MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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TO: File for Potassium Permanganate (CAS# 7722-64-7)

FROM: Keisha Williams, Air Quality Division

DATE: February 3, 2017

SUBJECT: Screening Level Update for Potassium Permanganate ($KMnO_4$)

The initial threshold screening level (ITSL) for acute exposure to potassium permanganate ($KMnO_4$) is 0.6 µg/m^3 (8 hour averaging time) based on the Michigan Department of Environmental Quality (MDEQ), Air Quality Division (AQD) Rule 336.1232 (1) (c).

Chronic exposure to $KMnO_4$ will be regulated in combination with manganese and other manganese compounds based on the MDEQ-AQD Rule 336.1229 (2) (b). However, a chronic ITSL will not be used for $KMnO_4$ alone, because the acute ITSL is restrictive enough to be health-protective for the effects protected by the potential chronic ITSL.

The following references or databases were searched to identify data to determine the screening level: United States Environmental Protection Agency's (EPA's) Integrated Risk Information System (IRIS), the Registry of Toxic Effects of Chemical Substances (RTECS), the American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values (TLV), National Institute of Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, MDEQ Library, International Agency for Research on Cancer (IARC) Monographs, Chemical Abstract Service (CAS) Online (June 1995-September 2015), National Library of Medicine (NLM), Health Effects Assessment Summary Tables (HEAST), National Toxicology Program (NTP) Status Report, EPA Aggregated Computational Toxicology Resource (ACToR) Database, EPA TSCATS database, EPA Superfund Provisional Peer Reviewed Toxicity Values, EPA Acute Exposure Guideline Levels for Airborne Chemicals, EPA High Production Volume Database, Agency for Toxic Substances and Disease Registry's (ATSDR's) Toxicological Profiles, United States Department of Labor Occupational Safety and Health Administration Permissible Exposure Limits, Spacecraft Maximum Allowable Concentrations, California Office of Environmental Health Hazard Assessments Reference Exposure Levels, Chemical Safety Program Protective Action Criteria, Texas Commission on Environmental Quality Effects Screening Levels, and European Chemicals Agency Registered Substances Dossiers.

Background Information

$KMnO_4$ (Figure 1) has been used for several purposes, including as a bleaching agent, in water treatment, in chemical manufacturing, and as a deodorizing agent (NCBI, Pubchem).

$KMnO_4$, an inorganic manganese compound, can be classified with other permanganates and manganates, as well as borates and chromates. One of its most notable characteristics is that it is a strong oxidizing agent with the highest oxidation state possible for a manganese compound. Chemical and physical properties are listed in Table 1.

Figure 1. Chemical structure for $KMnO_4$

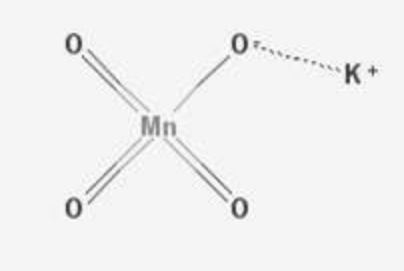

Table 1. Chemical and physical properties of $KMnO_4$

Color: purple, bronze, or opaque
Melting point: Decomposes at ≈464°F
Molecular weight: 158.03 grams/mole
Odor: Odorless
Physical state: solid
Taste: Sweet

(NCBI, Pubchem)

Very few chemical-specific health benchmarks were identified for $KMnO_4$; this chemical is often regulated in concert with manganese and other manganese compounds. Within the U.S. Department of Energy's (DOE's) Chemical Safety Program, protective action criteria (PAC) for $KMnO_4$ are 8.6, 14 and 78 mg/m^3 for PAC-1, PAC-2 and PAC-3, respectively (DOE, PAC database). These values seem to be derived from the manganese (CAS# 7439-96-5) PAC values with adjustment for differences in molecular weight. Similarly, the Texas Commission on Environmental Quality (TCEQ) regulates $KMnO_4$ along with other manganese compounds with the effect screening level (ESL) for long-term exposure being 0.2 µg/m^3 and the ESL for short-term exposure being 2 µg/m^3 (TCEQ, 2015). The TCEQ's ESLs are derived from the German occupational exposure limit values (Maximale Arbeitsplatz-Konzentration or MAK) for the inhalable fraction of manganese dust and inorganic compounds (Forschungsgemeinschaft, 2015). 1% and 0.1% of the 0.2 mg/m^3 MAK value are used for the short term and long term ESLs, respectively.

In the ATSDR's toxicological profile for manganese, they specifically note that

"If manganese is in the (VII) oxidation state (as in potassium permanganate), then ingestion may lead to severe corrosion at the point of contact… the influence of manganese oxidation state on manganese toxicity is not currently well understood. Manganese in the form of permanganate produces toxic effects primarily through its oxidizing capacity...Studies in animals and humans indicate that inorganic

manganese compounds have very low acute toxicity by any route of exposure. An exception is potassium permanganate, which is an oxidant that can cause severe corrosion of skin or mucosa at the point of contact" (ATSDR, 2012).

Both the ATSDR minimal risk limit (MRL) and the American Conference of Governmental Industrial Hygienists (ACGIH) threshold limit value primarily target inorganic manganese in the oxidation states of +2, +3 and +4 (ACGIH, 2013; ATSDR, 2012). The +7 oxidation state of $KMnO_4$ has been a side note in the documentation for both of these health benchmark values. The ATSDR (2012) states,

"because of its tendency to oxidize organic material, the permanganate ion is not stable in the environment; thus, the probability of exposure to this species around waste sites is considered very low. For this reason, data on exposures to permanganate are only briefly discussed" (ATSDR, 2012).

Although this information indicates that $KMnO_4$ may not persist for long in the atmosphere, AQD screening levels apply to reported emissions dispersed in the ambient air that are presumed to be present at and beyond secured property lines without assuming some degree of degradation.

In the chemical assessment performed by the USEPA (1993) it is noted that "insufficient information exists by which to determine the relative toxicities of different forms of Mn, and thus, for the purpose of deriving an [reference concentration] RfC for Mn, no distinction is made among various compounds of Mn" (USEPA, 1993). With this in mind, we considered $KMnO_4$-specific studies as well as whether $KMnO_4$ should be grouped with other manganese compounds.

A number of case studies have been published regarding $KMnO_4$ toxicity after oral ingestion (Young et al., 1996; Ong et al., 1997; Johnson et al., 2004; ATSDR, 2012). These reports indicate both portal of entry effects as well as systemic effects, including neurotoxicity commonly observed with exposure to other forms of manganese, and $KMnO_4$-induced fatalities. However, since controlled human studies are not available, *in vivo* data is the next best resource for derivation of a screening level.

There are few $KMnO_4$-specific inhalation studies compared to studies revolving around other manganese compounds like manganese dioxide (IPCS, 1981). As a result, in lieu of chemical-specific data, $KMnO_4$ will be grouped with other inorganic manganese compounds to consider chronic effects, especially the critical effect of neurotoxicity. However, unlike other manganese compounds, the strong oxidizing nature of $KMnO_4$ could potentially induce portal of entry toxicity. Although this effect has not been studied in regards to inhalation exposures, an acute ITSL is being established at this time to be protective against potential portal of entry effects with inhalation.

Evaluation of Cancer Risk

No studies were found to evaluate the carcinogenicity of $KMnO_4$ specifically. Furthermore, there are few studies that have been performed with other inorganic manganese compounds, such that manganese compounds are indicated as "not classifiable as a human carcinogen" (ACGIH, 2013; EPA, 1988). Since there is inadequate information to determine the carcinogenicity of $KMnO_4$, it will not be defined as a carcinogen at this time.

Review of Relevant Studies for Non-carcinogen Effects

Health benchmark formerly used to derive the ITSL

The original $KMnO_4$ ITSL (MDNR, 1995) was based on the manganese ITSL, which in turn was based on the USEPA's RfC. As stated in the original ITSL justification, "this value was derived from an EPA, RfC of 5E-5 mg/m^3, based on a LOAEL (HEC) of 0.05 mg/m^3 due to impairment of neurobehavioral function in occupational workers" (MDNR, 1995). Using Rules 336.1229 (2) (b) and 336.1232 (1) (a), as shown in Equation 1, the previously established ITSL was calculated as follows:

Equation 1.

$$Former\ ITSL = \frac{manganese\ RfC}{manganese\ molecular\ weight}\ x\ KMnO_4 molecular\ weight$$

where
manganese RfC=0.05 µg/m^3
manganese molecular weight=54.9 grams/mole
$KMnO_4$ molecular weight=158 grams/mole

$$Former\ ITSL = \frac{0.05\ \frac{\mu g}{m^3}}{54.9\ \frac{grams}{mole}}\ x\ 158\ \frac{grams}{mole} = 0.14\ \frac{\mu g}{m^3} \approx 0.1\ \frac{\mu g}{m^3}\ , 24\ hour\ averaging\ time$$

In 2014, the review of the ITSL for manganese and manganese compounds led to both a change in the ITSL to 0.3 µg/m^3, annual averaging time, as well as a change in the basis of the ITSL to ATSDR's chronic MRL (MDEQ, 2014). Although the ATSDR toxicological profile for manganese identifies reasons why acute toxicity may differ between $KMnO_4$ and other manganese compounds, $KMnO_4$ has been shown to produce similar neurotoxicity as the critical effect identified and used to derive the chronic manganese ITSL (ATSDR, 2012). As a result, $KMnO_4$ will be grouped under the chronic ITSL for manganese and manganese compounds. Thus, the current chronic ITSL for $KMnO_4$ is calculated as shown in Equation 2.

Equation 2.

$$Potential\ Chronic\ ITSL = \frac{manganese\ chronic\ MRL}{manganese\ molecular\ weight}\ x\ KMnO_4 molecular\ weight$$

where
manganese RfC=0.3 µg/m^3
manganese molecular weight=54.9 grams/mole
$KMnO_4$ molecular weight=158 grams/mole

$$Potential\ Chronic\ ITSL =$$

$$\frac{0.3\ \frac{\mu g}{m^3}}{54.9\ \frac{grams}{mole}}\ x\ 158\ \frac{grams}{mole} = 0.86\ \frac{\mu g}{m^3} \approx 0.9\ \frac{\mu g}{m^3}\ , annual\ averaging\ time$$

Acute ITSL Derivation

Apart from case reports, no inhalation studies on the acute effects of $KMnO_4$ were found. Numerous case studies as well as in vivo studies are available regarding $KMnO_4$-toxicity after oral exposure; however, the portal of entry effects observed with oral exposure suggest that extrapolation to the inhalation route of exposure would not be appropriate.

The TLV for "manganese, elemental and inorganic manganese compounds, respirable particulate matter", is the best available health-based exposure limit to derive an acute screening level, and it will be used to derive an ITSL to protect against potential acute effects from $KMnO_4$. Since the critical effect basis used to derive the TLV is "central nervous system impairment" and portal of entry effects are expected with $KMnO_4$ because it is a strong oxidizing agent, $KMnO_4$–specific studies should be considered as soon as they become available to better describe potential toxic effects and corresponding exposure concentrations.

Based on the TLV for inorganic manganese compounds, an acute ITSL could be derived as shown in Equation 3.

Equation 3.

$$acute\ ITSL = \frac{occupational\ exposure\ limit}{100}$$

$$acute\ ITSL = \frac{occupational\ exposure\ limit}{100}\ x\ molecular\ weight\ adjustment\ factor$$

$$molecular\ weight\ adjustment\ factor = \frac{TLV_{Mn\ and\ inorg.\ Mn\ compounds}\ x\ mol.wt._{KMnO_4}}{mol.wt._{Mn}}$$

$$molecular\ weight\ adjustment\ factor = \frac{0.02\frac{mg}{m^3}\ x\ 158.03\frac{g}{mole}}{54.94\frac{g}{mole}} = 0.058\frac{mg}{m^3}$$

$$acute\ ITSL = \frac{0.058\ \frac{mg}{m^3}}{100}\ x\ \frac{1000\frac{\mu g}{m^3}}{\frac{mg}{m^3}} = 0.58\frac{\mu g}{m^3} \approx \mathbf{0.6}\frac{\boldsymbol{\mu g}}{\boldsymbol{m^3}}\boldsymbol{,\ 8\ hour\ averaging\ time}$$

References

ACGIH. 2013. Documentation of the Threshold Limit Values and Biological Exposure Indices. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

Act 451 of 1994, Natural Resources and Environmental Protection Act and Air Pollution Control Rules, Michigan Department of Environmental Quality.

Agency for Toxic Substances and Disease Registry (ATSDR). 2012. Toxicological profile for Manganese. Atlanta, GA: U.S. Department of Health and Human Services, Public Health Service.

DOE. Chemical Safety Program Protective Action Criteria Database. Accessed October 15, 2015. http://www.atlintl.com/DOE/teels/teel/search.html

Forschungsgemeinschaft, D. Procedure of the Permanent Senate Commission for the Investigation of Health Hazards of Chemical Compounds in the Work Area for Making Changes in or Additions to the List of MAK and BAT Values. List of MAK and BAT Values 2015, XXVII-XXVII.

Holzgraefe, M., W. Poser, H. Kijewski, and W. Beuche. 1986. Chronic enteral poisoning caused by potassium permanganate: a case report. Clinical Toxicology, 24(3), 235-244. As cited by ATSDR, 2012.

Johnson, T. B., D.D. Cassidy. 2004. Unintentional ingestion of potassium permanganate. Pediatric emergency care, 20(3), 185-187.

MDEQ. 2014. Memo from Robert Sills to File for Manganese and Manganese Compounds (CAS No. 7439-96-5). Subject: Updated ITSL for manganese and manganese compounds. May 12, 2014.

MDNR. 1995. Memo from Marco Bianchi to File for Potassium Permanganate. Subject: Initial Threshold Screening Level. June 29, 1995.

National Center for Biotechnology Information. PubChem Compound Database. Accessed October 15, 2015. CID=516875, https://pubchem.ncbi.nlm.nih.gov/compound/516875

Ong, K. L., T.H. Tan, W.L. Cheung. 1997. Potassium permanganate poisoning--a rare cause of fatal self poisoning. Journal of accident and emergency medicine, 14(1), 43-45.

TCEQ. 2015. Effects Screening Levels (ESL) Lists Used in the Review of Air Permitting Data: Current ESL List. Accessed October 16, 2015. http://www.tceq.texas.gov/toxicology/esl/list_main.html/#esl_1

USEPA. 1988. Manganese (CASRN 7439-96-5) Weight of Evidence for Cancer. Accessed October 16, 2015. http://cfpub.epa.gov/ncea/iris2/chemicalLanding.cfm?substance_nmbr=373

USEPA. 1993. Manganese (CASRN 7439-96-5) Reference Concentration for Inhalation Exposure. Accessed October 16, 2015. http://cfpub.epa.gov/ncea/iris/iris_documents/documents/subst/0373_summary.pdf#nameddest=rfc

IPCS. 1981. International Programme on Chemical Safety: Environmental Health Criteria 17, Manganese. World Health Organization, Geneva, Switzerland. Accessed November 10, 2015. http://www.inchem.org/documents/ehc/ehc/ehc017.htm

Young, R. J., J.A.J.H. Critchley, K.K. Young, R.C. Freebairn, A.P. Reynolds, Y.I. Lolin. 1996. Fatal acute hepatorenal failure following potassium permanganate ingestion. Human and

experimental toxicology, 15(3), 259-261.

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/m^3 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/m^3 (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., PM_{10}-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 PM_{10}-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 µg/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 ug/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 µg/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 µg/m^3 (as established in 2000), with a 2008 proposed change to 0.3 µg/m^3. In September 2012, ATSDR finalized the change to a chronic inhalation MRL of 0.3 µg/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 µg Mn/m^3 and a total dust concentration of 948 µg Mn/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 µg/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 µg/m^3 for the MRL development. The MRL of 0.3 µg/m^3 was derived by adjusting the POD to a continuous exposure basis (142 µg Mn/m^3 X 5/7 X 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 $BMCL_{10}$ values within an approximate 2-4-fold range of the POD (142 µg Mn/m^3) selected for the MRL derivation.

The ITSL is currently being revised to 0.3 µg/m^3 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 ($MnCl_2$), manganese sulfate ($MnSO_4$), manganese acetate (MnOAc), manganese phosphate ($MnPO_4$), manganese dioxide (MnO_2), manganese tetroxide (Mn_3O_4) and manganese carbonate ($MnCO_3$) (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 PM_{10} rather than TSP (because PM_{10}-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 PM_{10} size fraction (i.e., PM_{10}-Mn) for association with the ITSL, over the use of PM2.5-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 PM_{10}-Mn data are absent, as a *screening* assessment of the significance of the monitoring data. If PM_{10}-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 PM_{10}-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 (AEGLs, acute RELs, or acute or intermediate MRLs) for manganese are not available, the toxicological literature suggests that an ITSL of 0.3 µg/m^3 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 (AEGLs, acute RELs, or MRLs) for manganese are not available, the toxicological literature suggests that an ITSL of 0.05 µg/m^3 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 µg/m^3 (1 hr AT), which was derived as 1% of the manganese occupational exposure level (OEL) of the TLV of 0.2 mg/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 mg/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.

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2012. Toxicological Profile for Manganese. U.S. DHHS. September, 2012.

Air Quality Division (AQD). 2009. Screening Level for Manganese. March 2, 2009. MDEQ-AQD Interoffice Communication from Gary Butterfield, Bob Sills, and Christina Rose Bush.

Air Quality Division (AQD). 2012. Ambient Air Levels of Manganese in Southeast Michigan: Evaluation and Recommendations by the AQD Manganese Workgroup. Michigan Department of Environmental Quality. March 27, 2012. http://www.michigan.gov/documents/deq/deq-aqd-aqe-monitoring-Mn-Report-Michigan-Sept-8-2011_402342_7.pdf

Barr Engineering Company. 2014. A Comparison of Chronic Inhalation Values for Manganese to Protect for Noncancer Effects. February 7, 2014.

Benson, B. 2014. Personal communication (emails) from Dr. Bob Benson, Toxicologist, EPA Region 8, with Robert Sills, MDEQ-AQD.

Bollweg, G. 2013a. Personal communication from Dr. George Bollweg, EPA Region 5, to Robert Sills, MDEQ-AQD.

Bollweg, G. 2013b. USEPA Region 5 Summary Remarks: Health study of airborne manganese (Mn) in Ohio adults – preliminary results. East Liverpool Ohio. Presentation, July 11, 2013.

Bowler, R.B. 2010. Relationship of residential airborne manganese exposure to neuropsychological, neurological and health status of adults. Presentation, June 20, 2010, Ohio Department of Health, Columbus, Ohio.

EPA. 1993. Integrated Risk Information System summary for manganese. Inhalation RfC assessment, last revised 12/1/1993.

Green, J. 2014. Personal communication. Email from Joseph Green to Robert Sills, February 28, 2014, with attachments (see Barr Engineering Company, 2014, and MIG, 2012).

Kim, Y. et al. 2011. Motor function in adults of an Ohio community with environmental manganese exposure. NeuroToxicology 32:606-614.

Lucchini R, Apostoli P, Perrone C, Placidi D, Albini E, Migliorati P, Mergler D, Sassine M-P, Palmi S, Alession L. 1999. Long term exposure to “low levels” of manganese oxides and neurofunctional changes in ferroalloy workers. Neurotoxicology 20(2-3):287-298.

MIG. 2012. Comments of the Manganese Interest Group (MIG) on the U.S. Environmental Protection Agency’s Notice of Proposed Rulemaking for National Emissions Standards for Hazardous Air Pollutants: Ferroalloys Production. January 31, 2012.

Roels HA, Ghyselen P, Buchet JP, Ceulemans E, Lauwerys RR. 1992. Assessment of the

permissible exposure level to manganese in workers exposed to manganese dioxide dust. Br J Ind Med 49:25-34.

TCEQ. 2014. TCEQ ESLs list, including manganese:
http://www.tceq.state.tx.us/toxicology/esl/list_main.html/#esl_1
TCEQ AMCV list, including manganese:
http://www.tceq.texas.gov/toxicology/AirToxics.html/#list

RS:lh

MICHIGAN DEPARTMENT OF NATURAL RESOURCES

INTEROFFICE COMMUNICATION

June 29, 1995

TO: File for Potassium Permanganate (7722-64-7)

FROM: Marco Bianchi

SUBJECT: Initial Threshold Screening Level

The initial threshold screening level (ITSL) for potassium permanganate is 0.1 µg/m^3 based on a 24hr. averaging time.

The following references or databases were searched to identify data to determine the ITSL: IRIS, HEAST, NTP Management Status Report, RTECS, EPB-CCD, EPB library, CAS-online, NLM-online, IARC, NIOSH Pocket Guide, and ACGIH Guide.

Potassium permanganate ($KMnO_4$) produces toxic effects primarily through its oxidizing and corrosive properties. The only information available on potassium permanganate for this review were two oral LD_{50} studies and some incidental poisoning reports. The LD_{50}s listed in RTECS were both oral rodent studies; one study was from a foreign journal, and the other was a study by Smyth (1969). The Smyth study obtained an oral rat LD_{50} value of 1.09 mg/kg. Another study by Joardar (1990), showed clastogenic effects of $KMnO_4$ on sperm-head morphology directly related to concentration; however, a no-effect level was not determined.

The bulk of the information obtained for this compound was on elemental manganese, for which there is both an RfD and RfC. It was noted in the EPA, IRIS documentation for manganese that “at present, however, insufficient information exists by which to determine the relative toxicities of different forms of Mn, and thus, for the purposes of deriving an RfC for Mn, no distinction is made among the various compounds of Mn”. Consequently, the ITSL for manganese should be protective against toxicity from potassium permanganate (accounting for a molecular weight adjustment).

The current ITSL for manganese is 0.05 µg/m^3 based on a 24 hr. averaging. This value was derived from an EPA, RfC of 5 x 10^{-5} mg/m^3, based on a LOAEL (HEC) of 0.05 mg/m^3 due to impairment of neurobehavioral function in occupational workers.

Current ITSL = 0.05 µg/m^3; 24 hr. averaging

manganese MW = 54.9 g/mol
potassium permanganate =158 g/mol
Molecular Weight Ratios:

$$\frac{0.05\ \frac{\mu g}{m^3}}{54.9\frac{\mu g}{m^3}} = \frac{x\ \frac{\mu g}{m^3}}{158\ \frac{\mu g}{m^3}}$$

$$x = 0.14\ \frac{\mu g}{m^3}\ or\ 0.1\ \frac{\mu g}{m^3}$$

The ITSL for potassium permanganate = 0.1 µg/m^3 based on 24 hr. averaging.

References:

IRIS. 1994. Manganese; Inhalation RfC Assessment.

Symth HF. et al., 1969. Range-Finding Toxicity Data List: List VII. American Industrial Hygiene Association Journal. 30: 470-476.

Joardar M. et al., 1990. Comparison of clastogenecity of inorganic Mn administered in cationic and anionic forms *in vivo*. Mutation Research. 240:159-163.

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