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Development of manganese (Mn) pharmacokinetic data under Section 211(b) of the Clean Air Act (CAA)

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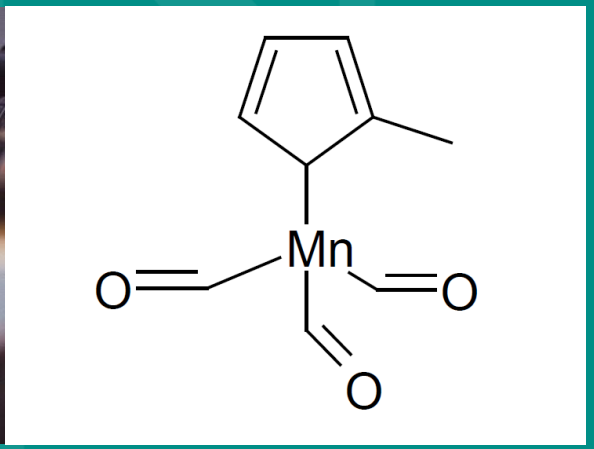

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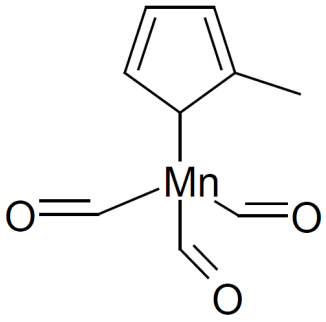
Manganese: an essential nutrient – a neurotoxicant

- Nutrient
  - Manganese is an essential nutrient
  - Abundant in many healthy foods
  - Component of
    - Superoxide dismutase
    - Glutamine synthetase

- Toxicant
  - Manganese is a neurotoxic metal
  - High prolonged inhalation exposure
    - Extrapyramidal motor system
    - Mn accumulates in striatum, globus pallidus, substantia nigra and other brain regions
    - Toxic to dopaminergic cells in pathways postsynaptic to the nigrostriatal system
    - Variety of mood and cognitive changes



MMT as a Motor Fuel Additive

- Methylcyclopentadienyl manganese tricarbonyl (MMT)
  - Trade name HiTec 3000
  - Orange liquid
  - Low vapor pressure
  - Missible in gasoline but not water soluble
  - Short environmental persistent due to UV degradation
- MMT is used to achieve desired octane rating if batch is slightly off specifications
- MMT allowable in US gasoline at maximum concentration of 0.03125 g Mn/gallon
- 10-15% Mn combusted is emitted from the vehicle, remainder apparently plated onto exhaust system

Methylcyclopentadienyl manganese tricarbonyl (MMT)

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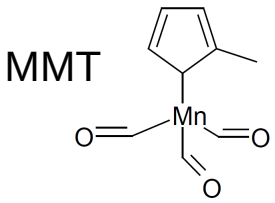
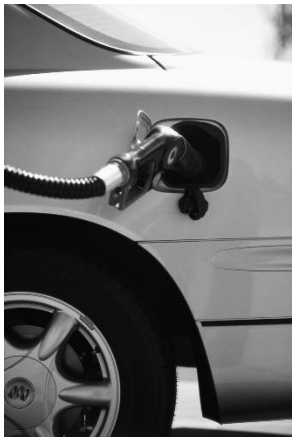
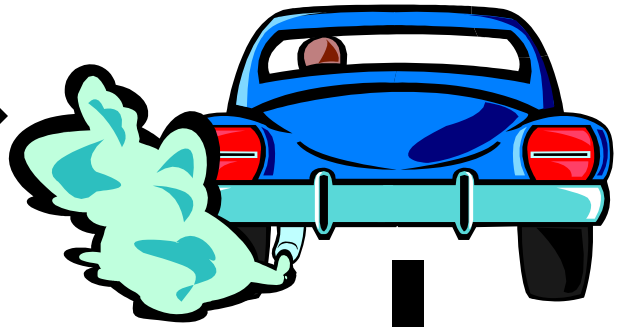
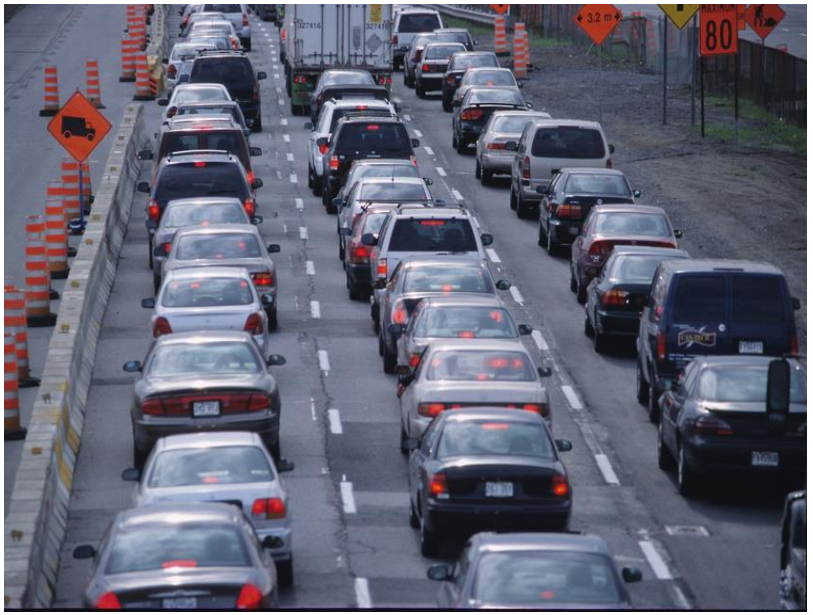






Mn combustion products



ala Dave Dorman

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Timeline

Years	Significant Actions
1970	EPA formed, Clean Air Act, Began phase out of lead from gasoline MMT introduced in unleaded gasoline
1977	MMT Registration cancelled
1977-1995	Multiple legal cases and petitions. MMT legally approved for use in US in 1995
1991	EPA Workshop on Mn Research Needs
1993	Mn RfC = 0.05 ug/m3
1994	Benchmark dose assessments 0.1-0.2 ug/m3 Health and Exposure Uncertainties overlap
1996-1998	Health testing negotiations and public comments
1999 - 2000	Alternative Tier 2 Test Rule proposed, and final
1998-2008	Multiple papers on Mn Health and bio-distribution
2007-2011	Multiple papers on Mn PK / PBPK models
2012	Final PBPK models published: Yoon et al 2012 and Shroeter et al., 2012 Reviews of the Tier II program published: Dorman et al., 2012; Taylor et al., 2012
2012-2016	Independent research based (in part) on 211(b) results

1993 U.S. EPA Inhalation Reference Concentration (RfC) for Mn (0.05 µg/m^3)

- Critical Study: (Roels et al., 1987; 1992)
  - Belgian battery factory workers exposed to manganese dioxide (MnO_2)
  - Neurobehavioral and motor impairments
  - Derived LOAEL for Mn = 0.15 mg/m^3
- Adjusted for continuous exposure duration LOAEL(adj) = 0.05 mg/m^3
- Total uncertainty factor applied (1000)
  - LOAEL instead of a NOAEL (10)
  - Extrapolation from subchronic to chronic exposure (10)
  - Protection of sensitive human subpopulations (10)
    - battery workers were healthy adult males
    - Limitations in the database
      - developmental and reproductive toxicity
      - forms of manganese (MnO_2, Mn_3O_4)
  - RfC = (0.05 mg/m^3 / 1000) = 0.00005 mg/m^3
    = 0.05 ug/m^3

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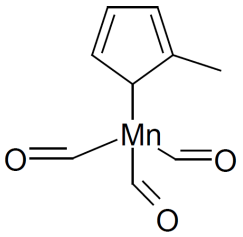
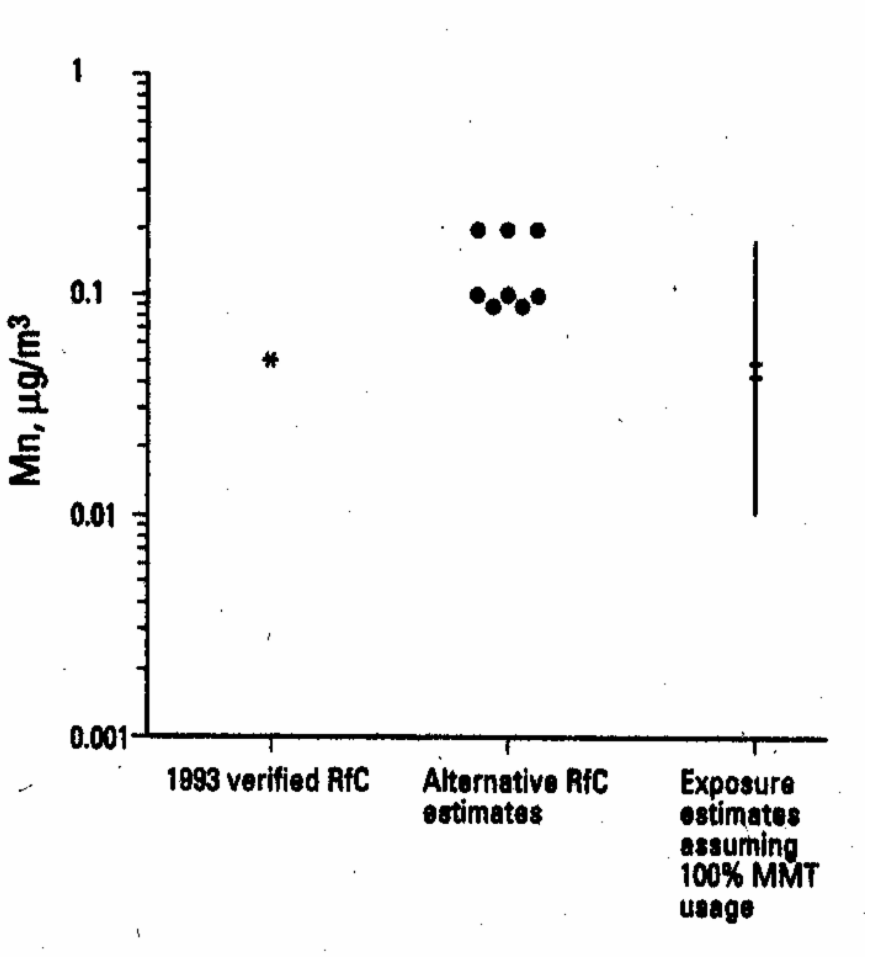
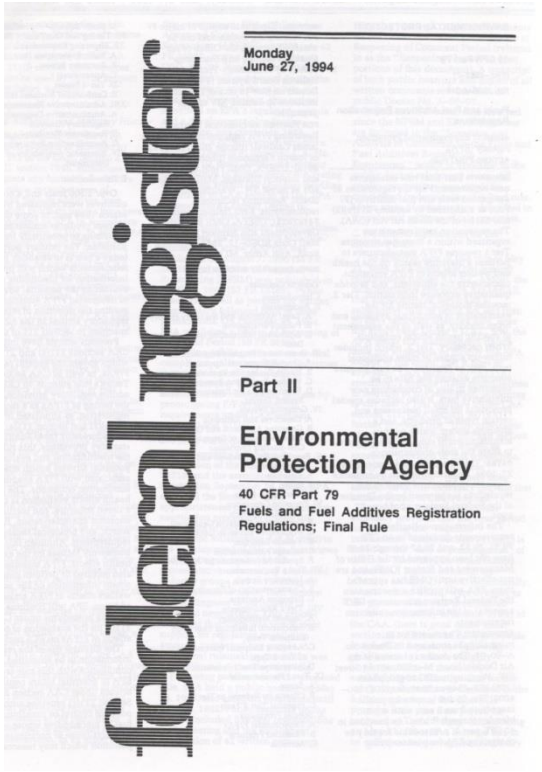


1994 EPA Assessment of MMT

- Risk characterization of potential use of MMT as a fuel additive
- Included
  - exposure assessment
  - dose-response relationships
- Derived “alternative” RfC’s
  - Benchmark dose approachs
  - Alternative dose-response models
  - Range ~0.1-0.2 ug/m^3
- The uncertainties of exposure and potential health outcomes overlapped
- EPA could not determine where there would be, or would not be a risk
- Stimulated both health and exposure research



CAA 211 (b)

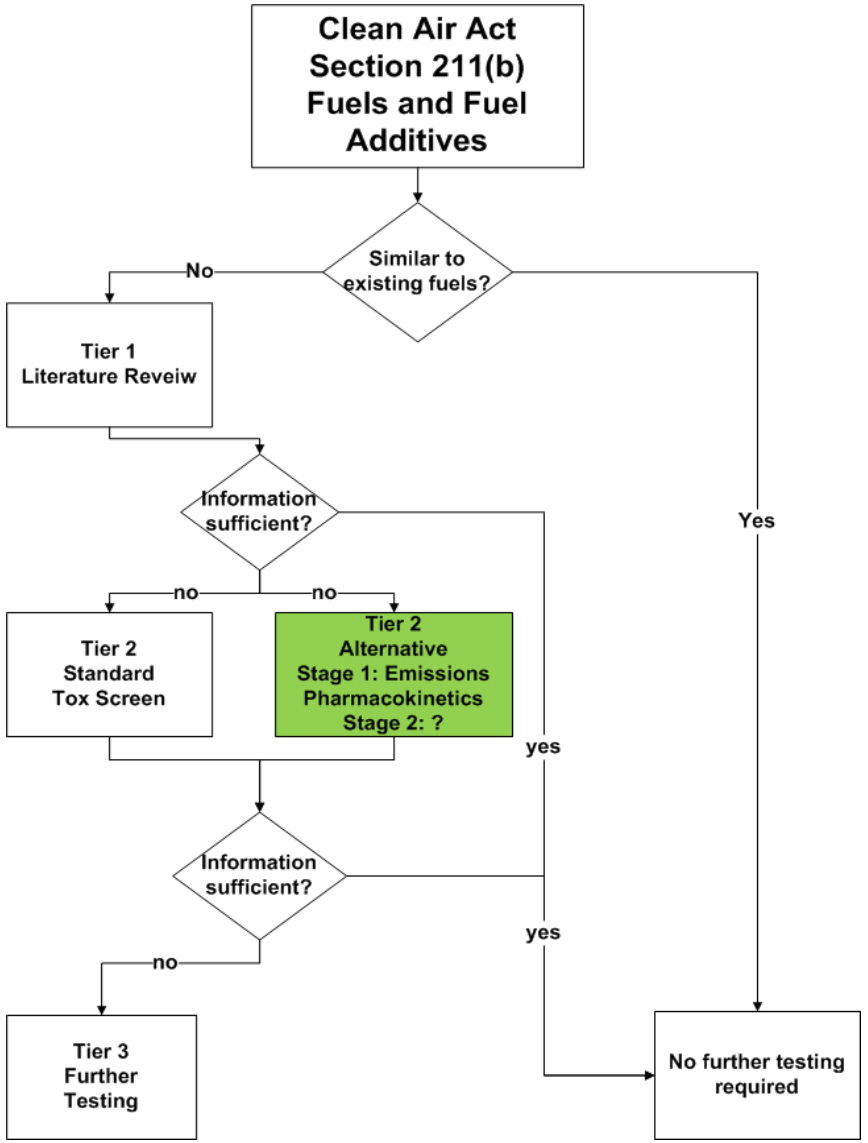

federal register

Monday
June 27, 1994

Part II

Environmental Protection Agency

40 CFR Part 79
Fuels and Fuel Additives Registration Regulations; Final Rule



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Components of the test rule

Epidemiological Basis	RA Uncertainty	211 (b) request
MnO_2	Combustion species	Emissions data PK data on combustion species
Adult males	Sensitive individuals	Old rats Adult males & females Prenatal & postnatal rats
8h/d, 5d/w, 5 y	24/7, lifetime	Dose rate and tissue Mn accumulation
Inhalation	Diet contribution	Oral v inhalation PK
Human	Rat v human data	Non-human primate

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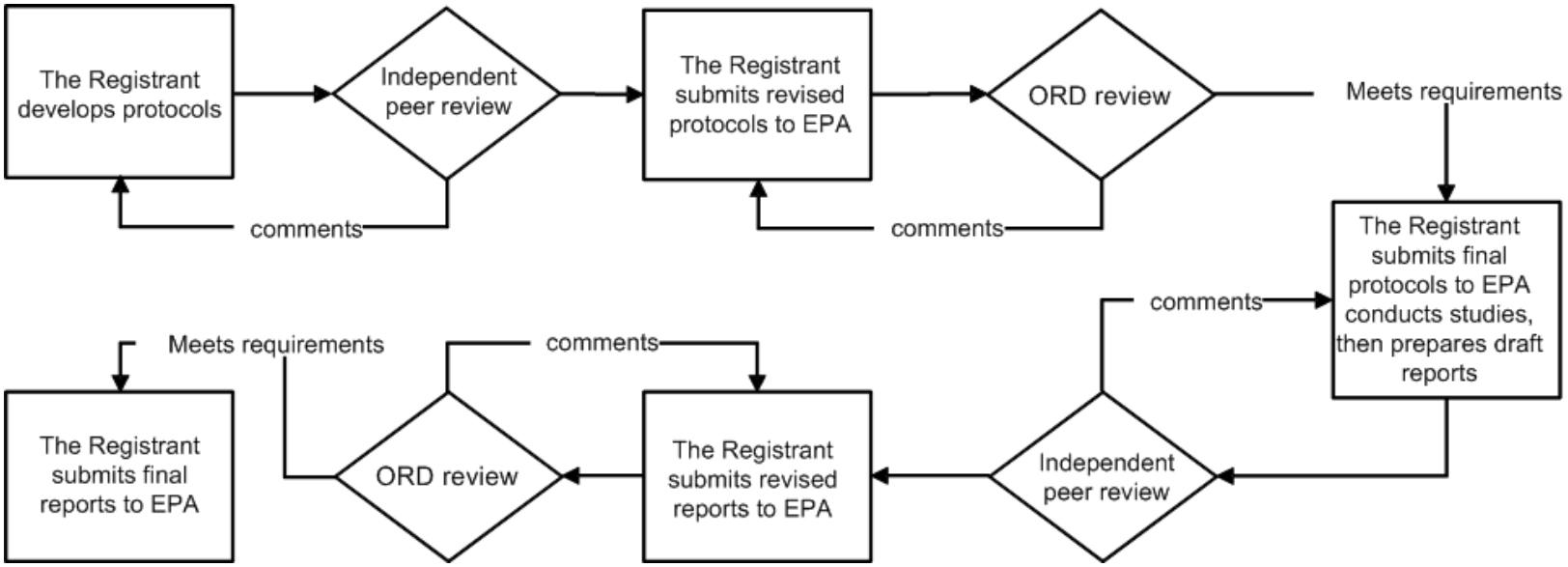
211(b) Alternative Tier 2 Review Process



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MMT Combustion Products

- What forms of Mn are emitted from engines running gasoline with MMT?
- Emissions in several forms of Mn
  - Mn phosphate
    - $Mn_5(PO_4)[PO_3(OH)]_2.4H_20$
    - predominant manganese species in the emission speciation testing
  - Trimanganese tetraoxide
    - Mn_3O_4
    - Previously thought to be the major emission species
  - Mn sulfate
    - $MnSO_4.H_2O$
    - The highest solubility and was chosen for the health testing.

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Selected Key Findings from 211(b) Research

Result	Reference
Soluble forms have highest uptake and distribution to brain	Vitarella et al 2000; Dorman et al., 2001
Nasal olfactory uptake into brain*	Brenneman et al., 2000
Dose-dependent uptake and clearance	Dorman et al., 2001
Susceptibility: old age and gender	Dorman et al., 2004
Dosimetry from gestation and lactation exposure	Dorman et al., 2005a; 2005b
Mn pharmacokinetics in non-human primates	Dorman et al., 2005, 2006

* in addition to 211(b) requirements

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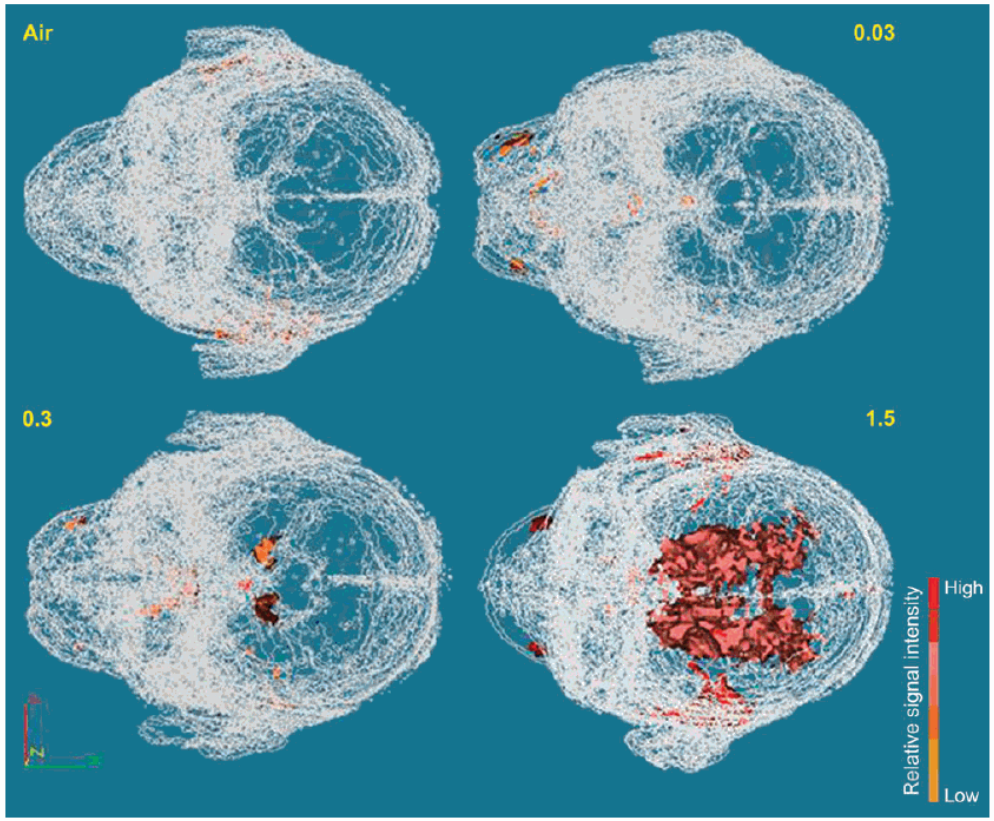
Mn pharmacokinetics in non-human primates

- Inhalation exposure to $MnSO_4$
- 0, 0.06, 0.3, 1.5 mg/m^3, 13 wks
- Brain MRI T1 relaxation time
- Brain region tissue Mn concentrations increased
  - Olfactory mucosa, bulb, cortex
  - Globus pallidus
  - Pituitary
  - Higher doses - more brain areas
- Linear correlation between tissue Mn concentration and MRI signal intensity



Dorman et al., 2005, 2006

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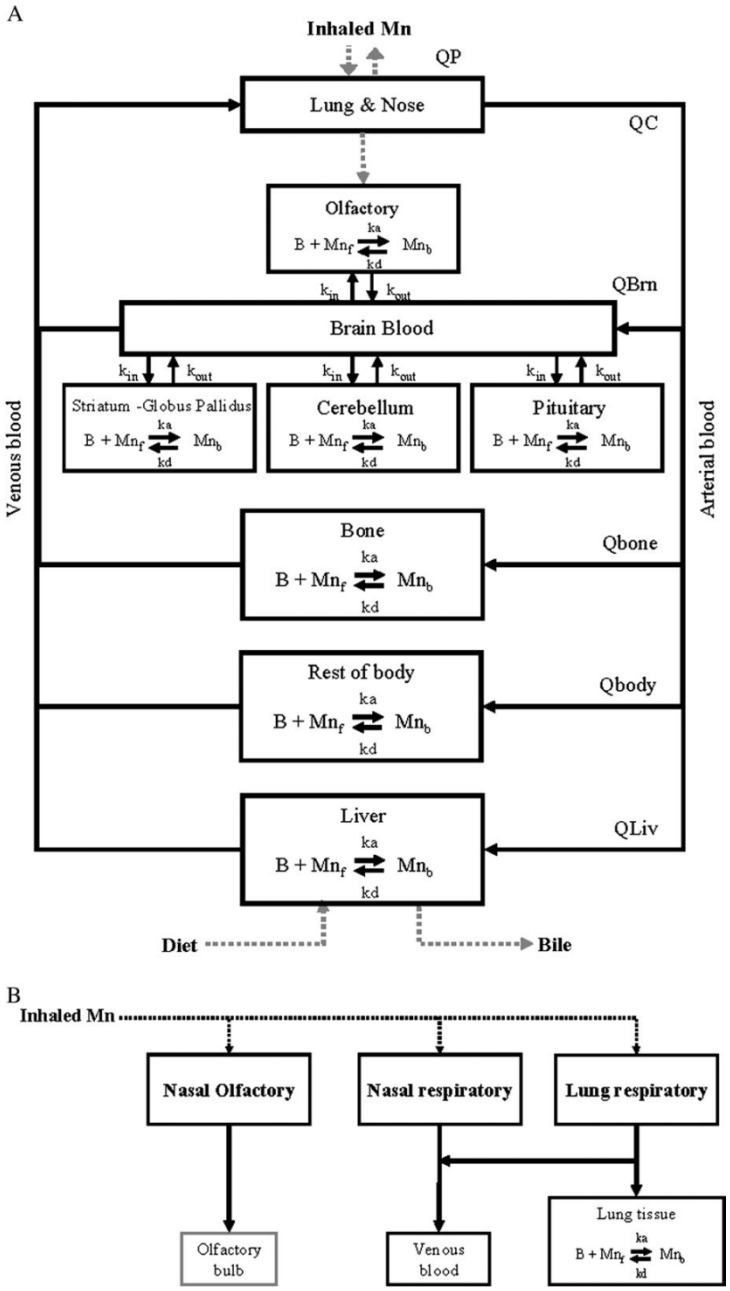
Physiologically-based pharmacokinetic (PBPK) models

- Schematic structure of the adult rat model (for example)
- Models developed
  - Adult rat
  - Pregnant rat and fetus
  - Lactating rat
  - Nonhuman primate
  - Human adult and fetus
- Inhaled and ingested Mn
- Olfactory and pulmonary uptake



Nong et al., 2009

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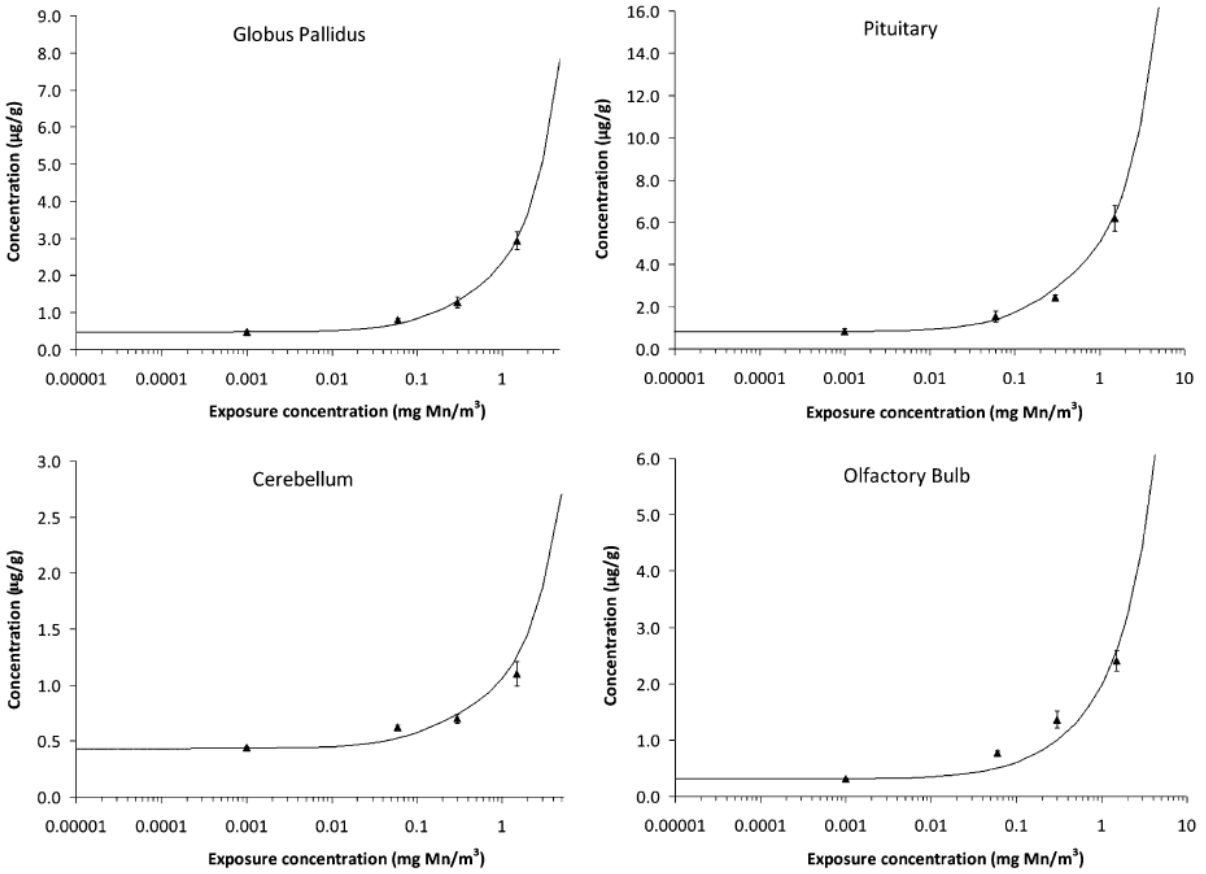
PBPK model of dose-dependent Mn accumulation in primate brain regions



Schroeter et al., 2012

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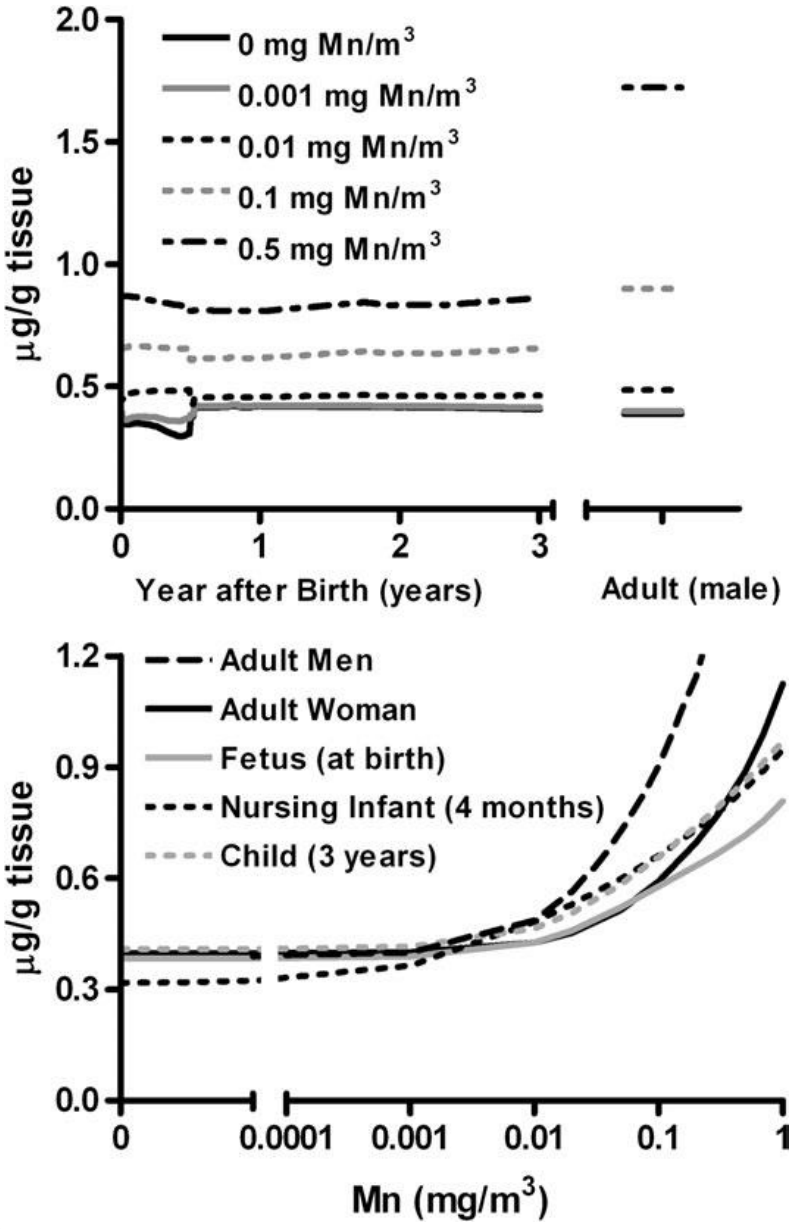
Estimated Mn concentration in human brain globus pallidus during postnatal development

Yoon et al., 2011



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Updates

- Mid 2000's, renewable fuel standards resulted in bio-ethanol in gasoline,
- MMT was not co-registered with ethanol, and therefore is not currently used in US automotive fuel
- Small piston engine aircraft require high octane fuel which currently contains tetraethyl lead
- MMT might be a substitute for lead in aviation fuels

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Conclusions

- Unique Program: 211(b) testing program represents an industry/government cooperation that has led to valuable data and models regarding Mn pharmacokinetics.

- Uncertainties: The data and models developed in this program help fill data gaps in existence at the time of derivation of the RfC, and may help address uncertainties in future assessments of Mn

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