

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

TO: File for Manganese and Manganese Compounds (CAS No. 7439-96-5)

FROM: Robert Sills, Toxics Unit Supervisor, Toxics Unit, Air Quality Division

DATE: May 12, 2014

SUBJECT: Updated ITSL for manganese and manganese compounds

Summary

The ITSL for *manganese and manganese compounds* is being revised to 0.3 µg/m³ with an annual averaging time (AT), consistent with the ATSDR (2012) chronic inhalation Minimal Risk Level (MRL). Previously, the manganese ITSL was 0.05 µg/m³ (annual AT), consistent with the United States Environmental Protection Agency (EPA) (1993) Reference Concentration (RfC).

Manganese in air emissions and manganese in the ambient air predominantly occur in particulate matter. This ITSL is most appropriately applied to the level of manganese in particulate matter in the respirable size range (i.e., PM₁₀-Mn) rather than in total suspended particulate (TSP-Mn) or PM_{2.5}-Mn, based on the method of measuring exposure levels and characterizing the dose-response relationship in the key study (Roels et al., 1992). The preferential use of the PM₁₀-Mn size fraction for estimating emissions and modeled ambient air impacts (as well as for evaluating ambient air monitoring data) should be clearly stated in a footnote to the manganese ITSL in the AQD screening level list.

A shorter averaging time ITSL is not being established at this time.

Background Summary and Basis for the Previous ITSL

Under the AQD air pollution control rules of Part 55 of NREPA, Rule 232(1)(a) states that an ITSL can be equal to the reference concentration (RfC) if an RfC can be determined from the best available information sources. Although this approach to ITSL derivation is generally regarded as the most appropriate basis, other approaches may be used. Further, Rule 232(2)(b) states that if the ITSL is derived from an RfC, then the averaging time is 24 hours. However, Rule 229(2)(b) states that an ITSL may be determined by any alternative methodology that is more appropriate based on toxicological grounds and is supported by the scientific data.

On January 19, 2007, the AQD (Catherine Simon, AQD Toxics Unit Supervisor) submitted to the EPA a request that the RfC for manganese be reassessed and updated by the EPA, as appropriate. The basis for the request was that the RfC was last updated in 1993, more recent toxicity studies were available that could warrant a change in the RfC derivation, and a benchmark dose calculation approach may also change the RfC value. On December 21, 2007, the EPA (72 FR No. 245, pp. 72715-72719) announced the IRIS 2008 agenda, which included manganese in a list of priority chemicals for 2008.

The AQD last updated the manganese ITSL assessment on March 2, 2009 (AQD, 2009). That review of the RfC basis, the basis for other agencies' values, and the toxicological literature, described alternative potential approaches to RfC and ITSL derivation. It was noted that manganese was a priority chemical on the 2008 EPA agenda, and that the EPA should review the RfC derivation given the updates in RfC calculation (i.e., BMDL analysis) and toxicological literature. In the meantime, the current RfC (0.05 $\mu\text{g}/\text{m}^3$) appeared to be defensible, pending the completion of the EPA's RfC review and update; however, there was a concern that the EPA reassessment may take a few years or longer to complete. Therefore, the AQD retained the existing ITSL value of 0.05 $\mu\text{g}/\text{m}^3$, with annual averaging, with a note that, "These will be reconsidered in the future as the EPA reassessment progresses" (AQD, 2009).

The AQD (2012) also evaluated the emerging results of environmental epidemiology studies in Ohio (e.g., Kim et al., 2011), and the AQD has continued to follow the interpretation of those studies (Bollweg, 2013b; Bowler, 2010). It is also noted that ATSDR (2012) included these studies in their literature review and assessment.

Recent EPA Contacts and Review of Studies

As noted above, in 2007, the AQD submitted to the EPA a formal request for the EPA to prioritize a review and update of the manganese RfC. Subsequently, the EPA placed manganese on their IRIS agenda. Seeing a lack of progress, the AQD continued to correspond with EPA and request prioritization of the effort. Through 2011, it appeared to the AQD that the EPA continued to have manganese on the IRIS reassessment list, although significant progress was not apparent. In October 2013, the EPA (Bollweg, 2013a, personal communication) informed the AQD that manganese was being de-prioritized for an IRIS update, and that this issue would be further pursued. In December 2013, the AQD noted that manganese was not on the "IRIS-track" list of chemicals under review on the IRIS database. An EPA representative on the IRIS hotline confirmed that the manganese IRIS file was no longer being updated, and recommended that further information could be obtained from the EPA IRIS Chemical Manager for manganese, Dr. Bob Benson. In further correspondence with Dr. Benson (2014, personal communication), he advised that the ATSDR chronic inhalation MRL would be an appropriate and more up-to-date benchmark than the 1993 EPA RfC; although they both relied upon the same key study (Roels et al., 1992), the ATSDR more appropriately utilized benchmark dose modeling and a reduced uncertainty factor. Further, Benson (2014; personal communication) opined that if the EPA were to perform an updated risk assessment using the same key study, they would derive an RfC that would be identical to the ATSDR MRL (after rounding to one significant figure).

Bollweg (2014, personal communication) suggested a review of a recent paper (Lucchini et al., 2012) that appeared to report adverse olfactory and neurological effects in an area with an average manganese airborne concentration of 0.0495 $\mu\text{g}/\text{m}^3$. A review of that paper revealed that the authors did not find an association between health effects and airborne manganese concentrations. Lucchini et al. (2012) stated that airborne dust had been found in two other studies (Riojas-Rodriguez et al., 2010; Menezes-Filho et al., 2011) to be associated with cognitive impairment (reduced IQ). However, review of those two papers revealed that airborne manganese levels were either not measured at all, or, were minimally reported and not associated with significant effects. Also, neither study accounted for early-life lead exposures (as a potential confounder), and both studies found that hair manganese (MnH) but not blood manganese (MnB) was correlated with decreased IQ. These two studies were conducted on populations with apparently widespread elevated environmental levels of manganese and other metals from historical mining operations, and multiple routes of exposure appeared feasible but

were not adequately characterized. Therefore, these three studies are not particularly informative for the development of a manganese health protective benchmark, and they did not detract from the appropriateness of the ATSDR chronic inhalation MRL.

Current Assessment

At the time of the last AQD assessment of the manganese ITSL (March 2, 2009), the ATSDR chronic inhalation MRL was $0.04 \mu\text{g}/\text{m}^3$ (as established in 2000), with a 2008 proposed change to $0.3 \mu\text{g}/\text{m}^3$. In September 2012, ATSDR finalized the change to a chronic inhalation MRL of $0.3 \mu\text{g}/\text{m}^3$. This MRL is intended to be applied to respirable dust (a particle size range was not further specified) (ATSDR, 2012).

As part of the current AQD evaluation, the focus was on the updated ATSDR (2012) Toxicological Profile and MRL development. Besides the additional papers noted above and the previous AQD (2009, 2012) assessments, other information recently submitted to AQD (Green, 2014, personal communication; Barr Engineering, 2014; MIG, 2012) were also reviewed. These also supported the use of the ATSDR chronic inhalation MRL as the AQD ITSL, with application to a respirable size fraction (i.e., not TSP-Mn). Based on all information reviewed, this reviewer determined that a more thorough literature review was not necessary or appropriate at this time for the screening level update.

An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. The ATSDR (2012) Toxicological Profile includes many references from 2011 and none from 2012, indicating that the ATSDR literature review occurred prior to 2012. This Toxicological Profile provides the most complete up-to-date review of the scientific literature available on the toxicological effects of manganese.

Key Study and MRL Derivation

Roels et al. (1992) is the key study utilized by ATSDR (2012) for derivation of the chronic inhalation MRL, by EPA (1993) for derivation of the RfC, and, it is one of the key studies cited by ACGIH (2001) for the TLV recommendation. In this study, manganese workers were exposed for an average (geometric mean) of 5.3 years (range: 0.2-17.7 years) to a respirable dust concentration of $215 \mu\text{g Mn}/\text{m}^3$ and a total dust concentration of $948 \mu\text{g Mn}/\text{m}^3$. Manganese concentrations were measured with personal samplers, with respirable dust being <5 microns in diameter. The authors noted that plant exposure conditions had not changed considerably in the last 15 years, suggesting that past exposures were consistent with those measured at the time of the study. Performance in measured neurobehavioral tests, especially on measures of simple reaction time, eye-hand coordination, and hand steadiness, was significantly worse in manganese-exposed workers than in the comparison group. Percent precision score in the eye-hand coordination test was the most sensitive end point among the end points showing statistically significantly elevated incidences of abnormal scores and was selected as the basis of the MRL. The LOAEL was identified as $179 \mu\text{g}/\text{m}^3$ (ATSDR, 2012). ATSDR (2012) utilized the EPA BMDS to fit available dichotomous models to the incidence data for abnormal eye-hand coordination scores. BMCL_{10} estimates from the different models were within an approximate 2-fold range. The logistic model was indicated as the best fitting model and was used to provide the point of departure (POD) of $142 \mu\text{g}/\text{m}^3$ for the MRL development. The MRL of $0.3 \mu\text{g}/\text{m}^3$ was derived by adjusting the POD to a continuous exposure basis ($142 \mu\text{g Mn}/\text{m}^3 \times 5/7 \times 8/24$) and dividing by a total uncertainty factor of 100. A UF of 10 was used by ATSDR for uncertainty about human variability including possibly enhanced

susceptibility of the elderly, infants, and children, individuals with chronic liver disease or diminished hepatobiliary function; and females and individuals with iron deficiency. A UF of 10 was applied by ATSDR for limitations/ uncertainties in the database including the 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. In addition, ATSDR stated that data on developmental toxicity for this route and duration of exposure are lacking. ATSDR (2012) noted that BMD analyses from other studies and analyses, including Health Canada (2010), resulted in BMCL₁₀ values within an approximate 2-4-fold range of the POD (142 µg Mn/m³) selected for the MRL derivation.

The ITSL is currently being revised to 0.3 µg/m³ with an annual AT, consistent with the ATSDR (2012) chronic inhalation MRL. This MRL accounts for the more recent toxicological studies data and benchmark dose modeling and is protective of sensitive populations.

Chemical Forms

The chemical form of Mn involved in the occupational exposure of the key study (Roels et al., 1992) was manganese dioxide (MnO₂) (ATSDR, 2012). Inorganic forms of Mn include manganese chloride (MnCl₂), manganese sulfate (MnSO₄), manganese acetate (MnOAc), manganese phosphate (MnPO₄), manganese dioxide (MnO₂), manganese tetroxide (Mn₃O₄) and manganese carbonate (MnCO₃) (ATSDR, 2012). ATSDR (2012) placed an emphasis on the health effects of compounds containing inorganic manganese in the Mn(II), Mn(III), or Mn(IV) oxidation states, since these are the forms most often encountered in the environment and the workplace. There is evidence in animals and humans that adverse neurological effects can result from exposure to different manganese compounds; much of this information on toxicity differences between species of manganese is from reports and experiments of acute exposures to very high doses (ATSDR, 2012). Results from animal studies indicate that the solubility of inorganic manganese compounds can influence the bioavailability of manganese and subsequent delivery of manganese to critical toxicity targets such as the brain; however, the influence of manganese oxidation state on manganese toxicity is not currently well understood (ATSDR, 2012). "There is conclusive evidence from studies in humans that inhalation exposure to high levels of manganese compounds (usually manganese dioxide, but also compounds with Mn(I) and Mn(II) can lead to a disabling syndrome of neurological effects referred to as 'manganism'" (ATSDR, 2012; p. 68). For AQD's review of Permit to Install applications and estimates of manganese emissions, there is often a lack of specificity of the form of manganese, and for the specific particle size range of particulate Mn. It is appropriate to apply the ITSL to total manganese emissions (as Mn) for elemental and inorganic forms of manganese, and for particulate manganese emissions it is more appropriate for the ITSL to be applied to PM₁₀ rather than TSP (because PM₁₀-Mn is the better match to the dose-response data for inhalable manganese from the key study (Roels et al., 1992); see further discussion below). The ITSL may also be applied to TSP manganese if that is the form of the available emissions (or ambient air) data, with a caveat that doing so introduces some conservatism to the assessment.

Particle size issue

Because airborne manganese will predominantly occur as particulate matter, the particle size range (i.e., respirable versus total dust) should be considered for determining how a sampled concentration of Mn in airborne dust or a modeled ambient air impact of manganese in particulate compares to the screening level. The ATSDR MRL and EPA RfC are based on the respirable dust exposure levels and dose-response relationship as reported by Roels et al.

(1992). Besides indicating “respirable dust”, these sources do not explicitly state a specific particle size range for application of the benchmark. As discussed by EPA (1993), the key study did not present detailed data on particle size, but the median cut point for the respirable dust fraction was 5 µm according to information provided by Roels et al. (1992) and further information provided to EPA by Dr. Roels in 1993. This tends to support the use of the PM₁₀ size fraction (i.e., PM₁₀-Mn) for association with the ITSL, over the use of PM_{2.5}-Mn or TSP-Mn (which are the other commonly available size fractions, for ambient air monitoring data). Information provided by EPA (1993) describes a higher dose-response relationship between *total Mn* dust exposure levels and critical effects, indicating that if an RfC or ITSL were to be established for total Mn dust utilizing such data, the value would be higher than if based on the levels of exposure to manganese in respirable dust. The AQD has historically (and currently) collected TSP-Mn data and compared it to the ITSL when PM₁₀-Mn data are absent, as a *screening* assessment of the significance of the monitoring data. If PM₁₀-Mn monitoring data or emissions data are available, they should be preferentially utilized over TSP-Mn data, for comparison to the ITSL. This should be clearly stated in a footnote to the AQD screening level list, accompanying the screening level value and averaging time. Beyond the use of PM₁₀-Mn data for comparison to this *screening* level, more detailed risk assessments (e.g., under Rule 226(d) or Rule 228) may account for more site-specific information, including any more appropriate available data on manganese particle size fractions.

Averaging Time Issue

Rule R232(2)(b) states that the averaging time for a screening level based on an RfC will be set at 24-hour averaging. Flexibility is provided by R229(2)(b), which states that an alternative methodology can be used if it is more appropriate based on toxicological grounds. The default averaging time for an MRL-based ITSL is not specified in the rules, but should likewise be appropriately based on toxicological grounds. The previous ITSL had an annual AT because it was considered to be reasonable and appropriate since the key study (Roels et al (1992)) involved a relatively long-term occupational exposure (an average of 5.3 years, range of 0.2 to 17.7 years). The final ATSDR MRL is “chronic;” i.e., for a period of 365 days or longer as per ATSDR policy. This supports the protectiveness of an ITSL with an annual averaging time. Although short term health protective benchmarks from other reliable sources (AEGs, acute RELs, or acute or intermediate MRLs) for manganese are not available, the toxicological literature suggests that an ITSL of 0.3 µg/m³ with an annual averaging time would be adequately protective for manganism or other adverse effects of manganese (see further discussion below).

Acute Toxicity Issue

Consideration was given to establishing a short term ITSL to accompany the above chronic ITSL. AQD (2009) stated that, “Although preferred acute health protective benchmarks (AEGs, acute RELs, or MRLs) for manganese are not available, the toxicological literature suggests that an ITSL of 0.05 µg/m³ with an annual averaging time would be adequately protective for manganism or other adverse effects of manganese.” The ATSDR (2012) stated that, “MRL values were not derived for acute- or intermediate-duration inhalation exposures to manganese. The available data on the toxicity of inhaled manganese were considered inadequate for derivation of acute- or intermediate-duration inhalation MRLs. Data are lacking on whether exposure to inhaled manganese across these durations has any significant adverse effects on numerous end points including reports on developmental and reproductive effects. Reports of human exposure at acute and intermediate durations (i.e., 15-364 days) indicate adverse respiratory and neurological effects, but these reports consist of anecdotal case studies and

lack quantitative exposure values...findings in rats and monkeys are consistent with the understanding that inflammation of respiratory tissues from high-level exposure to inhaled manganese particulates is likely a consequence of the inhaled particulate matter.” Also, ATSDR (2012) stated that, “It is expected that the chronic MRL for inhaled inorganic manganese would provide protection for intermediate-duration exposure scenarios,” and, “Studies in animals and humans indicate that inorganic manganese compounds have very low acute toxicity by any route of exposure,” with the notable exception of potassium permanganate, which can cause corrosion of skin or mucosa at the point of contact. These findings support the protectiveness of the particulate matter NAAQS and the manganese chronic inhalation MRL, for reasonably anticipated short term peak ambient air levels and exposures to manganese particulate. Therefore, a shorter averaging time ITSL is not being established at this time.

It is noted that Texas (TCEQ, 2014) has an interim short term Effects Screening Level (ESL) of $2 \mu\text{g}/\text{m}^3$ (1 hr AT), which was derived as 1% of the manganese occupational exposure level (OEL) of the TLV of $0.2 \text{ mg}/\text{m}^3$ (Lee, personal communication). DEQ could similarly derive an ITSL (with 8 hr AT) as 1% of the ACGIH TLV, however, the necessity and appropriateness of that approach is not particularly supported by the ATSDR (2012) assessment (see summary statements above). The ACGIH (2001) established a TLV-TWA of $0.2 \text{ mg}/\text{m}^3$ (as Mn) for “manganese and inorganic compounds,” intended to “minimize the potential for pre-clinical adverse effects in the lungs and CNS and adverse effects on the fertility of male workers exposure 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.” The ACGIH discussion of the TLV recommendation implies that the limit applies to total or inhalable dust, rather than “respirable” dust.

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