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Manganese Testing under a Clean Air Act Test Rule and the Application of Resultant Data in Risk Assessments

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Abstract

In the 1990's, the proposed use of methylcyclopentadienyl manganese tricarbonyl (MMT) as an octane-enhancing gasoline fuel additive led to concerns for potential public health consequences from exposure to manganese (Mn) combustion products in automotive exhaust. After a series of regulatory / legal actions and negotiations, the U.S. Environmental Protection Agency (EPA) issued under Clean Air Act (CAA) section 211(b) an Alternative Tier 2 Test Rule that required development of scientific information intended to help resolve uncertainties in exposure or health risk estimates associated with MMT use. Among the uncertainties identified were: the chemical forms of Mn emitted in automotive exhaust; the relative toxicity of different Mn species; the potential for exposure among sensitive subpopulations including females, the young and elderly; differences in sensitivity between test species and humans; differences between inhalation and oral exposures; and the influence of dose rate and exposure duration on tissue accumulation of Mn. It was anticipated that development of specific sets of pharmacokinetic (PK) information and models regarding Mn could help resolve many of the identified uncertainties and serve as the best foundation for available data integration. The results of the test program included development of several unique Mn datasets, and a series of increasingly sophisticated Mn physiologically-based pharmacokinetic (PBPK) models. These data and models have helped address each of the uncertainties originally identified in the Test Rule. The output from these PBPK models were used by the Agency for Toxic Substances and Disease Registry (ATSDR) in 2012 to inform the selection of uncertainty factors for deriving the manganese Minimum Risk Level (MRL) for chronic exposure durations. The EPA used the MRL in the Agency's 2015 evaluation of potential residual risks of airborne manganese released from ferroalloys production plants. This resultant set

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of scientific data and models likely would not exist without the CAA section 211(b) test rule regulatory procedure.

Keywords

MMT; Ferroalloy; PBPK model; risk assessment; CAA 211(b); CAA112; reference concentration (RfC); manganese

1. Introduction

Manganese (Mn) is both an essential dietary nutrient and, depending on factors such as: dose; Mn speciation; bioavailability; route of exposure; and individual susceptibility, a neurotoxicant. Similar to other trace nutrients such as zinc or copper, manganese is required for normal metabolic functions and is an abundant component of a typical healthy diet. The recommended adult daily dietary intake values range from 2–5 mg/day (FDA 2017, NRC 1989), with 3–10 percent of ingested Mn being systemically absorbed from the gut and elimination largely from the bile into the feces. At high levels of exposure via ingestion or inhalation, homeostatic controls of blood and tissue concentrations are overcome and manganese accumulates in the brain and other tissues, with potentially toxic results. Excessive exposure is associated with manganese accumulation in the striatum, globus pallidus, substantia nigra and other brain regions, and dysfunction of the nigrostriatal pathway. Mn accumulation in the globus pallidus region of the brain, in particular, has been the focus of work to understand the relationships between exposure and target tissue accumulation of manganese. The resulting impairments from Mn accumulation in the globus pallidus, a component of the basal ganglia, and other brain regions include a variety of mood and cognitive changes, and marked extrapyramidal motor signs that resemble idiopathic Parkinson's disease, but are distinct in the pathophysiology and responsiveness to dopaminergic pharmacotherapies.

1.1. MMT as a fuel additive

Manganese has a variety of uses in industry and commerce including steel production, welding, and as a component of some fungicides. The EPA recognized a potential public health concern from more widespread exposure to manganese through the proposed use of methylcyclopentadienyl manganese tricarbonyl (MMT) as an octane-enhancing fuel additive. MMT had been used in gasoline and other fuels to enhance octane and improve anti-knock performance since the 1950s. The Clean Air Act (CAA) and its amendment in 1977 requires fuels and fuel additives to be registered with EPA. In the mid-1970s the removal of lead from automotive fuel, an oil embargo that caused fuel shortages in the US, and other factors led to a proposal by the Ethyl Corporation (currently known as Afton Chemical) to register MMT as a fuel additive for unleaded gasoline in the US. This proposal generated concerns among the general public and public health authorities regarding the introduction of what was viewed as another neurotoxic heavy metal to gasoline to replace the lead that was being phased out. A series of petitions and legal actions ensued, lasting for nearly two decades (Davis 1998a, Davis 1998b). Ultimately, the Ethyl Corporation won the legal right to market MMT in the US as a gasoline fuel additive, but with the provision that a

series of research studies be conducted under a CAA Section 211(b) Alternative Tier 2 Test Rule regarding the emissions and potential health implications of MMT (Davis 1998b, Davis 1999).

Currently, although MMT is still a registered gasoline fuel additive, its use is prohibited in US reformulated gasoline with ethanol and in the state of California. Given the wide use of ethanol (which is high octane) in the US due to the Renewable Fuels Standard (RFS) program, the US market for other octane boosters such as MMT is very limited. MMT is marketed as a gasoline fuel additive, however, in a number of countries outside of the US.

2. The EPA's Reference Concentration for Manganese

The proposed use of MMT in gasoline in the 1990s prompted EPA to evaluate the potential health risks of exposure to Mn using the best data and risk assessment methodologies that were then available. The EPA's Reference Concentration (RfC) for a substance is intended to represent an airborne concentration within an order of magnitude that would be without adverse health consequences if exposure occurred over a lifetime, and to be protective of sensitive members of the population. The RfC for Mn was based on data from an occupational study (Roels et al 1992) of male Belgian alkaline-battery plant workers exposed to dust containing manganese dioxide (MnO_2), and who showed impaired performance relative to a matched control group on a number of neuro-motor tasks reflecting aspects of fine motor control such as visual reaction time, eye-hand coordination and hand steadiness (Davis 1998a, U.S. EPA 1993). There was no evidence for carcinogenicity of Mn and it was not classifiable regarding cancer risk. The inhalation route of exposure was the primary pathway of concern for MMT combustion products in exhaust emissions, so the risk assessment focused on the RfC. The lowest observed adverse effect level (LOAEL) was derived from an occupational-lifetime integrated respirable dust (IRD) concentration of MnO_2 (based on 8-hour time weighted average occupational exposure multiplied by individual work histories in years) expressed as $\text{mg Mn/m}^3 \times \text{years}$. The IRD concentrations ranged from 0.040 to 4.433 $\text{mg Mn/m}^3 \times \text{years}$, with a geometric mean of 0.793 $\text{mg Mn/m}^3 \times \text{years}$ and a geometric standard deviation of 2.907. A LOAEL was obtained from the Roels et al (1992) study by dividing the geometric mean integrated "respirable dust" concentration (0.793 $\text{mg Mn/m}^3 \times \text{years}$) by the average period of worker exposure (5.3 years) to eliminate time (in years) from the time-weighted average, thereby yielding 0.15 mg Mn/m^3 . The "respirable dust" was defined as the median of 5 μm from personal samplers based on the Johannesburg's curve for the cohort. The geometric mean concentration was used to represent the average exposure because the workers' exposure measurements were approximately log-normally distributed, and the arithmetic mean exposure period was used because it was the only average value reported in the study (Davis 1998a). In addition to the use of a respirable fraction, a default dosimetric adjustment was applied to account for differences in the approximate volume of air breathed during an 8 hour/day work schedule (10 m^3), in relation to a member of the general population potentially breathing air containing Mn around the clock (20 m^3). A duration adjustment was also applied to account for the 5 day/week versus the 7 day/week exposure to the general population. The resulting point of departure for the RfC was 0.05 mg/m^3 ($0.15 \text{ mg Mn/m}^3 \times 10 \text{ m}^3 / 20 \text{ m}^3 \times 5 \text{ days} / 7 \text{ days}$).

On this value, uncertainty factors (UFs) were applied to reflect a lack of sufficient information regarding protection of sensitive members of the population (10x), using a LOAEL instead of a No Observable Adverse Effects Level (NOAEL) (10x), and a composite UF (10x) reflecting database inadequacy and subsuming extrapolation from subchronic to chronic exposure (including a concern for aged), inadequate data of potential sensitive outcomes such as developmental toxicity, and unknown differences in toxicity among different forms (speciation) of manganese. From the point of departure, therefore, after dividing by a composite UF of 1000, the RfC was established as $(0.05 \text{ mg/m}^3) / 1000 = 5 \times 10^{-5} \text{ mg/m}^3$.

2.1. Alternatives to the RfC and an MMT Exposure Assessment

The establishment of an RfC for Mn of $0.05 \text{ } \mu\text{g/m}^3$ (U.S. EPA 1993) was followed a year later with an exposure assessment for the use of MMT in gasoline (U.S. EPA 1994), which included a set of alternative derivations of the RfC using several dose-response models of the data from Roels et al (1992) to explore the response and its variability, as well as an estimate of the potential Mn exposure to the population. The alternative estimates of the RfC using benchmark dose and Bayesian models provided estimates ranging between approximately 0.09 and $0.2 \text{ } \mu\text{g/m}^3$ (Davis 1998b, Davis 1999, U.S. EPA 1994). The alternative derivations of the RfC, however, were never incorporated into an updated peer-reviewed risk assessment and the official RfC for Mn remains at $0.05 \text{ } \mu\text{g/m}^3$.

The EPA's 1994 exposure assessment, based on data from Riverside California in 1990 (where MMT was used in gasoline), contained several assumptions, including that MMT would be present at the maximum legal concentration of 0.031 g Mn/gallon in 100% of the automobile gasoline nationwide (Davis 1998b, Davis 1999). The Riverside study exposure estimate was only conducted in the spring season in one location, leading to uncertainties regarding other seasons of the year and how representative Riverside would be of other geographic locations. In addition, the assumption that MMT would be used at the full legal concentration in 100% of the gasoline was a "worst case" conservative assumption for exposure, which did not reflect the actual practice of MMT usage. In refineries MMT was typically used on an as-needed basis to bring specific batches of fuel up to the desired octane specifications, and would likely not have been used in 100% of fuel at the maximum allowable limit. The analysis of projected exposure concentrations indicated that approximately 5 – 10 % of the Riverside population could be exposed to Mn concentrations of $0.1 \text{ } \mu\text{g/m}^3$ or greater (Davis 1999). Because of the overlap of the projected exposures with the verified RfC or the alternative estimates of the RfC, it was unclear whether it would be reasonable to expect health risks to the general population associated with MMT use in gasoline. The results of this study further supported the need for the Section 211 (b) Test Rule. Additional information gaps, in particular regarding which chemical species of Mn were being emitted in automobile exhaust, also contributed to development of testing requirements.

2.2. Test Rule Structure and Requirements

The uncertainties associated with the operational derivation of the inhalation RfC for Mn and in the characterization of potential exposures for the 1994 MMT risk assessment led to a

series of negotiations between Afton Chemical Corporation (formerly known as the Ethyl Corporation), their contractors, and EPA legal and scientific staff which continued from approximately 1996 – 1998, and culminated in a test rule order under CAA 211(b) (U.S. EPA 2000). The uncertainties associated with the Mn RfC and the MMT risk assessment led directly into the testing required under the 211(b) Test Rule (Table 1).

At the time, considerable uncertainty existed about which forms (species) of manganese would be emitted in the exhaust following combustion in the engine. The best available evidence at the time suggested the primary emission species would be a manganese oxide (Mn_3O_4). The Belgian battery workers were exposed to MnO_2 dust. In Mn_3O_4 , Mn is present in both +2 and +3 valence states, whereas MnO_2 only contains Mn^{2+} . Data indicated that the chemical form and valence state of Mn were potential factors influencing both bioavailability and neurotoxicity, but definitive quantitative data were lacking. One component of the test rule therefore required the Ethyl Corporation (now Afton) to determine which chemical forms of manganese were emitted from tailpipes of engines burning gasoline containing MMT.

The Roels cohort of Belgian workers was comprised of adult males, but the concern regarding MMT use in gasoline encompassed the entire population including females, and ages other than working adults, notably the aged who may incur other neural deficits. Therefore, the test rule required data to be developed regarding the sensitivity of males and females, pre- and post-natal animals, and elderly animals.

The working population from the Roels study was exposed during a standard work week and was employed for an average of approximately 5.3 years. The population of concern for the RfC, however, was potentially exposed continuously for a lifetime. Accordingly, the Test Rule also required data to inform the influence of dose-rate and duration on the potential bioaccumulation of manganese in tissues of concern, including the brain. It was also recognized that manganese could be neurotoxic by inhalation exposure despite much larger doses of manganese present in normal diets, therefore data were required to be developed about the relative bioavailability and pharmacokinetics of manganese by both oral and inhalation routes of exposure.

Finally, there was uncertainty about the use of rats as a primary animal model for evaluating manganese neurotoxicity. A review of manganese neurotoxicity studies using rats, mice or guinea pigs failed to reveal a pattern of extrapyramidal motor impairment that was consistent with the Parkinsonian symptoms observed in highly exposed humans (Boyes & Miller 1998). Therefore, the Test Rule required that data be developed in non-human primates as well as rats.

The test requirements focused initially on development of pharmacokinetic data, in order to enable subsequent development of quantitative physiologically-based pharmacokinetic (PBPK) models and also to better inform the design of health outcome studies, should those be necessary. As a key component of the PBPK models, multi-path particle dosimetry (MPPD) models were relied upon to characterize particle size distribution and ventilation rate as critical input to the aerodynamics and deposition in the respiratory tract (<https://>

www.ara.com/products/multiple-path-particle-dosimetry-model-mppd-v-304). Subsequent to the test rule, there has been a large amount of data published regarding manganese pharmacokinetics and several physiologically-based pharmacokinetic (PBPK) models developed (detailed below), but further health outcome testing has not been required to date.

3. Test Rule Results

A thorough review of the 211(b) Test Rule and the research conducted in response to the rule is found elsewhere (Dorman et al 2012, Taylor et al 2012). As described above, the test rule required data to be generated on the identification of manganese chemical species in the exhaust of engines running MMT in gasoline, and pharmacokinetic data related to the issues identified above as uncertainties in the risk assessment.

The emissions research identified three major manganese containing groups of compounds in engine exhaust including: a complex manganese phosphate, a manganese sulfate (MnSO_4) and manganese oxides (most likely Mn_3O_4) (Pfeifer et al 2004). The relative prevalence of the three species varied depending on the engine operating conditions. A commercially available hureaulite (a manganese-phosphate mineral) was used for testing purposes to represent the Mn phosphate species, in addition to MnSO_4 and Mn_3O_4 . Early pharmacokinetic work demonstrated that MnSO_4 , which was the most water soluble of the species tested, generated the highest concentrations of manganese in the brain after inhalation exposure (Vitarella et al 2000). Therefore, MnSO_4 represented a “worst-case” scenario and was used as the primary test material for most of the subsequent experiments.

Pharmacokinetic data were developed in rats to address issues of particle solubility and dissolution kinetics, dose-dependent whole-body clearance, dietary interactions, olfactory transport of inhaled manganese particles, and susceptibility based on gender and age (Table 1). The later included prenatal, postnatal and senescent ages. In addition, non-human primates were used to assess species differences in inhalation dosimetry (e.g., inhalability and respiratory tract deposition), pharmacokinetics (i.e., absorption, distribution, metabolism and elimination), and were also subjected to brain imaging, respiratory tract pathology and brain neurochemistry (Dorman et al 2012).

There were a number of key findings from this body of work. The solubility of the form of manganese influenced the concentration of manganese achieved in the respiratory tract and brain as well as the clearance from those tissues. Manganese deposited into the nasal olfactory epithelium was taken up into the olfactory tract and transported into the brain, primarily residing in the olfactory bulbs, but not transported to any great extent to more distant brain regions (Vitarella et al 2000). Manganese exposure caused dose-dependent accumulation of manganese in the basal ganglia and other brain regions, the material apparently arriving via bloodborne transport of inhaled manganese. Manganese concentrations in tissues including blood and brain were under homeostatic control, which included dose-dependent reduction of manganese GI uptake and enhanced biliary excretion of manganese in the face of higher levels of exposure. Inducible excretion of manganese was also observed in neonatal rats. The research identified differences in the pharmacokinetics of rats and primates (Nong et al 2009), but those differences were apparently insufficient to

account for the inability to produce manganese dependent extrapyramidal system toxicity in rats. Overall, rats and humans were similar in their homeostatic controls in response to changes in manganese exposure.

4. PBPK Models Based on the Test Rule Data

As mentioned above, the pharmacokinetic data collected during the test rule was used to generate physiologically-based pharmacokinetic (PBPK) models describing manganese tissue kinetics (Taylor et al 2012). The models were developed in an iterative fashion with new generations of models incorporating added complexity as required to fit newly generated data with specific features (e.g., life stage such as pregnancy or lactation). Among the issues that challenged the model development were to account for dose-dependent changes in gastrointestinal uptake and biliary excretion (Teeguarden et al 2007b, Teeguarden et al 2007c), to describe manganese intake across oral and inhalation routes, to account for variations in the amount of manganese in the diet including manganese excess and deficient diets (Teeguarden et al 2007a), characterization of free and bound manganese in the circulation and tissues (Nong et al 2009), and to model different ages and life stages including senescence, pregnancy (Yoon et al 2009a), lactation (Yoon et al 2009b), and pre- and postnatal growth with age-specific maturation of homeostatic mechanisms (Yoon et al 2011). In addition, the models described Mn uptake and clearance rates for key brain compartments, saturable binding, and specific transporters (Yoon et al 2009b). Models were also developed to describe olfactory uptake into the brain (Nong et al 2009, Nong et al 2008). Significantly, models were ultimately developed to describe non-human primates (Nong et al 2009), adult humans (Schroeter et al 2011), and human pregnancy and lactation (Yoon et al 2011).

A critically important feature of this suite of inhalation PBPK models (Nong et al 2008, Schroeter et al 2011, Yoon et al 2009a, Yoon et al 2009b, Yoon et al 2011) is that they rely on the free-access multi-path particle dosimetry (MPPD) model as input to characterize the species-specific inhalation dosimetry to predict inhalability and deposited dose to various regions in the respiratory tract (<https://www.ara.com/products/multiple-path-particle-dosimetry-model-mppd-v-304>). The MPPD model explicitly accounts for differences in inhaled deposition, in different species, due to the particle size, distribution and density of different particle exposures. Additionally, because ventilation rate and breathing mode (e.g., nose or nasal-oral) vary with age and activity pattern (e.g., resting or exercise), the use of the MPPD model provides a means for characterizing variabilities due to various population attributes (e.g., occupational versus ambient activities and populations). Thus, this coupling of the MPPD model to the PBPK models allow risk assessment applications to consider the impact of particle size and solubility of different manganese exposures that may occur and provide a quantitative approach for appropriate adjustment.

Due to the tight homeostatic control, the models showed a substantial range of air concentrations over which brain Mn concentrations were maintained at a steady level, after which there was a tipping point where brain concentrations begin to increase. For adult humans, based on experimental evidence from animals exposed to MnSO₄ with a mass median aerodynamic diameter (MMAD) of 2.0 µm, this transition into brain Mn

accumulation occurred at air concentrations above approximately 0.01 mg/m³ (Schroeter et al 2011), and between approximately 0.001 and 0.01 mg/m³ for developmental exposures (Yoon et al 2011).

4.1 Recent uses of PBPK models

Others have used the PBPK and MPPD models developed in the 211(b) program to address other questions and support alternative approaches to Mn risk assessment. Gentry et al (2017) applied the MPPD-PBPK model for adult humans (Schroeter et al 2011) to estimate the target tissue Mn concentrations associated with neurobehavioral deficits in 14 studies of occupationally-exposed populations. Their analysis included assuming a dietary intake of 3 mg Mn/day, and used the MPPD model applied to studies with sufficient exposure data to account for particle deposition using a definition of an (MMAD) 10 µm as the “respirable” fraction. They used the MPPD-PBPK models to estimate the concentrations of Mn in globus pallidus associated with a lack of neurological deficits in each study, and determined concentration of approximately 0.8 µg/g as a target tissue concentration NOAEL. They estimated, again using the MPPD-PBPK model, that an airborne concentration of respirable dust of 150 µg/m³ continuous exposure would be required to produce a Mn concentration in the globus pallidus of about 1 µg/g. They then estimated the target tissue concentrations associated with exposure to typical ambient air concentrations of Mn, and a “margin of safety” was calculated between exposure levels associated with neurobehavioral deficits and ambient air concentrations.

An approach by Ramoju et al (2017) combined the use of MPPD-PBPK models of Schroeter et al (2011) with categorical regression analysis. The MPPD-PBPK models were used to estimate blood and brain globus pallidus tissue concentrations in occupational epidemiology studies. In this regard, the approach was similar to that of Gentry et al., except it was based on eight rather than 14 studies, and representative particle size distribution data for the different studies were based on personal cascade impactor measurements for similar workplaces (see Table 1). This analysis also differed in that significant adverse outcomes were converted to a binary categorical severity score for regression analysis. The PBPK model predictions were compared to blood Mn analysis in three of the studies, demonstrating that the model adequately predicted measured blood values and giving confidence to use of the model to predict Mn concentrations in the globus pallidus. Then, similar to Gentry et al., the model was used to predict globus pallidus Mn concentrations of about 0.4 µg/g in control populations who were unexposed from air, but consumed 3 mg Mn/day in their diet. The model simulations of workers exposed over an 8 h/d, 5 d/w work shift for 5 years, showed a 10% increased probability of an increased severity score adverse neurological outcomes occurred at globus pallidus Mn concentrations of 0.55 µg/g. This brain concentration value was associated with a workplace exposure concentration (8 h/d, 5 d/w) of about 70 µg/m³. Both Gentry et al. and Ramoju et al. demonstrate the usefulness of risk assessment approaches employing the PBPK models to identify critical target tissue concentrations as a point of departure. They differed in their set of occupational epidemiology studies considered, definitions of critical input parameters (e.g., particle size distribution), categorizations of adverse outcomes, exposure conditions modeled, and

determinations of the effect levels of concern. Neither study considered developmental exposures or other potentially susceptible members of the population.

5. Manganese Health Benchmark Evaluations Currently Available for Regulatory Decisions

There are several evaluations of the potential risk associated with exposure to manganese from well recognized authoritative organizations (e.g., government agencies) and deemed appropriate for use in regulatory decisions. Risk evaluations which have derived a quantitative estimate for acceptable exposure levels (reference values) for manganese have been reviewed previously (U.S. EPA 2012). This discussion will focus on the approaches taken to characterize uncertainty and variability, and in the derivation of three chronic reference values available from authoritative bodies: the Reference Concentration (RfC) developed by the EPA, which has been previously discussed; the Reference Exposure Level (REL) authored by the Office of Environmental and Health Hazard Assessment (OEHHA) of the California EPA; and the Minimal Risk Level (MRL) derived by the Agency for Toxic Substances and Disease Registry (ATSDR). Table 2 provides an abstracted summary from the more comprehensive comparison document developed by EPA (U.S. EPA 2012).

The RfC for manganese (U.S. EPA 1993) was derived based on a study of occupationally-exposed battery plant workers (Roels et al 1987, Roels et al 1992), as were the other two reference values described here. The RfC was derived using now-dated default approaches which included use of a LOAEL as reported in Roels et al (1987), Roels et al (1992); reliance on the study's definition of "respirable"; an adjustment for occupational ventilation and duration; and three UFs of 10 to account for potential variability between individuals, the use of a LOAEL instead of a NOAEL; and application of a database factor to account for "database limitations reflecting both the less-than-chronic periods of exposure and the lack of developmental data, as well as potential but unquantified differences in the toxicity of different forms of Mn" (U.S. EPA 1993).

The Office of Environmental and Health Hazard Assessment (OEHHA) of the state of California developed a chronic Reference Exposure Level (REL) for manganese (OEHHA 2008), again based on the work of Roels et al (1992) (Table 2). In deriving the chronic REL, OEHHA used the same dosimetric and duration adjustments as the EPA did in developing the RfC. OEHHA, however, used the results of a benchmark concentration analysis to derive a point of departure in contrast to the LOAEL used in the RfC. OEHHA calculated a 95% lower confidence limit for the benchmark concentration for a 5% extra risk change from controls (BMCL₀₅). Additionally, the choice of UFs for the REL were not the same as used in developing the RfC: the total UF of 300 included factors of 10 each for toxicokinetic differences across the human population due to concern of "greater absorption and lung deposition in children," and toxicodynamic differences due to "greater susceptibility of children to neurotoxicity"; and a factor of 3 to adjust for the use of a subchronic duration study (average worker exposures were for 5.3 years) in deriving a chronic duration value.

The ATSDR MRL is the most recently derived value of the three considered in this discussion (ATSDR 2012) and incorporated the lessons learned from the CAA 211(b) testing

research to the greatest extent. ATSDR used an algebraic adjustment from an 8-hr/day occupational work day to a 24-hr/day continuous exposure whereas EPA and OEHHA applied a more dosimetric approach by adjusting based on a ratio of the volume of air breathed during an occupational day to the average human daily breathing volume ($10 \text{ m}^3/20\text{m}^3$). Like OEHHA, ATSDR applied benchmark dose analysis but used a 10% extra risk change from controls (BMCL_{10}) as opposed to the BMCL_{05} used by OEHHA. ATSDR applied a cumulative UF of 100, with a UF of 10 to cover database uncertainties, (“lack of epidemiological data for humans chronically exposed to soluble forms of manganese and the concern that the general population may be exposed to more soluble forms of manganese than most of the manganese-exposed workers in the principal and supporting studies”), and another factor of 10 for interindividual human variability based on the possibility of “enhanced susceptibility of the elderly, infants, and children; individuals with chronic liver disease or parenteral nutrition; and females and individuals with iron deficiency.” Most notably, ATSDR revised their stance on applying an additional modifying factor of 5 from their prior MRL (ATSDR 2000) to account for the potential of differential kinetics in the young leading to increased susceptibility in children. The evidence cited as justification for this change in strategy (ATSDR 2012) was work which was performed as part of the CAA 211(b) testing program (Dorman 2000, Dorman et al 2005, Dorman et al 2004, Dorman et al 2000, Schroeter et al 2011, Yoon et al 2011).

It is important to note, however, that none of the existing inhalation reference values, including the ATSDR MRL, use the full potential of the PBPK models (Nong et al 2009, Nong et al 2008, Schroeter et al 2011, Yoon et al 2009a, Yoon et al 2009b, Yoon et al 2011) developed through the 211(b) test program. Recent publications (Gentry et al 2017; Ramoju et al 2017) illustrate the utility of the combined MPDD-PBPK model constructs to take into account many of the critical variables related to exposure to manganese compounds or susceptibilities of exposed individuals (chemical species, particle size distribution, life-stages, etc.).

6. EPA Ferroalloys Production Residual Risk Assessment

6.1. NESHAPS and Residual Risk

The RfC and other health benchmarks for Mn, although based on data originally envisioned to support evaluation of the fuel additive MMT, are applicable to other risk assessments. In addition to potentially being emitted from mobile sources, manganese can be emitted from stationary sources such as ferroalloys production facilities, iron and steel production facilities, and ore crushing and handling facilities. Under section 112 of the Clean Air Act, EPA is required to develop technology-based standards for hazardous air pollutants (HAP), including manganese, emitted by industrial source categories. Eight years after issuing the technology-based rules, EPA is required to review those standards for health and environmental risks that might remain (i.e., residual risks). The CAA requires EPA to revise the technology-based standards and set more stringent standards if necessary, to reduce emissions to protect public health or the environment.

6.2. The Ferroalloys Production Source Category

One of the industrial source categories evaluated, as described above, is the ferroalloys production source category. Ferroalloys are alloys of iron and another element such as nickel, chromium, manganese, or silicon. They are typically used in the production of iron and steel to give those products special characteristics (e.g., malleability). After manganese-containing ores are crushed to the appropriate size, ferroalloys are produced by smelting the ores in an electric arc furnace and then pouring the molten product into casting beds. The product is then crushed and sized for the buyer's needs. A more detailed description of the ferroalloys production process can be found in Chapter 12 of the EPA's AP-42: Compilation of Air Emission Factors (U.S. EPA 1986).

The production of ferroalloys containing manganese (e.g., ferromanganese, silicomanganese), at facilities that are major sources of HAP, are included in the ferroalloys production source category. Major sources of HAP are those stationary sources that emit or have the potential to emit 10 tons per year or more of a HAP or 25 tons per year or more of a combination of HAP. The initial technology-based standard for this category was issued in May 1999 (U.S. EPA 1999a). The rule established emission limits based on particulate matter emissions. Specific emission limits vary by product produced and type of furnace used. The rule also set limits on opacity from furnace buildings at the facility.

EPA completed the residual risk assessment for the ferroalloys production source category in June 2015. As part of the assessment, EPA used an air dispersion model to estimate ambient concentrations of manganese surrounding the facilities included in the source category. The maximum estimated annual average ambient air concentration modeled where people reside was 1.1 ug/m3 (U.S. EPA 2015b). Results of that assessment showed that the original technology-based standard needed revisions in order to protect public health. The health effects estimated from the magnitude of manganese emissions from ferroalloy production facilities were a primary factor in the decision to require revisions to the standard. Those revisions were promulgated in June 2015 (U.S. EPA 2015a) and included tightening of the particulate matter and opacity limits, as well as adding emissions standards for HAP that were not regulated in the initial MACT standard.

6.3. Hazard assessment of the Ferroalloys Production Source Category

EPA conducts residual risk analyses using the four-step risk assessment approach described in the 1983 National Academy of Science's publication "Risk Assessment in the Federal Government: Managing the Process" (NRC 1983). How these general steps are used specifically for residual risk can be found in EPA's "Residual Risk Report to Congress" (U.S. EPA 1999b). The four steps described in these documents are: hazard identification, dose-response assessment, exposure assessment, and risk characterization. For the hazard identification step of a residual risk assessment, EPA relies on the list of hazardous air pollutants in section 112 of the CAA to be those that have been identified as pollutants of concern. The list is then narrowed based on which HAP are emitted from facilities in the specific source category being evaluated. The exposure assessment and risk characterization steps conducted for residual risk assessments are specific to each source category evaluated.

The RTR program relies on available peer-reviewed dose-response assessments conducted by EPA or other authoritative bodies such as the ATSDR. The currently available dose-response assessments for manganese are described earlier in this manuscript. For residual risk assessments, including the assessment of the ferroalloys production source category, EPA uses the Office of Air Quality Planning and Standards' existing recommendations for HAP chronic dose-response values, which are found in "Table 1. Prioritized Chronic Dose-Response Values" (U.S. EPA 2014b). The values in this table have been prioritized from the several sources of dose-response information based on (1) conceptual consistency with EPA risk assessment guidelines and (2) level of peer review received (U.S. EPA 2014a). In general, for chronic non-carcinogenic exposures, the following sources are used in this order: U.S. EPA's IRIS; U.S. ATSDR MRLs; and the California Environmental Protection Agency (CalEPA) Reference Exposure Levels (RELs).

6.4. Rationale for using the MRL vs RfC

As shown in the prioritized table of dose-response values, EPA has selected to use the MRL from ATSDR as the chronic value for Mn and that value was used in the residual risk assessment in support of the (U.S. EPA 2014a)final 2015 ferroalloys rule (U.S. EPA 2015a). The existing IRIS RfC for Mn (U.S. EPA 1993) was used in the residual risk assessment in support of the 2011 ferroalloys proposal (76 FR 72508) (U.S. EPA 2011). In 2012, ATSDR published a MRL value for Mn based on their 2012 assessment of Mn toxicity (ATSDR 2012). The same study (Roels et al 1992) was the basis for both values. However, as described above, ATSDR used a benchmark dose approach, a newer method for dose-response modeling in their assessment, in addition to considering pharmacokinetic data and PBPK models (also described above). EPA relied on the ATSDR MRL value in the ferroalloys production residual risk assessment, which was in line with the recommendations made by the EPA Science Advisory Board (U.S. EPA 1998) and consistent with Agency policy. This rationale can also be found in the *Federal Register* notice for the final ferroalloys rule (79 FR 60247).

7. Conclusions

Under the CAA 211(b) a Test Rule was developed that, over several years, enabled the development of a set of data and PBPK models designed to address stated uncertainties regarding the potential risks of manganese exposure. The research conducted in response to the 211(b) Test Rule has influenced both scientific and regulatory decisions. Scientifically, in addition to characterization of the bioavailability for different species of Mn, among the significant results was an improved understanding of the homeostatic control of manganese tissue concentrations in blood and tissues, including the brain, related to the evolutionary role of manganese as an essential nutrient. The work revealed levels of manganese exposure in adults and developing individuals at which homeostatic controls were overcome and tissue concentrations began to increase above normal values. The homeostatic control mechanisms included dose-dependent reduction of gastrointestinal uptake, and increased biliary excretion, of manganese in response to higher levels of manganese exposure. Among other things, this illustrates why blood manganese concentrations are generally unresponsive

to low level changes in manganese exposure and make relatively poor biomarkers of exposure.

Another important lesson from these studies was that the dose rate was a primary determinant of when the homeostatic control mechanisms were overcome leading to brain manganese accumulation, and therefore the dose-rate was a more appropriate metric of exposure than was cumulative dose. This body of work also produced PBPK models of manganese exposure in adult and developing humans. These models enabled evaluation of potential tissue accumulation of manganese following different exposure rates or durations. The suite of available MPPD-PBPK models also allow assessment of different exposure (particle size, species) and physiological conditions that might alter susceptibility, such as ventilation patterns, deficient or excess manganese in the diet, and evaluation of potential susceptibility factors, such as age or gender.

In the regulatory arena, the pharmacokinetic data and models developed in the 211(b) program were influential in subsequent setting of ATSDR minimum dose-response levels for manganese. Prior to this work, a composite uncertainty factor for the RfC was set by EPA at 1000, among the highest margins for compounds with established IRIS values. After publication of this work, and considering the PBPK models, the ATSDR more recently set an uncertainty factor of 100 based on assessment of the same original data from Belgian battery workers. The establishment by ATSDR of the MRL for manganese was in turn used by EPA as a dose-response value in a subsequent determination of residual risk for exposures to emissions from ferroalloys production plants.

The 211(b) program was designed to address important topics of public health concern, which may not have been addressed otherwise, and is an example of successful cooperation between the EPA and industry. Even though the problem formulation was intended to address the proposed use of MMT in gasoline, the data and models developed later became significant considerations in addressing potential residual risks of emissions from ferroalloys production plants, an application not considered in the original program. The data and models may well see additional use in future assessments that are not currently being considered, and to answer questions we have not yet imagined.

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Table 1:

Components of the CAA 211(b) Alternative Tier 2 Test Rule and their basis in the US EPA 1993 RfC based on Roels (1992), and uncertainty factors or the MMT risk assessment (U.S. EPA, 1993; U.S. EPA, 1994)

Epidemiological Basis	RA Uncertainty	211 (b) Request	Result	Reference
MnO	Combustion emission species	Emissions data, PK data on combustion species	Mn sulfate, Mn Phosphate, Mn Oxides. Solubility determines uptake and distribution to brain.	Vitarella et al 2000; Dorman et al., 2001
Adult males	Sensitive individuals	Old rats Adult males & females Prenatal & postnatal rats	Data on susceptibility by old age and gender. Dosimetry from gestation and lactation exposure.	Dorman et al., 2004 Dorman et al., 2005a; 2005b
8h/d, 5d/w, 5 y	24/7, lifetime	Dose rate and tissue Mn accumulation	Dose-dependent uptake and clearance.	Dorman et al., 2001
Inhalation	Diet contribution	Oral v inhalation PK	Inhalation exposure with excess or deficient diets.	Dorman et al., 2002
Human	Rat v human data	Non-human primate	Mn PK in non-human primates.	Dorman et al., 2005, 2006

Table 2.

Comparisons of the derivation processes used in deriving the RfC, REL, and MRL chronic reference values.

Agency	Principal Study; Critical Effect; and POD ¹	UFs ²	Toxicity Value
U.S. EPA 1993	Roels et al., 1992	1000	$5 \times 10^{-5} \text{ mg/m}^3$
	Impairment of neurobehavioral function resulting from occupational exposure to manganese oxide	UF _H = 10 UF _L = 10 UF _D = 10	
	LOAEL(HEC) = $0.15 \text{ mg/m}^3 \times (5/7) \times (10/20)$ = 0.05 mg/m^3		
OEHHA, 2008	Roels et al., 1992	300	$9 \times 10^{-5} \text{ mg/m}^3$
	Impaired neurobehavior: visual reaction time, eye-hand coordination, hand steadiness	UF _{H-k} = 10 UF _{H-d} = 10 UF _S = 3	
	BMCL ₀₅ (HEC) = $0.026 \text{ mg/m}^3 \times (5/7) \times (10/20)$ = 0.033 mg/m^3		
ATSDR 2012	Roels et al., 1992	100	$3 \times 10^{-4} \text{ mg/m}^3$
	Incidence of workers with abnormal scores on an eye-hand coordination test	UF _H = 10 UF _D = 10	
	BMCL ₁₀ (HEC) = $0.142 \text{ mg/m}^3 \times (5/7) \times (8/24)$ = 0.033 mg/m^3		
ATSDR 2000	Roels et al., 1992	500	$4 \times 10^{-5} \text{ mg/m}^3$
	Incidence of workers with abnormal scores on an eye-hand coordination test	UF _H = 10 UF _D = 10 MF = 5	
	BMCL ₁₀ (HEC) = $0.074 \text{ mg/m}^3 \times (5/7) \times (8/24)$ = 0.017 mg/m^3		

¹Point of Departure (POD)²Uncertainty Factor (UF) component definitions: UF_H – inter-human variability; UF_A – animal to human variability; UF_L – LOAEL to NOAEL adjustment; UFS – subchronic to chronic adjustment; UF_{DB} – database uncertainty; MF – Modifying Factor