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Comments of the Manganese Interest Group

to the
Independent Regulatory Review Commission

regarding
Pennsylvania Department of Environmental Protection/Environmental Quality Board Rulemaking:
Water Quality Standard for Manganese and Implementation

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On behalf of the Manganese Interest Group ("MIG"), we submit the following comments to the Independent Regulatory Review Commission ("IRRC") regarding the Pennsylvania Department of Environmental Protection ("DEP" or "Department") rulemaking to establish a human health-based water quality criterion for manganese of 0.3 mg/L.

MIG is an *ad hoc* coalition of trade associations and companies interested in the scientifically sound evaluation and regulation of manganese ("Mn") and its compounds. MIG members include steel producers, metalworkers, chemical manufacturers, ferroalloy producers, and other like-minded stakeholders, many of whom operate in Pennsylvania.[1]

MIG previously submitted comments to DEP addressing the scientific literature regarding the potential for adverse effects from exposure to Mn in drinking water, including the primary studies relied on by DEP to support the current rulemaking. As detailed in those comments, we do not believe the standard advanced by DEP is reflective of the best available current science. In fact, as detailed in comments on behalf of the Pennsylvania Coal Alliance,[2] the best available current science demonstrates that the current manganese ambient water quality criterion of 1 mg/L is fully protective of human health.

The following comments focus on the Department's misplaced concerns regarding the most important recent science for evaluating potential manganese toxicity, particularly with respect to the low-level environmental exposures at issue in the current rulemaking: human physiologically-based pharmacokinetic ("PBPK") models for manganese inhalation and ingestion.

I. DEP's Concerns About the Credibility and Reproducibility of the PBPK Models for Manganese Are Misplaced.

The DEP Final-Form Rulemaking addressing a "Water Quality Standard for Manganese and Implementation" states that "additional studies by independent research groups should be conducted to validate these models and any associated animal studies . . . to ensure that the reported results are credible and reproducible."[3] The DEP's concerns about the credibility and reproducibility of the PBPK models for manganese are misguided. All of the data on which the PBPK models are based were derived from research programs developed and closely managed by the U.S.

[1] Group members include: the American Iron and Steel Institute, the Steel Manufacturers Association, the Specialty Steel Industry of North America, the International Manganese Institute, the National Slag Association, Afton Chemical Corporation, American Zinc Recycling, Carpenter Technology Corp., Cliffs Natural Resources, Electralloy, Eramet Marietta, Inc., New Castle Stainless Plate LLC, Nucor Steel, S.H. Bell Company, Universal Stainless & Alloy Products, and U.S. Steel.

[2] MIG endorses and fully supports the comments submitted by the Pennsylvania Coal Alliance regarding this rulemaking.

[3] Final-Form Rulemaking at 10.

Environmental Protection Agency ("EPA"), Health Canada, and Environment Canada. In addition, most of the animal data on which the PBPK models are based have been independently reproduced and corroborated by academic researchers.

As the DEP correctly observes, a substantial portion of the research on which the PBPK models are based was funded by Afton Chemical Corporation ("Afton"), the producer of the octane-enhancing fuel additive knows as mmt.[4] As the manufacturer of mmt, Afton is subject to the registration testing requirements developed by EPA to implement the requirements of section 211(b) of the Clean Air Act ("Act") (42 U.S.C. § 7545(b)). Section 211(b) of the Act directs that EPA "require the manufacturer of any fuel or fuel additive . . . to conduct tests to determine potential public health and environmental effects of the fuel or fuel additive (including carcinogenic, teratogenic, or mutagenic effects) . . . ." Implementing that responsibility for mmt, EPA issued an "Alternative Tier 2 test rule" for mmt in 2000 that effectively mandated development of the PBPK models for manganese. As reflected in the following schematic, moreover, all elements of the research program were subjected to multiple layers of independent peer-review intended to ensure, so far as possible, generation of valid and appropriate scientific information.

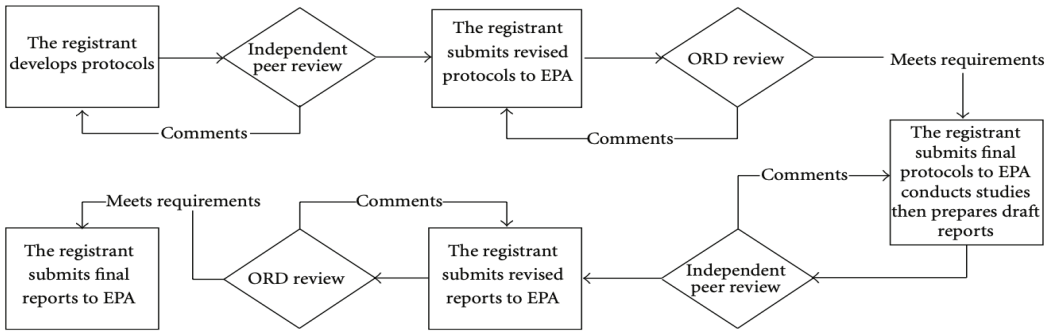

FIGURE 1: Schematic overview of steps used to develop and review study protocols and produce final reports. Independent peer review was carried out by the appropriate TAP. Completed final reports for all of the manganese studies can be found in the Federal Docket Management System (FDMS) at http://www.regulations.gov identified by docket number EPA-HQ-OAR-2004-0074. EPA: Environmental Protection Agency; ORD: EPA Office of Research and Development.

Additional information about the Alternative Tier 2 test fuel for mmt can be found at www.regulations.gov in docket EPA-HQ-OAR-2004-0074 and in the following two scientific publications, neither of which the DEP has yet reviewed (based on the reference list in the Final-Form Rulemaking document):

- Dorman, D., et al., Update on a Pharmacokinetic-Centric Alternative Tier II Program for MMT - Part I: Program Implementation and Lessons Learned, Journal of Toxicology, Volume 2012, Article ID 946742 (hereafter "Dorman et al., 2012").

[4] mmt® is a registered trademark owned by Afton Chemical Corporation.

- Smith, D, et al., Manganese Testing Under a Clean Air Act Test Rule and the Application of Resultant Data in Risk Assessments, Neurotoxicology. 2018 January; 64: 177-184 (hereafter "Smith et al., 2018").

The Dorman et al., 2012 paper clearly states: "All required study protocols, protocol amendments, and draft final reports underwent independent scientific review by project specific 'technical advisory panels' (TAPs) composed of individuals with expertise in inhalation toxicology, pharmacokinetics, and neurotoxicity (Figure 1). Members of the TAPs, which changed for different facets of the test program, were chosen by the study sponsor with input from the testing laboratory and approved by the USEPA. All study results underwent additional independent peer review during subsequent publication of the work in scientific journals." (emphasis added)

At about the same time EPA developed its Alternative Tier 2 test rule for mmt, Health Canada and Environment Canada initiated a parallel research program to investigate the emission by-products of mmt when used in gasoline as part of the Canadian Toxic Substances Research Initiative ("TSRI"). The research program was headed by Dr. Joseph Zayed of the University of Montreal. The TSRI manganese research program resulted in the following scientific publications:

- St. Pierre, A., et al., Bioaccumulation and Locomotor Effect of Manganese Dust in Rats. Inhalation Toxicology, 13:623-632, 2001.
- Normandin, L., et al., Assessment of Bioaccumulation, Neuropathology, and Neurobehavior Following Subchronic (90 Days) Inhalation in Sprague-Dawley Rats Exposed to Manganese Phosphate. Toxicology and Applied Pharmacology 183, 135-145 (2002).
- Salehi, F., et al., Bioaccumulation and locomotor effects of manganese phosphate/sulfate mixture in Sprague-Dawley rats following subchronic (90 days) inhalation exposure. Toxicology and Applied Pharmacology 191 (2003) 264-271.
- Normandin, L., et al., Manganese Distribution in the Brain and Neurobehavioral Changes Following Inhalation Exposure of Rats to Three Chemical Forms of Manganese. NeuroToxicology 25 (2004) 433-441.
- Beaupre, L. A., et al., Physical and Chemical Characterization of Mn Phosphate/Sulfate Mixture Used in an Inhalation Toxicology Study. Inhalation Toxicology, 16:231-244, 2004.
- Tapin, D., et al., Bioaccumulation and locomotor effects of manganese sulfate in Sprague-Dawley rats following subchronic (90 days) inhalation exposure. Toxicol Appl Pharmacol. 2006 Mar 1; 211(2): 166-174.
- Salehi, F., et al. Neuropathology, tremor and electromyogram in rats exposed to manganese phosphate/sulfate mixture. J Appl Toxicol. 2006 Sep-Oct; 26(5): 419-26.

The PBPK models for manganese are based on data generated from the Alternative Tier 2 test rule for mmt, *as well as the data generated in the Canadian TSRI manganese research program led by Dr. Zayed from the University of Montreal*, so there is no need

for these data to be reproduced by other academic researchers, as the DEP has recommended.

II. The PBPK Models for Manganese Have Been Validated and Used in Manganese Risk Assessment

The DEP has rejected reliance on the PBPK models for manganese, arguing that they have not been adequately validated. Once again, DEP's concern is misplaced. The PBPK models for manganese were developed in a stepwise fashion consistent with the nature of the animal research program on which the models are ultimately based. A rat PBPK model was developed first and validated against the comprehensive manganese tissue concentration data obtained in the Alternative Tier 2 test program for mmt and the TSRI manganese research program conducted in Canada by the University of Montreal. The model was shown to adequately match the hundreds of measured tissue concentrations obtained from the rodent inhalation research programs.

The second step was development of the primate PBPK model and its validation using tissue concentration data derived from testing in primates as part of the Alternative Tier 2 test rule for mmt, as well as other available primate research studies. As with the rodent PBPK model, the primate model was shown to match the available measured manganese tissue concentration data. *Accordingly, both the rodent and primate PBPK models are fully validated in the fashion that DEP has identified as necessary for the human model.*

The third step was development of a human PBPK model. Unlike the rodent and primate models, however, there is no repository of measured manganese tissue concentrations against which to validate the models directly (as testing in humans similar to that which occurred in rodents and primates is not an option). Therefore, a somewhat different approach was applied for development of the human PBPK model, first, by scaling various physiological parameters across species (*e.g.*, breathing rates, food intake, weight, blood flow, *etc*.) and then by comparing modeled results against available human data wherever possible (*i.e.*, tissue concentration data obtained via autopsies, manganese blood concentrations measured in occupational studies involving inhaled manganese, and radioactive manganese studies conducted in volunteers). The genesis of the human PBPK models is described in more detail in two recent scientific publications that are not included on the DEP's reference list:

- Gentry, P.R., et al. A tissue dose-based comparative exposure assessment of manganese using physiologically based pharmacokinetic modeling - the importance of homeostatic control for an essential metal. Toxicology and Applied Pharmacology 322 (2017)27-40.
- Ramoju, S.P., et al. The application of PBPK models in estimating human brain tissue manganese concentrations. NeuroToxicology 38 (2017) 226-237.

The Smith et al., 2018, noted above, also addresses the human PBPK models and their development.

Though noted in MIG's prior comments, the DEP is apparently unaware that the human PBPK models for manganese have also been applied in manganese risk assessment. The 2012 *Toxicological Profile for Manganese* prepared by the U.S. Department of Health and Human Services' Agency for Toxic Substances Disease Registry ("ATSDR") includes a very detailed assessment of the available PBPK models for manganese (pages 264-293) and ATSDR relied on the human neonatal and lactating PBPK model in its derivation of a "minimal risk level" for manganese (page A-6).

* * * * *

With these considerations in mind, MIG respectfully requests that the IRRC disapprove the rulemaking to enable the DEP to undertake additional assessment of the PBPK models before making a final determination on the water quality standard for manganese. As detailed in MIG's prior comments, consideration of the PBPK models demonstrates that the studies relied on by DEP to assert adverse impacts from low-level manganese exposure are not biologically plausible.

MIG appreciates the opportunity to provide comments to the IRRC on the rule. If you have any questions, please contact Joseph Green, counsel to MIG, at 202.342.8849 or JGreen@KelleyDrye.com.