changes In Testes. After Manganese Inhalation. Study In Mice. Toxicologist 78(1-S):157.
Manganese (Mn) has been used as an antiknocking agent in gasoline. Its increase in the atmosphere enhances the risk of its inhalation and the induction of systemic damage. Some

reports mention that oral administration of MnCl2 induces reproductive delay in male mice. Prostatic cancer has been identified among exposed workers. The objective of this study was to identify in a murine inhalation model in CD-1 male mice. Animals inhaled MnCl2 0.02M, 1h, twice a week, for 4 weeks, sacrificed once a week and processed for light and electron microscopy. Light changes evidenced necrosis of stem cells, binucleated spermatocytes and dense nuclear structures. Ultrastructural changes in Leydig cells consisted in hyperplastic endoplasmic reticulum forming whorl-like structures. As a consequence of these modifications the function of the testes might be altered, as well as its endocrine function.

10. Bourre JM. (2004) The role of nutritional factors on the structure and function of the brain: an update on dietary requirements. Revue Neurologique 160(8-9):767-792.
The brain is an organ elaborated and functioning from substances present in the diet. Dietary regulation of blood glucose level (via ingestion of food with a low glycemic index ensuring a low insulin level) improves the quality and duration of intellectual performance, if only because at rest the adult brain consumes 50 p. 100 of dietary carbohydrates, 80 p. 100 of them for energy purposes. The nature of the amino acid composition of dietary proteins contributes to good cerebral function; tryptophan plays a special role. Many indispensable amino acids present in dietary proteins help to elaborate neurotransmitters and neuromodulators. Omega-3 fatty acids provided the first coherent experimental demonstration of the effect of dietary nutrients on the structure and function of the brain. First it was shown that the differentiation and functioning of cultured brain cells requires omega-3 fatty acids. It was then demonstrated that alpha-linolenic acid (ALA) deficiency alters the course of brain development, perturbs the composition and physicochemical properties of brain cell membranes, neurones, oligodendrocytes, and astrocytes (ALA). This leads to physicochemical modifications, induces biochemical and physiological perturbations, and results in neurosensory and behavioral upset. Consequently, the nature of polyunsaturated fatty acids (in particular omega-3) present in formula milks for infants (premature and term) conditions the visual and cerebral abilities, including intellectual abilities. Moreover, dietary omega-3 fatty acids are certainly involved in the prevention of some aspects of cardiovascular disease (including at the level of cerebral vascularization), and in some neuropsychiatric disorders, particularly depression, as well as in dementia, notably Alzheimer's disease. Their deficiency can prevent the satisfactory renewal of membranes and thus accelerate cerebral aging. Iron is necessary to ensure oxygenation, to produce energy in the cerebral parenchyma, and for the synthesis of neurotransmiters. The iodine provided by the thyroid hormone ensures the energy metabolism of the cerebral cells. The absence of iodine during pregnancy induces severe cerebral dysfunction, leading to cretinism. Manganese, copper, and zinc participate in enzymatic mechanisms that protect against free radicals, toxic derivatives of oxygen. The use of glucose by nervous tissue implies the presence of vitamin B1. Vitamin B9 preserves memory during aging, and with vitamin B12 delays the onset of signs of dementia, provided it is administered in a precise clinical window, at the onset of the first symptoms. Vitamins B6 and B12, among others, are directly involved in the synthesis of neurotransmitters. Nerve endings contain the highest concentrations of vitamin C in the human body. Among various vitamin E components, only alpha-tocopherol is involved in nervous membranes. The objective of this update is to give an overview of the effects of dietary nutrients on the structure and certain functions of the brain.

11. Bourre JM. (2006) Effects of nutrients (in food) on the structure and function of the nervous system: Update on dietary requirements for brain. Part 1: Micronutrients. Journal of Nutrition Health & Aging 10(5):377-385.
The objective of this update is to give an overview of the effects of dietary nutrients on the structure and certain functions of the brain. As any other organ, the brain is elaborated from substances present in the diet (sometimes exclusively, for vitamins, minerals, essential amino-acids and essential fatty acids, including omega-3 polyunsaturated fatty acids). However, for long it was not fully accepted that food can have an influence on brain structure, and thus on its function, including cognitive and intellectuals. In fact, most micronutrients (vitamins and trace-elements) have been directly evaluated in the setting of cerebral functioning. For instance, to produce energy, the use of glucose by nervous tissue implies the presence of vitamin B I; this vitamin modulates cognitive performance, especially in the elderly. Vitamin B9 preserves brain during its development and memory during ageing. Vitamin B6 is likely to benefit in treating premenstrual depression. Vitamins B6 and B 12, among others, are directly involved in the synthesis of some neurotransmitters. Vitamin B 12 delays the onset of signs of dementia (and blood abnormalities), provided it is administered in a precise clinical timing window, before the onset of the first symptoms. Supplementation with cobalamin improves cerebral and cognitive functions in the elderly, it frequently improves the functioning of factors related to the frontal lobe, as well as the language function of those with cognitive disorders. Adolescents who have a borderline level of vitamin B 12 develop signs of cognitive changes. In the brain, the nerve endings contain the highest concentrations of vitamin C in the human body (after the suprarenal glands). Vitamin D (or certain of its analogues) could be of interest in the prevention of various aspects of neurodegenerative or neuroimmune diseases. Among the various vitamin E components (tocopherols and tocotrienols), only alpha-tocopherol is actively uptaken by the brain and is directly involved in nervous membranes protection. Even vitamin K has been involved in nervous tissue biochemistry. Iron is necessary to ensure oxygenation and to produce energy in the cerebral parenchyma (via cytochrome oxidase), and for the synthesis of neurotransmitters and myelin; iron deficiency is found in children with attention-deficit/hyperactivity disorder. Iron concentrations in the umbilical artery are critical during the development of the foetus, and in relation with the IQ in the child; infantile anaemia with its associated iron deficiency is linked to perturbation of the development of cognitive functions. Iron deficiency anaemia is common, particularly in women, and is associated, for instance, with apathy, depression and rapid fatigue when exercising. Lithium importance, at least in psychiatry, is known for a long time. Magnesium plays important roles in all the major metabolisms: in oxidation-reduction and in ionic regulation, among others. Zinc participates among others in the perception of taste. An unbalanced copper metabolism homeostasis (due to dietary deficiency) could be linked to Alzheimer disease. The iodine provided by the thyroid hormone ensures the energy metabolism of the cerebral cells; the dietary reduction of iodine during pregnancy induces severe cerebral dysfunction, actually leading to cretinism. Among many mechanisms, manganese, copper, and zinc participate in enzymatic mechanisms that protect against free radicals, toxic derivatives of oxygen. More specifically, the full genetic potential of the child for physical growth ad mental deveopment may be compromised due to deficiency (even subclinical) of micronutrients. Children and adolescents with poor nutritional status are exposed to alterations of mental and behavioural functions that can be corrected by dietary measures, but only to certain extend. Indeed, nutrient composition and meal pattern can exert either immediate or long-term effects, beneficial or adverse. Brain diseases during aging can also be due to failure

for protective mechanism, due to dietary deficiencies, for instance in anti-oxidants and nutrients (trace elements, vitamins, non essential micronutrients such as polyphenols) related with protection against free radicals. Macronutrients are presented in the accompanying paper.

12. Bowler RM, Mergler D, Sassine MP, Larribe F, Hudnell K. (1999) Neuropsychiatric effects of manganese on mood. Neurotoxicology 20(2-3):367-378.
Adverse mood effects of overexposure to Manganese (Mn) have been described in 15 studies which frequently report an association of Mn exposure with adverse effects in six dimensions of mood: 1) anxiety, nervousness, irritability; 2) psychotic experiences; 3) emotional disturbance; 4) fatigue lack of vigor, sleep disturbance; 5) impulsive/compulsive behavior; 6) aggression hostility. Only 1.15 studies used a standardized psychological measure of mood, while the current study of environmental Mn exposure used two standardized mood scales in evaluating low levels of Mn exposure and mood sequelae. The Profile of Moods State (POMS) and Brief Symptom Inventory (BSI) were used, and results indicate that men who are older and have higher Mn levels show significant disturbances on four of the six mood dimensions. Increased scores were seen in the anxiety, nervousness, irritability; emotional disturbance; and aggression, hostility dimensions relative to those who had lower levels of Mn. The BSI and POMS are useful adjuncts in the assessment of mood/Mn effects. (C) 1999 Inter Press, Inc.

13. Breault JL, Campbell H. (1997) Manganese toxicity. Journal of Family Practice 45(1):15-16.

14. Chu NS, Hochberg FH, Calne DB, Olanow CW. (1995) Neurotoxicology of manganese. Chang, L. W. and R. S. Dyer (Ed.). Neurological Disease and Therapy, Vol. 36. Handbook of Neurotoxicology. Xxi+1103p. Marcel Dekker, Inc.: New York, New York, USA; Basel, Switzerland. Isbn 0-8247-8873-7.; 0 (0). 1995. 91-103. Biosis copyright: biol abs. rrm book chapter human absorption parkinson's disease

15. Crossgrove J, Zheng W. (2004) Manganese toxicity upon overexposure. Nmr in Biomedicine 17(8):544-553.
Manganese (Mn) is a required element and a metabolic byproduct of the contrast agent mangafodipir trisodium (MnDPDP). The Mn released from MnDPDP is initially sequestered by the liver for first-pass elimination. which allows an enhanced contrast for diagnostic imaging. The administration of intravenous Mn impacts its homeostatic balance in the human body and can lead to toxicity. Human Mn deficiency has been reported in patients oil parenteral nutrition and in micronutrient studies. Mn toxicity has been reported through occupational (e.g. welder) and dietary overexposure and is evidenced primarily in the central nervous system, although lung. cardiac, liver. reproductive and fetal toxicity have been noted. Mn neurotoxicity results from all accumulation of the metal in brain tissue and results in a progressive disorder of the extrapyramidal system which is similar to Parkinson's disease. In order for Mn to distribute from blood into brain tissue, it must cross either the blood-brain barrier (BBB) or the blood-cerebrospinal fluid barrier (BCB). Brain import, with no evidence of export, would lead to brain Mn accumulation and neurotoxicity. The mechanism for the neuro-degenerative damage specific to select brain regions is not clearly understood. Disturbances in iron homeostasis and the valence state of Mn have been implicated as key factors in contributing to Mn toxicity. Chelation therapy with EDTA and supplementation with levodopa are the current treatment options, which are mildly and transiently efficacious. In conclusion. repeated administration of Mn Or

compounds that readily release Mn. may increase the risk of Mn-induced toxicity. Copyright (C) 2004 John Wiley Soils. Ltd.

16. Davis JM. (1998) Methylcyclopentadienyl manganese tricarbonyl: Health risk uncertainties and research directions. Environmental Health Perspectives 106:191-201.
With the way cleared for increased use of the fuel additive methylcyclopentadienyl manganese tricarbonyl (MMT) in the United States, the issue of possible public health impacts associated with this additive has gained greater attention. In assessing potential health risks of particulate Mn emitted from the combustion of MMT in gasoline, the U.S. Environmental Protection Agency not only considered the qualitative types of toxic effects associated with inhaled Mn, but conducted extensive exposure-response analyses using various statistical approaches and also estimated population exposure distributions of particulate Mn based on data from an exposure study conducted in California when MMT was used in leaded gasoline. Because of limitations in available data and the need to make several assumptions and extrapolations, the resulting risk characterization had inherent uncertainties that made it impossible to estimate health risks in a definitive or quantitative manner. To support an improved health risk characterization, further investigation is needed in the areas of health effects, emission characterization, and exposure analysis.

17. Davis JM. (1999) Inhalation health risks of manganese: An EPA perspective. Neurotoxicology 20(2-3):511-518.
In 1994, the U.S. Environmental Protection Agency (EPA) denied a petition by Ethyl Corporation to allow the use of methylcyclopentadienyl manganese tricarbonyl (MMT) in unleaded gasoline, because of health concerns related to the inhalation of manganese (Mn) particulate emissions from combusted MMT: Although Ethyl successfully challenged EPA's denial of the petition on legal grounds, issues raised in EPA's health risk assessment have not been resolved to date. This paper summarizes features of the EPA health risk characterization, which included the use of various statistical techniques to derive several estimates of inhalation reference concentration (RfC) values for Mn as alternatives to the established value of 0.05 mu g Mn/m(3). An exposure assessment projected distributions of personal exposure levels to particulate Mn if MMT were used in all unleaded gasoline. If was estimated that exposure levels of 5-10% of the modeled population might exceed a possible alternative RfC value of 0.1 mu g Mn/m(3). However, due to data limitations, the risk characterization for Mn/MMT could raise only qualitative concerns about potential public health impacts and was unable to provide a quantitative estimate of risk. To improve the risk characterization, better information on Mn/MMT population exposures and health effects is needed. Much of this information is expected to be obtained under provisions of Section 211 of the Clean Air Act. Among the specific issues that remain to be resolved are the form or forms of Mn emitted from the combustion of MMT in gasoline and the potentially different toxic properties of Mn in different forms. (C) 1999 Inter Press, Inc.

18. Davis JM, Dorman D. (1998) Health risk assessments of manganese - Differing perspectives: Session VIII summary and research needs. Neurotoxicology 19(3):488-489.

19. De Miguel E, Iribarren I, Chacon E, Ordonez A, Charlesworth S. (2007) Risk-based evaluation of the exposure of children to trace elements in playgrounds in Madrid (Spain). Chemosphere 66(3):505-513.
Eighty samples of sandy substrate were collected in November 2002 and 2003, from 20 municipal playgrounds in Madrid (Spain) to assess the potential adverse health effects of the exposure of children to trace elements in this material during their games. In each playground, two 500 g samples were collected, dried at 45 degrees C for 48 h, sieved below 100 mu m, acid digested and analyzed by ICP-MS. Doses contacted through ingestion and inhalation and the dose absorbed through the skin were calculated using USEPAs hourly exposure parameters for children and the results of an in situ survey. The toxicity values considered in this study were mostly taken from the US DoEs RAIS compilation. The results of the risk assessment indicate that the highest risk is associated with ingestion of soil particles and that the trace element of most concern is arsenic, the exposure to which results in a cancer risk value of 4.19 x 10(-6), close to the 1 x 10(-5) probability level deemed unacceptable by most regulatory agencies. Regarding non-cancer effects, exposure to playground substrate yields an aggregate Hazard Index of 0.28, below the threshold value of I (with As, again, as the largest single contributor, followed by Pb, Cr, Al and Mn). Although the uncertainties associated with the estimates of toxicity values and exposure factors should be reduced before any definite conclusions regarding potential health effects are drawn, risk assessment has proven to be a very useful tool to identify the contaminants and exposure pathways of most concern in urban environments. (c) 2006 Elsevier Ltd. All rights reserved.

20. Desoize B. (2003) Metals and metal compounds in carcinogenesis. In Vivo 17(6):529-539.
Several metals and metal containing compounds are potent mutagens and carcinogens. The most often blamed are chromium, arsenic, nickel, vanadium, iron, copper and manganese. Although each of them has its own mechanism of action, it is believed that most of their mechanisms of action involve reactive oxygen species (ROS). Furthermore, nickel modulates gene expression by induction of DNA methylation and/or suppression of histone acetylation. Arsenic activity on cell metabolism is multiple; it seems that cell transformation is induced by long-term exposure to a low level of arsenic. The paradox of arsenic is that it has also a valuable therapeutic efficacy in cancer treatment. Manganese is known to cause DNA damage, although it does not represent a significant carcinogenic risk. Magnesium deficiency and iron excess,are not exactly carcinogenetic, but certain concentrations of these metal ions are needed to prevent cancer.

21. Dobson AW, Erikson KM, Aschner M. (2004) Manganese neurotoxicity. Redox-Active Metals in Neurological Disorders. NEW YORK: NEW YORK ACAD SCIENCES. pp 115-128.
Manganese is an essential trace element and it is required for many ubiquitous enzymatic reactions. While manganese deficiency rarely occurs in humans, manganese toxicity is known to occur in certain occupational settings through inhalation of manganese-containing dust. The brain is particularly susceptible to this excess manganese, and accumulation there can cause a neurodegenerative disorder known as manganism. Characteristics of this disease are described as Parkinson-like symptoms. The similarities between the two disorders can be partially explained by the fact that the basal ganglia accumulate most of the excess manganese compared with other brain regions in manganism, and dysfunction in the basal ganglia is also the etiology of Parkinson's disease. It has been proposed that populations already at heightened risk for neurodegeneration may also be more susceptible to manganese neurotoxicity, which highlights

the importance of investigating the human health effects of using the controversial compound, methylcyclopentadienyl manganese tricarbonyl (MMT), in gasoline to increase octane. The mechanisms by which increased manganese levels can cause neuronal dysfunction and death are yet to be elucidated. However, oxidative stress generated through mitochondrial perturbation may be a key event in the demise of the affected central nervous system cells. Our studies with primary astrocyte cultures have revealed that they are a critical component in the battery of defenses against manganese-induced neurotoxicity. Additionally, evidence for the role of oxidative stress in the progression of manganism is reviewed here.

22. Egyed M, Wood GC. (1996) Risk assessment for combustion products of the gasoline additive MMT in Canada. Science of the Total Environment 190:11-20.
Methylcyclopentadienyl manganese tricarbonyl (MMT) has been used as an octane enhancer in Canadian gasoline since 1976. The main potential health concern is from manganese oxides produced on combustion (mainly Mn3O4), given the known neurotoxicity of chronic inhalation of manganese (Mn) dust from mining and industrial use. Relevant epidemiological studies of occupational exposure to respirable Mn are briefly reviewed; an ambient air reference value of 0.1 mu g Mn/m(3), and associated inhalation tolerable daily intake (TDI) and tolerable daily uptake (TDU) of 0.035 and 0.021 mu g/kg b.w./day are derived. Ambient levels of PM(2.5) (respirable) Mn in Canadian cities have remained unchanged or have decreased between 1986 and 1992, and do not reflect large changes in MMT usage during that time. Ambient levels of PM(10) Mn in Canadian cities in 1992 were less than or equal to 0.025 mu g Mn/m(3). Mean, 90th and 98th percentiles of PM(10) Mn inhalation uptake based on ambient monitoring data from high traffic areas and from estimates of personal exposure are below the inhalation uptake criterion. An assessment of exposure from air, food, water and soil revealed that <1% of total daily Mn uptake is derived from inhalation for all age groups. Therefore, based on current information, Mn derived from the combustion of MMT-containing gasoline is unlikely to represent a significant health risk to Canadians.

23. EPA. 2004. Drinking Water Health Advisory for Manganese. U.S. Environmental Protection Agency Office of Water. Report nr EPA-822-R-04-003.

24. Erikson KM, Aschner M. (2003) Manganese neurotoxicity and glutamate-GABA interaction. Neurochemistry International 43(4-5):475-480.
Brain extracellular concentrations of amino acids (e.g. aspartate, glutamate, taurine) and divalent metals (e.g. zinc, copper, manganese) are primarily regulated by astrocytes. Adequate glutamate homeostasis is essential for the normal functioning of the central nervous system (CNS). Glutamate is of central importance for nitrogen metabolism and, along with aspartate, is the primary mediator of the excitatory pathways in the brain. Similarly, the maintenance of proper manganese levels is important for normal brain functioning. Several in vivo and in vitro studies have linked increased manganese concentrations with alterations in the content and metabolism of neurotransmitters, namely dopamine, gamma-antinobutyric acid, and glutamate. It has been reported by our laboratory and others, that cultured rat primary astrocytes exposed to manganese displayed decreased glutamate uptake, thereby increasing the excitotoxic potential of glutamate. Furthermore, decreased uptake of glutamate has been associated with decreased gene expression of glutamate:aspartate transporter (GLAST) in manganese-exposed astroctyes. Additional studies have suggested that attenuation of astrocytic glutamate uptake by manganese may be a

consequence of reactive oxygen species (ROS) generation. Collectively, these data suggest that excitotoxicity may occur due to manganese-induced altered glutamate metabolism, representing a proximate mechanism for manganese-induced neurotoxicity. (C) 2003 Elsevier Science Ltd. All rights reserved.

25. Erikson KM, Syversen T, Aschner JL, Aschner M. (2005) Interactions between excessive manganese exposures and dietary iron-deficiency in neurodegeneration. Environmental Toxicology and Pharmacology 19(3):415-421.
For nearly a century, manganese has been recognized as an essential nutrient for proper bone formation, lipid, amino acid and carbohydrate metabolism. While manganese deficiency is characterized by symptoms ranging from stunted growth and poor bone remodeling to ataxia, it is manganese toxicity that is far more devastating from a public health standpoint. Most cases of manganese toxicity are the result of occupational exposure to high levels of the metal, and are characterized by specific neurological symptoms referred to as manganism. While manganism shares many common features with Parkinson's disease, there are distinct differences between the two disorders suggesting that manganism might indirectly affect nigrostriatal dopaminergic function. Recent studies from our laboratory show that dietary iron deficiency is a risk factor for brain manganese accumulation and that the striatum is particularly vulnerable. This review briefly discusses manganese from nutritional and toxicological aspects. © 2005 Elsevier B.V. All rights reserved.

26. Erikson KM, Syversen T, Soldin OP, Wu Q, Aschner M. (2003) Iron deficiency-induced manganese accumulation in the developing rat brain is associated with increased DMT-1 protein levels. Drug Metabolism Reviews 35:96-96.

27. Erikson KM, Thompson K, Aschner J, Aschner M. (2007) Manganese neurotoxicity: A focus on the neonate. Pharmacology & Therapeutics 113(2):369-377.
Manganese (Mn) is an essential trace metal found in all tissues, and it is required for normal amino acid, lipid, protein, and carbohydrate metabolism. While Mn deficiency is extremely rare in humans, toxicity due to overexposure of Mn is more prevalent. The brain appears to be especially vulnerable. Mn neurotoxicity is most commonly associated with occupational exposure to aerosols or dusts that contain extremely high levels (> 1-5 mg Mn/m(3)) of Mn, consumption of contaminated well water, or parenteral nutrition therapy in patients with liver disease or immature hepatic functioning such as the neonate. This review will focus primarily on the neurotoxicity of Mn in the neonate. We will discuss putative transporters of the metal in the neonatal brain and then focus on the implications of high Mn exposure to the neonate focusing on typical exposure modes (e.g., dietary and parenteral). Although Mn exposure via parenteral nutrition is uncommon in adults, in premature infants, it is more prevalent, so this mode of exposure becomes salient in this population. We will briefly review some of the mechanisms of Mn neurotoxicity and conclude with a discussion of ripe areas for research in this underreported area of neurotoxicity. (c) 2006 Elsevier Inc. All rights reserved.

28. Finley JW. (2004) Does environmental exposure to manganese pose a health risk to healthy adults? Nutrition Reviews 62(4):148-153.
Manganese is an essential nutrient that also may be toxic at high concentrations. Subjects chronically exposed to manganese-laden dust in industrial settings develop neuropsychological

changes that resemble Parkinson's disease. Manganese has been proposed as an additive to gasoline (as a replacement for the catalytic properties of lead), which has generated increased research interest in the possible deleterious effects of environmental exposure to manganese. Low-level exposure to manganese has been implicated in neurologic changes, decreased learning ability in school-aged children, and increased propensity for violence in adults. However, a thorough review of the literature shows very weak cause-and-effect relationships that do not justify concern about environmental exposure to manganese for most of the North American population.

29. Finley JW, Davis CD. (1999) Manganese deficiency and toxicity: Are high or low dietary amounts of manganese cause for concern? Biofactors 10(1):15-24.
Manganese is an essential trace element that is required for the activity of several enzymes. Manganese is also quite toxic when ingested in large amounts, such as the inhalation of Mn-laden dust by miners. This review examines Mn intake by way of the food supply and poses the question: Is there reason to be concerned with Mn toxicity or deficiency in free-living populations in North America? Although much remains to be learned of the Functions of Mn, at present there are only a few vaguely described cases of Mn deficiency in the medical literature. Given the heterogeneity of the North American food supply, it is difficult to see the possibility of more than greatly isolated and unique instances of Mn deficiency. However, low Mn-dependent superoxide dismutase activity may be associated with cancer susceptibility, and deserves further study. There may be reasons, however, to be concerned about Mn toxicity under some very specialized conditions. Increasing numbers of young people are adopting a vegetarian lifestyle which may greatly increase Mn intake. Iron deficiency may increase Mn absorption and further increase the body-burden of Mn, especially in,vegetarians. Mn is eliminated primarily through the bile, and hepatic dysfunction could depress Mn excretion and further contribute to the body burden. Would such a combination of events predispose substantial numbers of people to chronic Mn toxicity? At present, there is no definite proof of this occurring, but given the state of knowledge at the present time, more studies with longer time-frames and more sensitive methods of analysis are needed.

30. Fitsanakis VA, Aschner M. (2005) The importance of glutamate, glycine, and gamma-aminobutyric acid transport and regulation in manganese, mercury and lead neurotoxicity. Toxicology and Applied Pharmacology 204(3):343-354.
Historically, amino acids were studied in the context of their importance in protein synthesis. In the 1950s, the focus of research shifted as amino acids were recognized as putative neurotransmitters. Today, many amino acids are considered important neurochemicals. Although many amino acids play a role in neurotransmission, glutamate (Glu), glycine (Gly), and gamma-aminobutyric acid (GABA) are among the more prevalent and better understood. Glu, the major excitatory neurotransmitter, and Gly and GABA, the major inhibitory neurotransmitters, in the central nervous system, are known to be tightly regulated. Prolonged exposure to environmental toxicants, such as manganese (Mn), mercury (Hg), or lead (Pb), however, can lead to dysregulation of these neurochemicals and subsequent neurotoxicity. While the ability of these metals to disrupt the regulation of Glu, Gly and GABA have been Studied, few articles have examined the collective role of these amino acids in the respective metal's mechanism of toxicity. For each of the neurotransmitters above, we will provide a brief synopsis of their regulatory function, including the importance of transport and re-uptake in maintaining their

optimal function. Additionally, the review will address the hypothesis that aberrant homeostasis of any of these amino acids, or a combination of the three, plays a role in the neurotoxicity of Mn, Hg, or pb. (c) 2004 Elsevier Inc. All rights reserved.

31. Fitsanakis VA, Au C, Erikson KM, Aschner M. (2006) The effects of manganese on glutamate, dopamine and gamma-aminobutyric acid regulation. Neurochemistry International 48(6-7):426-433.
Exposure to high levels of manganese (Mn) results in a neurological disorder, termed manganism, which shares a similar phenotype to Parkinson's disease due to the involvement of the basal ganglia circuitry in both. The initial symptoms of manganism are likely due to the involvement of the globus pallidus, a region rich gamma-aminobutyric acid (GABA) projections, while those of Parkinson's disease are related to the degeneration of the substantia nigra, a dopaminergic nucleus. Additionally, it is known that glutamate regulation is affected by increases in brain Mn levels. As Mn predominantly accumulates in the basal ganglia, it potentially could affect the regulation and interactions of all three neurotransmitters. This review will focus on the circuitry of these neurotransmitters within the basal ganglia and address potential sites for, as well as the temporal relationship, between Mn exposure and changes in the levels of these neurotransmitters. While most research has focused on perturbations in the dopaminergic system, there is evidence to support that early consequences of manganism, also include disturbances in GABA regulation as well as glutarnatergic-related excitotoxicity. Finally, we suggest that current research focus on the interdependence of these basal ganglial neurochemicals, with a greater emphasis on the GABAergic and glutamatergic systems. (C) 2006 Elsevier Ltd. All rights reserved.

32. Fitsanakis VA, Zhang N, Avison MJ, Gore JC, Aschner JL, Aschner M. (2006) The use of magnetic resonance imaging (MRI) in the study of manganese neurotoxicity. Neurotoxicology 27(5):798-806.
Manganese (Mn), an element found in many foods, is an important and essential nutrient for proper health and maintenance. It is toxic in high doses, however, and exposure to excessive levels can result in the onset of a neurological disorder similar to, but distinct from, Parkinson's disease. Historically, Mn neurotoxicity was most commonly associated with various occupations, such as Mn mining, welding and steel production. More recently, increases in both blood and brain Mn levels have been observed in persons with liver disease or those receiving prolonged parenteral nutrition. Additionally, rodent data suggest that iron deficiency and anemia may be risk factors for Mn neurotoxicity. Clinically, brain Mn accumulation can be monitored in vivo using non-invasive magnetic resonance imaging (MRI) due to the paramagnetic nature of this element. Indeed, MRI has been used in a variety of settings to evaluate the brain Mn deposition in various populations. This review focuses on the use of MRI technology in studies related specifically to Mn neurotoxicity. Thus, we will examine reports using MRI to confirm brain Mn accumulation in human populations, and conclude with data from non-human primate and rodent models of Mn neurotoxicity. (C) 2006 Elsevier Inc. All rights reserved.

33. Forbes A, Jawhari A. (1996) Manganese toxicity and parenteral nutrition. Lancet 347(9017):1774-1774.

34. FreelandGraves JH, Turnlund JR. (1996) Deliberations and evaluations of the approaches, endpoints and paradigms for manganese and molybdenum dietary recommendations. Journal of Nutrition 126(9):S2435-S2440.
The background of the current dietary recommendations for manganese and molybdenum are described. This article reviews how the previous and current estimated safe and adequate daily dietary intakes (ESADDI) were set, shortcomings in the methods used, concerns about the current recommendations, and brief summaries of new research reports. New approaches, endpoints and paradigms to use for the development of useful recommendations are given.

35. Friberg L, Nordberg GF, Vouk VB. (2007) Handbook of the Toxicology of Metals. 3rd ed., Elsevier Science Publishing Company; pp. 476.
Handbook of the Toxicology of Metals is the standard reference work for physicians, toxicologists and engineers in the field of environmental and occupational health. This new edition is a comprehensive review of the effects on biological systems from metallic elements and their compounds. An entirely new structure and illustrations represent the vast array of advancements made since the last edition. Special emphasis has been placed on the toxic effects in humans with chapters on the diagnosis, treatment and prevention of metal poisoning. This up-to-date reference provides easy access to a broad range of basic toxicological data and also gives a general introduction to the toxicology of metallic compounds.

36. Gassmann B. (2001) Dietary reference intakes, report 4: Trace elements. Ernahrungs-Umschau 48(4):148-+.
Part 2 deals with a set of reference values established for chromium, copper, iodine, iron, manganese, molybdenum, and zinc to replace Recommended Dietary Allowances (RDAs), Estimated Safe and Adequate Daily Dietary Intakes published in 1989. In addition, the evidence of beneficial and adverse effects of arsenic, boron, nickel, silicon, and vanadium has been analyzed. AU RDAs, Adequate Intakes (AIs), and Tolerable Upper Intake Levels (ULs] reported are summarized, commented and compared with the DACH reference values 2000. Many questions that were raised about requirements for and recommended intakes of trace elements were not answered fully because of inadequacies in the published database. Thus RDAs have only been set for copper, iodine, iron, molybdenum, and zinc. Far most of the trace elements, there is no direct information allowing to estimate the amounts required by children, adolescents, the elderly, and pregnant and lactating women. Because of the lack of data to estimate average requirements of adults, AIs have to be set for chromium and manganese based on representative dietary intake data from healthy individuals in the United States. in the case of arsenic, boron, nickel, silicon, and vanadium, there is evidence that they have a beneficial role in physiological processes in some species. In some cases measurable responses of human subjects to changes in dietary intake have been demonstrated. However, the available data are not sufficient to determine average requirements. Nor could data available about dietary intake be used to establish an AI. For boron, copper, iodine, iron, manganese, molybdenum, nickel, vanadium, and zinc ULs have been established. For arsenic, chromium, and silicon data were sparse for setting ULs, precluding reliable estimates of how much can be ingested safely. Although there are some differences in their reference values, the Institute pf Medicine and DACH Societies used similar models for establishing reference intakes of trace elements.

37. Grandjean P, Landrigan PJ. (2006) Developmental neurotoxicity of industrial chemicals. Lancet 368(9553):2167-2178.
Neurodevelopmental disorders such as autism, attention deficit disorder, mental retardation, and cerebral palsy are common, costly, and can cause lifelong disability. Their causes are mostly unknown. A few industrial chemicals (eg, lead, methylmercury, polychlorinated biphenyls [PCBs], arsenic, and toluene) are recognised causes of neurodevelopmental disorders and subclinical brain dysfunction. Exposure to these chemicals during early fetal development can cause brain injury at doses much lower than those affecting adult brain function. Recognition of these risks has led to evidence-based programmes of prevention, such as elimination of lead additives in petrol. Although these prevention campaigns are highly successful, most were initiated only after substantial delays. Another 200 chemicals are known to cause clinical neurotoxic effects in adults. Despite an absence of systematic testing, many additional chemicals have been shown to be neurotoxic in laboratory models. The toxic effects of such chemicals in the developing human brain are not known and they are not regulated to protect children. The two main impediments to prevention of neurodevelopmental deficits of chemical origin are the great gaps in testing chemicals for developmental neurotoxicity and the high level of proof required for regulation. New, precautionary approaches that recognise the unique vulnerability of the developing brain are needed for testing and control of chemicals.

38. Hazell AS. (2002) Astrocytes and manganese neurotoxicity. Neurochemistry International 41(4):271-277.
Increasing evidence suggests that astrocytes are the site of early dysfunction and damage in manganese neurotoxicity. Astrocytes accumulate manganese by a high affinity, high capacity, specific transport system. Chronic exposure to manganese leads to increased pallidal signal hyperintensities on T1-weighted magnetic resonance images and selective neuronal loss in basal ganglia structures together with characteristic astrocytic changes known as Alzheimer type II astrocytosis. Manganese is sequestered in mitochondria where it inhibits oxidative phosphorylation. Exposure of astrocytes to manganese results in important changes including (i) decreased uptake of glutamate; (ii) increased densities of binding sites for the "peripheral-type" benzodiazepine receptor (PTBR), a class of receptor localized to mitochondria of astrocytes and involved in oxidative metabolism, mitochondrial proliferation, and neurosteroid synthesis; (iii) increased gene expression and activity of the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH), known to be associated with apoptosis; (iv) increased uptake of L-arginine, a precursor of nitric oxide, together with increased expression of the inducible form of nitric oxide synthase (iNOS). Potential consequences of these alterations in astrocytic gene expression include failure of energy metabolism, production of reactive oxygen species (ROS), increased extracellular glutamate concentration and excitotoxicity which could play a key role in manganese-induced neuronal cell death as a direct result of impaired astrocytic-neuronal interactions.

39. Keen CL, Ensunsa JL, Clegg MS. (2000) Manganese metabolism in animals and humans including the toxicity of manganese. Metal Ions in Biological Systems, Vol 37. NEW YORK: MARCEL DEKKER. pp 89-121.

40. Keen CL, Ensunsa JL, Watson MH, Baly DL, Donovan SM, Monaco MH, Clegg MS. (1999) Nutritional aspects of manganese from experimental studies. Neurotoxicology 20(2-3):213-223.
In experimental animals, dietary manganese deficiency can result in numerous biochemical and structural abnormalities. Deficient animals can be characterized by impaired insulin production, alterations in lipoprotein metabolism, an impaired oxidant defense system, and perturbations in growth factor metabolism. if the deficiency occurs during early development there can be pronounced skeletal abnormalities and an irreversible ataxia. Several lines of evidence suggest that manganese deficiency may be a problem in some human populations. Manganese toxicity can also pose a significant health risk. In experimental animals, acute manganese toxicity can result in numerous biochemical pathologies. However, the above occurs typically when the manganese is given via injection; most animals show considerable resistance to dietary manganese toxicosis. Similarly, confirmed cases of manganese toxicity in humans are currently restricted to cases of exposure to high levels of airborne manganese, and to cases when manganese excretory pathways are compromised. (C) 1999 Inter Press, Inc.

41. Kim Y. (2006) Neuroimaging in manganism. Neurotoxicology 27(3):369-372.
Neuroimaging such as magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) have been used in the last decade for investigating the neurotoxicolgy of manganese (Mn). Increased signal intensities on a T1-weighted image may reflect increased Mn deposits (e.g., due to exposure to Mn) but not necessarily manganism. In a biologically based dose-response model, our recent results strongly suggest that signal intensities in T1-weighted MRI reflect a target site dose. However, the threshold of signal intensity associated with clinical symptoms of manganism remains lobe solved. Functional neuroimaging such as PET or SPECT examines the integrity of the nigrostriatal dopaminergic system, and thus is very important for the differential diagnosis of manganism. However, neuroimaging research should also aim at developing specific and sensitive parameters for manganism in Mn-exposed individuals. (c) 2005 Elsevier Inc. All rights reserved.

42. Lee JW. (2000) Manganese intoxication. Archives of Neurology 57(4):597-599.
Manganese plays an important role as a cofactor in many enzymatic reactions in humans but in excess amounts can cause irreversible nervous system damage.(1,2) Although manganism is a rare condition, it can be the cause of complex nervous system symptoms, especially in the setting of environmental exposure.(3,4) Specifically, manganese is a well-known cause of dystonic parkinsonism.(5) This article highlights several historical descriptions of the clinical manifestations, pathological changes, and attempted therapeutic intervention in manganese intoxication.

43. Lewis RJS. 2004. Sax's Dangerous Properties of Industrial Materials: Manganese 7439-96-5. Sax's Dangerous Properties of Industrial Materials John Wiley & Sons, Inc.

44. Liang Yx, Su Z, Wu Wa, Lu Bq, Fu Wz, Yang L, Gu Jy. (2003) New trends in the development of occupational exposure limits for airborne chemicals in China. Regulatory Toxicology and Pharmacology 38(2):112-123.

Occupational exposure limits (OELs) are well established in many countries, which serve occupational professionals as benchmarks of industrial hygiene practice at workplaces worldwide. Starting in the mid-1950s, the central government of...

45. McMillan DE. (1999) A brief history of the neurobehavioral toxicity of manganese: Some unanswered questions. Neurotoxicology 20(2-3):499-507.
It was observed by Couper in 1837 that manganese dust produces a neurological syndrome characterized by muscle weakness, tremor, bent posture, whispered speech and excess salivation. The similarity of these symptoms to those of Parkinson's disease were not recognized for many years. In addition to its Parkinson-like effects, manganese produces behavioral symptoms in humans including nervousness, hallucinations. memory loss, cognitive problems, bizarre behaviors and flight of ideas. Despite these signs and symptoms, there have been few systematic attempts to study the effects of manganese on behavior using animal models. The need to better understand the effects of manganese on behavior is becoming more important due to the potential of increased environmental exposure to manganese due to its use, or proposed use as a gasoline additive in a number of countries. However, there is debate as to which manganese compounds should receive priority for testing, what route of administration should be used in this testing, what dosing regimens should be used, what species are appropriate for behavioral testing, and what behavioral tests should be selected. Research to answer these questions is needed so that the behavioral effects of manganese can be described comprehensively and the mechanisms underlying these effects can be understood. (C) 1999 Inter Press, Inc.

46. Mergler D, Baldwin M. (1997) Early manifestations of manganese neurotoxicity in humans: An update. Environmental Research 73(1-2):92-100.
BIOSIS COPYRIGHT: BIOL ABS. It is possible to detect early signs of neurotoxic dysfunction associated with occupational and environmental exposure to manganese; neurophysiologic and neurobehavioral tests can be used in the absence of clinical manifestations. Although outcomes from individual studies vary, they collectively show a pattern of slowing motor functions, increased tremor, reduced response speed, enhanced olfactory sense, possible memory and intellectual deficits, and mood changes. This overall portrait is consistent with the action of manganese on the central nervous system. In reports to date, there is little consistency in dose-effect relationships between internal parameters of manganese exposure (blood manganese, urinary manganese, hair manganese) and external measures and neurologic outcomes. Several studies suggest the existence of dose-effect relationships, but additional clarification is needed.

47. Misselwitz B, Muhler A, Weinmann HJ. (1995) A Toxicologic Risk for Using Manganese Complexes - a Literature Survey of Existing Data through Several Medical Specialties. Investigative Radiology 30(10):611-620.
This article summarizes data from the literature about biologic functions, toxicity, and biokinetics of manganese to help the reader assess the importance of complex stability of manganese-based contrast agents. Free manganese may present a greater risk than free gadolinium, especially because it has a physiologic role and can therefore trigger multiple functions, Of particular interest are the deleterious effects of manganese on the central nervous system (it can cross the intact blood-brain barrier) and on developing life (it penetrates the placental barrier as well and is teratogenic), After intravenous contrast injection, normal (enteral) regulation mechanisms for manganese homeostasis are bypassed, and there is a danger of

individual overdosing, Excess manganese, for example in patients with chronic liver disease or with chronic parenteral nutrition, has already been detected by magnetic resonance imaging in the basal ganglia and was found to coincide with neurologic symptoms. Decomplexation with release of free manganese substantially prolongs the elimination of the metal because manganese can be excreted only slowly via the biliary system, This may be of particular importance in patients with impaired hepatic function. Although minimal amounts of free manganese ions are not considered harmful to the human body, significant decomplexation of manganese complexes will require careful analysis of the diagnostic benefit versus the potential risk posed by the free metal ions.

48. Montgomery EB. (1995) Heavy-Metals and the Etiology of Parkinsons-Disease and Other Movement-Disorders. Toxicology 97(1-3):3-9.
Heavy metals, such as iron and manganese, are involved in neurologic disease. Most often these diseases are associated with abnormal environmental exposures or abnormal accumulations of heavy metals in the body. There is increasing recognition that heavy metals normally present in the body also may play a role in disease pathogenesis through free radical formation. When a part of the brain known as the basal ganglia is affected, movements become disordered. Parkinson's disease is one of the most common movement disorders and is related to destruction of neurons in the substantia nigra pars compacta (SNpc) of the basal ganglia. The combination of high concentration of iron and the neurotransmitter, dopamine, may contribute to the selective vulnerability of the SNpc. Dopamine can auto-oxidize to produce free radicals particularly in the presence of iron and other heavy metals.

49. Neu E, Gebefuegi I, Graw J, Jaekl G, Magour S, Michailov MC, Seidenbusch W, Weiss DG, Welscher U. (2001) Complex pathophysiological and genotoxic effects of radiation, heavy metals (Cd, Hg, Mn, Pb, Pu, U), and other toxicants. Toxicology 164(1-3):72-72.

50. NIOSH. 2007. Pocket Guide to Chemical Hazards: Manganese compounds and fume (as Mn) In: NIOSH, editor. NIOSH Pocket Guide: NIOSH.
NIOSH REL*: TWA 1 mg/m3 ST 3 mg/m3 [*Note: Also see specific listings for Manganese cyclopentadienyl tricarbonyl, Methyl cyclopentadienyl manganese tricarbonyl, and Manganese tetroxide.

51. OEHHA. 2001. Prioritization of Toxic Air Contaminants - Children’s Environmental Health Protection Act for Manganese & Compounds California Environmental Protection Agency (Cal/EPA). 1-8 p.

52. Ostiguy C, Asselin P, Malo S. (2006) The emergence of manganese-related health problems in Quebec: An integrated approach to evaluation, diagnosis, management and control. Neurotoxicology 27(3):350-356.
This paper describes the strategy developed in Quebec to deal with an emerging problem: manganism in welders. Only two cases of manganism had been reported to the Commission de la sante et de la securite du travail (CSST, Workers Compensation Board in Quebec) before 2000. In the fall of 200 1, the CSST was informed of a possible cluster of manganism and received 20 compensation claims from one plant. Action was rapidly taken to understand and tackle this emerging problem. Under the leadership of the CSST, a coordinating working group

implemented medical and environmental subcommittees involving representatives of the different partners of the prevention network. After a literature review to document the health risks associated with manganese and the lack of some important information, a panel of international experts was formed to try to reach agreement on the parameters to consider in the diagnosis and management of manganism. The CSST compensation management policies would be adjusted accordingly. Simultaneously, all the available industrial hygiene data were analyzed to estimate where and at what levels workers were exposed to manganese. To complete these data, the exposure of workers in more than 50 industrial plants was evaluated and existing control measures were documented. All these data have been presented for a revision of the Quebec permissible exposure limit (PEL). In this integrated approach, the next step targets the formation of neurologists and neuropsychologists for a standardized medical evaluation, to complete workplace evaluation in the high risk sectors, inform workers and employers and recommend control measures where required, based on a revised PEL. Many strategies will be used to inform the prevention network (about 1000 people), employers and employees of the risks of overexposure to manganese and of the measures to control exposure in all the plants where workers are susceptible to be exposed to manganese.

53. Park RM, Bowler RM, Eggerth DE, Diamond E, Spencer KJ, Smith D, Gwiazda R. (2006) Issues in neurological risk assessment for occupational exposures: The Bay Bridge welders. Neurotoxicology 27(3):373-384.

The goal of occupational risk assessment is often to estimate excess lifetime risk for some disabling or fatal health outcome in relation to a fixed workplace exposure lasting a working lifetime. For sub-chronic or sub-clinical health effects measured as continuous variables, the benchmark dose method can be applied, but poses issues in defining impairment and in specifying acceptable levels of excess risk. Such risks may also exhibit a dose-rate effect and partial reversibility such that effects depend on how the dose is distributed over time. Neurological deficits as measured by a variety of increasingly sensitive neurobehavioral tests represent one such outcome, and the development of a parkinsonian syndrome among welders exposed to manganese fume presents a specific instance. Welders employed in the construction of piers for a new San Francisco-Oakland Bay Bridge in San Francisco were previously evaluated using a broad spectrum of tests. Results for four of those tests (Rey-Osterrieth Complex Figure Test, Working Memory Index, Stroop Color Word Test and Auditory Consonant Trigrams Test) were used in the benchmark dose procedure. Across the four outcomes analyzed, benchmark dose estimates were generally within a factor of 2.0, and decreased as the percentile of normal performance defining impairment increased. Estimated excess prevalence of impairment, defined as performance below the 5th percentile of normal, after 2 years of exposure at the current California standard (0.2 mg/m(3), 8 h TWA), ranged 15-32% for the outcomes studied. Because these exposures occurred over a 1-2-year period, generalization to lifetime excess risk requires further consideration of the form of the exposure response and whether short-term responses can be generalized to equivalent 45-year period. These results indicate unacceptable risks at the current OSHA PEL for manganese (5.0 mg/m(3) 15 min) and likely at the Cal OSHA PEL as well.

54. Pfeifer GD, Roper JM, Dorman D, Lynam DR. (2004) Health and environmental testing of manganese exhaust products from use of methylcyclopentadienyl manganese tricarbonyl in gasoline. Science of the Total Environment 334-35:397-408.
This paper reviews recent research on the environmental effects of methylcyclopentadienyl manganese tricarbonyl (MMT), personal exposures to airborne Mn as a result of MMT use, chemical characterization of the manganese particulates emitted from the tailpipe and progress in developing a Physiologically based Pharmacokinetic (PBPK) model for manganese in rodents. Recent studies show that manganese is emitted as a mixture of compounds with an average valence of about 2.2. The major products are sulfate, phosphate, and smaller amounts of oxides. Because only small amounts of Mn are used in gasoline (< 18 mg Mn/gal) and less than 15% of the combusted Mn is emitted, soil along busy roads is not elevated in Mn, even after long-term use of MMT. A very large population-based study of manganese exposures in the general population in Toronto, where MMT has been used continuously for over 20 years, showed that manganese exposures were quite low, the median annual exposure was 0.008 mug Mn/m(3). A great amount of toxicological research on Mn has been carried out during the past few years that provides data for use in developing a PBPK model in rodents. These data add greatly to the existing body of knowledge regarding the relationship between Mn exposure and tissue disposition. When complete, the PBPK model will contribute to our better understanding of the essential neurotoxic dynamics of Mn. (C) 2004 Elsevier B.V. All rights reserved.

55. Powers KM, Smith-Weller T, Franklin GM, Longstreth WT, Swanson PD, Checkoway H. (2003) Parkinson's disease risks associated with dietary iron, manganese, and other nutrient intakes. Neurology 60(11):1761-1766.
Background: Dietary influences on oxidative stress have been thought to play important role in the etiology of PD. Objective: To examine associations of PD with dietary nutrients, including minerals, vitamins, and fats. Methods: A population-based case-control study was conducted among newly diagnosed case (n = 250) and control subjects (n = 388) identified between 1992 and 2002 from enrollees of the Group Health Cooperative health maintenance organization in western Washington state. Controls were frequency matched to cases on sex and age. In-person interviews elicited data on food frequency habits during most of adult life. Nutrient intakes were calculated and analyzed by adjusting each person's nutrient intake by their total energy intake (the nutrient density technique). Results: Subjects with an iron intake in the highest quartile compared with those in the lowest quartile had an increased risk of PD (odds ratio = 1.7, 95% CI: 1.0, 2.7, trend p = 0.016). There was an apparent joint effect of iron and manganese; dietary intake above median levels of both together conferred a nearly doubled risk compared with lower intakes of each nutrient (odds ratio = 1.9, 95% CI: 1.2, 2.9). No strong associations were found for either antioxidants or fats. Conclusion: A high intake of iron, especially in combination with high manganese intake, may be related to risk for PD.

56. Sayre LM, Perry G, Atwood CS, Smith MA. (2000) The role of metals in neurodegenerative diseases. Cellular and Molecular Biology 46(4):731-741.
There is increasing evidence in a number of neurodegenerative diseases that transition metal-mediated abnormalities play a crucial role in disease pathogenesis. In this treatise, we review the role of metal homeostasis as it pertains to alterations in brain function in neurodegenerative diseases. In fact, while there is documented evidence for alterations in transition metal homeostasis, redox-activity and localization, it is also important to realize that alterations in

specific copper- and iron-containing metalloenzymes also appear to play a crucial role in the neurodegenerative process.

57. Solomons NW, Ruz M. (1998) Trace element requirements in humans: An update. Journal of Trace Elements in Experimental Medicine 11(2-3):177-195.
Concepts about nutrient intake requirements and recommendations have emerged from a period of relative consensus about concepts and goals to one of vertiginous shifts of paradigms and a proliferation of agendas, often competing, for making nutrient and dietary recommendations in public policy. The recommendations for intakes of those trace elements considered to be essential in human nutrition are updated in the context of the ferment and controversy regarding how to establish a recommended intake. It is our contention that making universal recommendations for the intake of trace elements to cover all societies among the diverse geographic and ecological settings of the world is a futile effort. Differences in ethnicity, body size, traditional diets, genetics, and environmental stressors condition distinct needs at distinct locations. It is speculated that lower than "usual" body stores of certain trace elements may be adaptive, i.e., to improve human survival under certain adverse and challenging environmental conditions. Additionally, gaps in our knowledge regarding the bases for nutrient recommendations in the very old and the impact of new, engineered foods and dietary guidelines for intake regimes that prevent chronic diseases need to be filled. As trace elements are inorganic and can accumulate in tissues, recommendations for usual intakes confront the issue of the upper limits of tolerance and potential toxic consequences. Iron, copper, and manganese are among the trace elements for which this consideration is ever latent. The community of scientists involved in trace element biology must follow closely the chaotic situation regarding changing paradigms and agendas of oral intake recommendations, participate in the discussions when called upon, but continue to produce new findings. J. Trace Elem. Exp. Med. 11:177-195, 1998. (C) 1998 Wiley-Liss,Inc.

58. Sunderman FW. (2001) Review: Nasal toxicity, carcinogenicity, and olfactory uptake of metals. Annals of Clinical and Laboratory Science 31(1):3-24.
Occupational exposures to inhalation of certain metal dusts or aerosols can cause loss of olfactory acuity, atrophy of the nasal mucosa, mucosal ulcers, perforated nasal septum, or sinonasal cancer. Anosmia and hyposmia have been observed in workers exposed to Ni- or Cd-containing dusts in alkaline battery factories, nickel refineries, and cadmium industries. Ulcers of the nasal mucosa and perforated nasal septum have been reported in workers exposed to Cr(VI) in chromate production and chrome plating, or to As(III) in arsenic smelters. Atrophy of the olfactory epithelium has been observed in rodents following inhalation of NiSO4 or alpha Ni3S2. Cancers of the nose and nasal sinuses have been reported in workers exposed to Ni compounds in nickel refining, cutlery factories, and alkaline battery manufacture, or to Cr(VI) in chromate production and chrome plating. III animals, several metals (eg, Al, Cd, Co, Hg, Mn, Ni, Zn) have been shown to pass via olfactory receptor neurons from the nasal lumen through the cribriform plate to the olfactory bulb. Some metals (eg. Mn, Ni, Zn) can cross synapses in the olfactory bulb and migrate via secondary olfactory neurons to distant nuclei of the brain. After nasal instillation of a metal-containing solution, transport of the metal via olfactory axons can occur rapidly within hours or a few days (eg, Mn), or slowly other days or weeks (eg, Ni). The olfactory bulb tends to accumulate certain metals (eg, Al, Bi, Cu, Mn, Zn) with greater avidity than other regions of the brain. The molecular mechanisms responsible for metal translocation in

olfactory neurons and deposition in the olfactory bulb are unclear, but complexation by metal-binding molecules such as carnosine (beta -alanyl-L-histidine) may be involved.

59. Takeda A. (2004) Essential trace metals and brain function. Yakugaku Zasshi-Journal of the Pharmaceutical Society of Japan 124(9):577-585.
Trace metals such as zinc, manganese, and iron are necessary for the growth and function of the brain. The transport of trace metals into the brain is strictly regulated by the brain barrier system, i.e., the blood-brain and blood-cerebrospinal fluid barriers. Trace metals usually serve the function of metalloproteins in neurons and glial cells, while a portion of trace metals exists in the presynaptic vesicles and may be released with neurotransmitters into the synaptic cleft. Zinc and manganese influence the concentration of neurotransmitters in the synaptic cleft, probably via the action against neurotransmitter receptors and transporters and ion channels. Zinc may be an inhibitory neuromodulator of glutamate release in the hippocampus, while neuromodulation by manganese might mean functional and toxic aspects in the synapse. Dietary zinc deficiency affects zinc homeostasis in the brain, followed by an enhanced susceptibility to the excitotoxicity of glutamate in the hippocampus. Transferrin may be involved in the physiological transport of iron and manganese into the brain and their utilization there. It is reported that the brain transferrin concentration is decreased in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease and that brain iron metabolism is also altered. The homeostasis of trace metals in the brain is important for brain function and also for the prevention of brain diseases.

60. Taylor A. (1996) Detection and monitoring of disorders of essential trace elements. Annals of Clinical Biochemistry 33:486-510.

61. Tenorio FA, Ensunsa JL, Keen CL, Symons JD. (2002) Does manganese deficiency reduce arginase activity to an extent whereby vascular function is altered? Arteriosclerosis Thrombosis and Vascular Biology 22(5):A45-A45.

62. Tilson HA. (1996) Evolution and current status of neurotoxicity risk assessment. Drug Metabolism Reviews 28(1-2):121-139.

63. Verity MA. (1999) Manganese neurotoxicity: A mechanistic hypothesis. Neurotoxicology 20(2-3):489-497.
This review provides a summary of the presentations and abstracts presented at the 15(th) International Neurotoxicology Conference which may contribute to an understanding of the mechanism and pathogenesis of manganese (Mn2+) neurotoxicity. We propose that an understanding of the pathogenesis of Mn2+ neurotoxicity must incorporate data on (I) the factors controlling Mn2+ uptake and distribution within the CNS, (2) account for the apparent selectivity of dopaminergic neurons, (3) analyze the role of mitochondrial dysfunction and (4) provide da ta to support or refute the role of oxidative injury in the genesis of toxicity. We propose a multifactor hypothesis coupling Mn2+ uptake with coincident transport of aluminum and iron. Selectivity of dopaminergic neurons is dependent upon interactions of Mn2+ with dopamine transport and the role of Mn2+ as a pro-oxidative toxicant in conjunction with changes in iron concentration. Within the synaptic milieu, Mn2+-mitochondrial interaction will influence mitochondrial - Ca2+ transport kinetics leading to defective mitochondrial function, decreased oxidative phosphorylation, decreased ATP and accumulation of reactive oxygen species. Under

the influence of excessive depolarization, energy failure will occur leading to secondary activation of an excitotoxic state. These conceptual ideas provide for mechanistic based hypotheses and testing and are likely to lead to rational therapeutic avenues directed against Mn2+ neurotoxicity. (C) 1999 Inter Press, Inc.

64. Weiss B. (1999) Manganese in the context of an integrated risk and decision process. Neurotoxicology 20(2-3):519-525.
Current approaches to risk assessment regard it as a process that should embody both health and ecological risks, soc-ietal values, and cost-benefit analysis, that should seek the views of affected parties, and that should examine available options more holistically than in the past. Even with a single agent, manganese, the process requires a greath breadth of information and keen attention to how all of its different components fit together. An evaluation of exposure variables alone needs to consider contributions from multiple media, their physical forms and path ways such as inhaled fumes and particles, and ingestion of water, food soil, and dust (especially by children). Endpoints need also to be broadened, especially to include susceptibility across the life cycle and the impact of low-level neurotoxicity on rate of aging. Finally, the pursuit of risk reduction options for manganese should be embedded in a process that clarifies all the consequences of a particular option, including the raising or lowering of other risks and the full economic consequences. (C) 1999 Inter Press, Inc.

65. WHO. 2000. Air Quality Guidelines for Europe. Report nr 91. 288 p.
The second edition of the guidelines that aim to provide a basis for protecting public health from adverse effects of air pollutants and to eliminate or reduce exposure to those pollutants that are known or likely to be hazardous to human health or wellbeing. New data and research are included.

66. Yokel RA. (2005) Selective Blood-Brain Barrier Transport Of Aluminum, Manganese, And Other Metals In Metal-Induced Neurodegeneration. Toxicol Sci 84(1-S):338-339.
Excessive concentrations of aluminum (Al), copper (Cu), iron (Fe), mercury (Hg), manganese (Mn), tin (Sn) and zinc (Zn) have been shown or hypothesized to contribute to one or more neurodegenerative diseases, including Alzheimer's disease (AD), Parkinson's disease (PD), Wilson's disease (WD) and Friedreich's ataxia. The uptake of metals into the brain is often mediated by selective carriers or transporters localized at the blood-brain barrier (BBB). Thus, the regulation of metal transport by the BBB is fundamental to subsequent metal-induced neurotoxicities. This presentation will first review the evidence supporting and refuting roles of Mn in PD and Al in AD, including disparities between Mn-induced Parkinsonism and idiopathic PD, epidemiological evidence of Al neurotoxicity, clinical studies of brain Al in AD patients, and biochemical effects produced by Al that mimic AD. It will then focus on the selective metal transporters at the BBB as a key factor in the potential for metals to produce neurotoxicity. The specific interaction of a unique chemical species (form) of a neurotoxic metal with a particular membrane transporter at the BBB serves as a good example of selective transport of metals by the BBB. The ability of the methyl-Hg-cysteine complex to mimic methionine and to serve as a substrate for an amino acid transporter illustrates this mechanism of brain metal entry. Another mechanism that may mediate brain entry of several metals is transferrin - receptor mediated endocytosis. This presentation will further discuss the role of similar mechanisms in Al and Mn brain influx and efflux. The evidence for carriermediated influx and efflux of Al across the BBB

will be presented, as will the evidence for carrier-mediated influx, but only diffusion-mediated efflux, of Mn. Our incomplete knowledge of the mechanisms mediating Al and Mn flux across the BBB will be contrasted to the understanding of the Cu transporter that plays a central role in WD and the paucity of data on BBB flux of Sn and Zn.

67. Yokel RA. (2006) Blood-brain barrier flux of aluminum, manganese, iron and other metals suspected to contribute to metal-induced neurodegeneration. Journal of Alzheimers Disease 10(2-3):223-253.
The etiology of many neurodegenerative diseases has been only partly attributed to acquired traits, suggesting environmental factors may also contribute. Metal dyshomeostasis causes or has been implicated in many neurodegenerative diseases. Metal flux across the blood-brain barrier (the primary route of brain metal uptake) and the choroid plexuses as well as sensory nerve metal uptake from the nasal cavity are reviewed. Transporters that have been described at the blood-brain barrier are listed to illustrate the extensive possibilities for moving substances into and out of the brain. The controversial role of aluminum in Alzheimer's disease, evidence suggesting brain aluminum uptake by transferrin-receptor mediated endocytosis and of aluminum citrate by system Xc(-) and an organic anion transporter, and results suggesting transporter-mediated aluminum brain efflux are reviewed. The ability of manganese to produce a parkinsonism-like syndrome, evidence suggesting manganese uptake by transferrin-and non-transferrin-dependent mechanisms which may include store-operated calcium channels, and the lack of transporter-mediated manganese brain efflux, are discussed. The evidence for transferrin-dependent and independent mechanisms of brain iron uptake is presented. The copper transporters, ATP7A and ATP7B, and their roles in Menkes and Wilson's diseases, are summarized. Brain zinc uptake is facilitated by L- and D-histidine, but a transporter, if involved, has not been identified. Brain lead uptake may involve a non-energy-dependent process, store-operated calcium channels, and/or an ATP-dependent calcium pump. Methyl mercury can form a complex with L-cysteine that mimics methionine, enabling its transport by the L system. The putative roles of zinc transporters, ZnT and Zip, in regulating brain zinc are discussed. Although brain uptake mechanisms for some metals have been identified, metal efflux from the brain has received little attention, preventing integration of all processes that contribute to brain metal concentrations.

68. Zatta P, Lucchini R, van Rensburg SJ, Taylor A. (2003) The role of metals in neurodegenerative processes: aluminum, manganese, and zinc. Brain Research Bulletin 62(1):15-28.
Until the last decade, little attention was given by the neuroscience community to the neurometabolism of metals. However, the neurobiology of heavy metals is now receiving growing interest, since it has been linked to major neurodegenerative diseases. In the present review some metals that could possibly be involved in neurodegeneration are discussed. Two of them, manganese and zinc, are essential metals while aluminum is non-essential. Aluminum has long been known as a neurotoxic agent. It is an etiopathogenic factor in diseases related to long-term dialysis treatment, and it has been controversially invoked as an aggravating factor or cofactor in Alzheimer's disease as well as in other neurodegenerative diseases. Manganese exposure can play an important role in causing Parkinsonian disturbances, possibly enhancing physiological aging of the brain in conjunction with genetic predisposition. An increased environmental burden of manganese may have deleterious effects on more sensitive subgroups of the population, with sub-threshold neurodegeneration in the basal ganglia, generating a pre-

Parkinsonian condition. In the case of zinc, there has as yet been no evidence that it is involved in the etiology of neurodegenerative diseases in humans. Zinc is redox-inactive and, as a result of efficient homeostatic control, does not accumulate in excess. However, adverse symptoms in humans are observed on inhalation of zinc fumes, or accidental ingestion of unusually large amounts of zinc. Also, high concentrations of zinc have been found to kill bacteria, viruses, and cultured cells. Some of the possible mechanisms for cell death are reviewed.

69. Zayed J. (2001) Use of MMT in Canadian gasoline: Health and environment issues. American Journal of Industrial Medicine 39(4):426-433.
Background Methylcyclopentadienyl manganese tricarbonyl (MMT) is an organic derivative of manganese (Mn) used in Canadian gasoline since 1976 as an antiknock agent and to improve octane rating. Combustion products of MMT are mainly a mixture of Mn phosphate and Mn sulfate. In 1997 the Canadian federal government adopted a law (C-29) which banned both the interprovincial trade and the importation for commercial purposes of manganese-based substances, including MMT: However the government reworded this law in July 1998 so that manganese-based fuel additives were not included in the restrictions, MMT is now approved for use in Argentina, Australia, Bulgaria, the United States, France, Russia, and conditionally in New Zealand. Nevertheless, these countries are nor using MMT intensively and they are waiting for strong evidence of the absence of effects on human health. Even after several years of use of MMT in Canada, many uncertainties remain. Methods Different methods were used in order to assess (1) environmental contamination and human exposure to the parental form of MMT (2) nitrogen oxides (NOx) and carbon monoxide (CO) emissions associated with the use of MMT and (3) qualitative and quantitative assessments of Mn emissions to the environment. Results The results provide timely information with regard to the impact of MMT on environmental/ecosystem Mn contamination in abiotic and biotic systems as well as on human exposure. Moreover results raise major concerns with regard to public health effects related to exposure to Mn. Conclusions Obviously, there is still an important lack of adequate toxicological information and further studies are needed to provide successful implementation of evidence-based risk assessment approaches.

70. Zheng W. (2001) Neurotoxicology of the brain barrier system: New implications. Journal of Toxicology-Clinical Toxicology 39(7):711-719.
The concept of a barrier system in the brain has existed for nearly a century. The barrier that separates the blood from the cerebral interstitial fluid is defined as the blood-brain barrier, while the one that discontinues the circulation between the blood and cerebrospinal fluid is named the blood-cerebrospinal fluid barrier. Evidence in the past decades suggests that brain barriers are subject to toxic insults from neurotoxic chemicals circulating in blood. The aging process and some disease states render barriers more vulnerable to insults arising inside and outside the barriers. The implication of brain barriers in certain neurodegenerative diseases is compelling, although the contribution of chemical-induced barrier dysfunction in the etiology, of any of these disorders remains poorly understood. This review examines what is currently, understood about brain barrier systems in central nervous system disorders by focusing on chemical-induced neurotoxicities including those associated with nitrobenzenes, N-methyl-D-aspartate, cyclosporin A, pyridostigmine bromide, aluminum, lead, manganese, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine, and 3-nitropropionic acid. Contemporary research questions arising from this

growing understanding show enormous promises for brain researchers, toxicologists, and clinicians.

71. Zheng W. (2001) Toxicology of choroid plexus: Special reference to metal-induced neurotoxicities. Microscopy Research and Technique 52(1):89-103.
The chemical stability in the brain underlies normal human thinking, learning, and behavior. Compelling evidence demonstrates a definite capacity of the choroid plexus in sequestering toxic heavy metal and metalloid ions. As the integrity of blood-brain and blood-CSF barriers, both structurally and functionally, is essential to brain chemical stability, the role of the choroid plexus in metal-induced neurotoxicities has become an important, yet under-investigated research area in neurotoxicology. Metals acting on the choroid plexus can be categorized into three major groups. A general choroid plexus toxicant can directly damage the choroid plexus structure such as mercury and cadmium. A selective choroid plexus toxicant may impair specific plexus regulatory pathways that are critical to brain development and function, rather than induce massive pathological alteration. The typical examples in this category include lead-induced alteration in transthyretin production and secretion as well as manganese interaction with iron in the choroid plexus. Furthermore, a sequestered choroid plexus toxicant, such as iron, silver, or gold, may be sequestered by the choroid plexus as an essential CNS defense mechanism. Our current knowledge on the toxicological aspect of choroid plexus research is still incomplete. Thus, the future research needs have been suggested to focus on the role of choroid plexus in early CNS development as affected by metal sequestration in this tissue, to explore how metal accumulation alters the capacity of the choroid plexus in regulation of certain essential elements involved in the etiology of neurodegenerative diseases, and to better understand the blood-CSF barrier as a defense mechanism in overall CNS function. (C) 2001 Wiley-Liss, Inc.

APPENDIX E:

KEY REFERENCES NOT OBTAINED IN PDF

KEY REFERENCES NOT OBTAINED IN PDF (83)

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