Texas Commission on Environmental Quality (TCEQ) Responses to Public Comments Received on the November 2017 Proposed Manganese and Inorganic Manganese Compounds Development Support Document

The Development Support Document (DSD) for manganese and inorganic manganese compounds (except inorganic manganese compounds in the (VII) oxidation state such as permanganates) was proposed in August 2017. The International Manganese Institute Association and the Manganese Interest Group submitted comments on the proposed DSD. The TCEQ appreciates the effort put forth to provide comments on the proposed DSD for manganese. The goal of the Toxicology Division and TCEQ is to protect human health and welfare based on the most scientifically-defensible approaches possible (as documented in the DSD), and evaluation of these comments furthered that goal. Both commenters essentially provided the same substantive comments. These comments were very similar and therefore they were combined into sections and are provided below, followed by TCEQ responses.

Comment 1:

Manganese Interest Group (MIG):

First, MIG applauds the TCEQ's focus upon the most up-to-date scientific publications concerning manganese and, in particular, the TCEQ's reliance upon various studies that have applied validated, human physiologically-based pharmacokinetic models (PBPK) for manganese. As the TCEQ notes in the DS Document, the most recent PBPK derived science demonstrates that tissue manganese concentrations are not "linearly-related to ambient air concentration, particularly at lower air concentrations." To that end, Gentry et al., 2017 clearly shows that the maximum biologically plausible uncertainty factor that can be applied in the case of manganese is approximately 10. Application of a ten-fold uncertainty factor to derive the chronic ReV for manganese (rather than the 60-fold factor proposed by TCEQ) generates a chronic ReV of 5 $\mu g/m^3$. MIG respectfully requests that the TCEQ consider reducing the total uncertainty factor for derivation of the chronic ReV for manganese from 60 to 10.

International Manganese Institute (IMnI):

The International Manganese Institute (IMnI) wishes to express our gratitude for the excellent work by TCEQ to focus on the most up-to-date scientific publications concerning manganese and, in particular, TCEQ's reliance upon validated, human physiologically-based pharmacokinetic models (PBPK) for manganese. As such, we wish to highlight that tissue manganese concentrations are not "linearly-related to ambient air concentration, particularly at lower air concentrations" and that Gentry et al., 2017, clearly shows that the maximum biologically plausible uncertainty factor that can be applied in the case of manganese is approximately 10; thus, generating a chronic ReV of 5 $\mu g/m^3$. In this regard, the IMnI respectfully asks that TCEQ reduce the total uncertainty factor for derivation of the chronic ReV for manganese from 60 to 10.

TCEQ Response:

To be abundantly clear, for the key chronic analysis, the TCEQ did not use PBPK with tissue concentration as the exposure metric as these comments may be interpreted to imply. Rather, like ATSDR (2012), the TCEQ used benchmark dose modeling of incidence data for abnormal eye-hand coordination scores with air concentration as the exposure metric. Regardless, the comments' reference to a factor of 10 being "the maximum biologically plausible" is alluding to the point that as tissue concentrations approach those at background at lower manganese exposures, the application of progressively higher UFs become less effective at lowering predicted globus pallidus concentrations (e.g., see Table 4 of Gentry et al. 2017). The only UF that TCEQ applied which may be construed to concern biologically plausible differences in brain concentrations is the intrahuman UF (UF_H), for which a value of 10 was in fact used. Table 4 of Gentry et al. (2017) shows that applying a factor of 10 to a POD_{HEC} of approximately 50 µg/m^3, as was done in our assessment (UF_H of 10), is more effective at reducing the predicted globus pallidus concentration relative to higher factors (i.e., 100, 1000) for purposes of reducing the globus pallidus concentration (as it approaches background concentrations). Importantly, the referenced Gentry et al. (2017) results concern toxicokinetic considerations as opposed to database uncertainties (e.g., Table 4 of Gentry et al. 2017). The additional factor of 6 used in TCEQ's assessment is to account for database uncertainty (UF_D) and was not selected based on toxicokinetic/PBPK considerations or intended to result in a commensurate 6-fold decrease in brain manganese concentration as the comment seems to suggest. The UF_D of 6 was retained in the final DSD.

The TCEQ did use PBPK results to verify both the protectiveness and reasonableness of the key chronic analysis. Results from the Gentry et al. (2017) PBPK study suggest that at environmental air concentrations of respirable manganese similar to the chronic ReV and ESL (i.e., < 1 µg Mn/m^3), manganese concentrations in the brain (i.e., globus pallidus) would be similar to background (see Figure 8 and Tables 3 and 4 of the study). Likewise, the chronic ReV and ESL (0.84 and 0.25 µg Mn/m^3) are below continuous air concentrations predicted to increase brain concentrations in human fetuses (10 µg Mn/m^3) and nursing infants (1 µg Mn/m^3) (Yoon et al. 2011 as cited by ATSDR 2012). The same cannot be said for a chronic value of 5 µg Mn/m^3. Thus, as 1 µg Mn/m^3 is the estimated lower end, continuous daily exposure threshold for brain manganese accumulation and this value is very similar to the chronic ReV of 0.84 µg Mn/m^3, recent PBPK studies support the chronic ReV as health protective without being unduly conservative, regardless of the particular procedures employed in its derivation.

Comment 2:

MIG:

Second, the adoption of a chronic ReV for manganese of 5 µg/m^3 is not unprecedented. In 2011, the scientific importance of the human manganese PBPK models was also recognized as part of the Toxicology Excellence for Risk Assessment (TERA) /International Toxicity Estimates for Risk (ITER) peer review process. The purpose of the ITER database is to provide risk

assessors and managers with the latest human health risk values from organizations around the world. ITER includes chronic human health risk data from the Agency for Toxic Substances Disease Registry (ATSDR), Health Canada, the International Agency for Research on Cancer, the National Institute of Public Health and the Environment (RIVM) – The Netherlands, the U.S. Environmental Protection Agency (EPA), and independent parties whose risk values have undergone peer review. Because the peer-reviewed literature contains many more risk values that may be of value to risk practitioners, TERA developed a process to include these peer-reviewed, "literature-based" values on the ITER database.

The publication reviewed in the TERA/ITER peer review process in 2011 proposed a safe manganese reference value in the range of 2-7 $\mu g/m^3$. Following the standard TERA/ITER peer review process, the proposed RfC range was added to the ITER database. As reflected in the TERA/ITER meeting report, the reviewers relied upon the human PBPK models for manganese for much of the technical justification for the proposed manganese reference value range. As the peer reviewers ultimately noted, "[t]his proposed range of values is fairly different from values already loaded on ITER, but it uses the most recent epidemiology studies and PBPK models" and therefore "is likely to be valuable to the risk assessment community as well." For this reason as well, MIG respectfully recommends that TCEQ increase the chronic ReV for manganese to 5 $\mu g/m^3$.

IMnI:

IMnI would also like to emphasize that in 2011 the Toxicology Excellence for Risk Assessment (TERA) / International Toxicity Estimates for Risk (ITER) peer review process put forth a safe manganese reference value in the range 2-7 $\mu g/m^3$. ITER includes chronic human health risk data from the Agency for Toxic Substances Disease Registry (ATSDR), Health Canada, the International Agency for Research on Cancer, the National Institute of Public Health and the Environment (RIVM) - The Netherlands, the U.S. Environmental Protection Agency (EPA), and independent parties whose risk values have undergone peer review. Because the peer-reviewed literature contains many more risk values that may be of value to risk practitioners, TERA developed a process to include these peer-reviewed, "literature-based" values on the ITER database.

As with TCEQ, the TERA / ITER reviewers relied upon the human PBPK models for manganese for much of the technical justification for the proposed manganese reference value range and they subsequently noted, "This proposed range of values is fairly different from values already loaded on ITER, but it uses the most recent epidemiology studies and PBPK models" and therefore "is likely to be valuable to the risk assessment community as well." In addition to our statement above, IMnI respectfully recommends that TCEQ increase the chronic ReV for manganese to 5 $\mu g/m^3$.

TCEQ Response:

These comments do not provide justification for revising any particular portion of the TCEQ assessment based on superior scientific reasoning and/or defensibility. We acknowledge the utility of the ITER database, that values may differ between agencies (due to various factors),

and that the consideration of values from other agencies may be beneficial to risk assessors for a variety of reasons (e.g., greater context, to be better informed about the range of possible approaches and similarities/differences). As indicated above, for our chronic manganese assessment, the TCEQ used recent PBPK modeling results to support the chronic ReV (0.84 µg Mn/m^3) as health protective without being unduly conservative. We are confident in our chronic values as 1 µg Mn/m^3 is the estimated lower end, continuous daily exposure threshold for brain manganese accumulation considering various life stages. The same cannot be said for a chronic value of 5 µg Mn/m^3.

TEXAS
COMMISSION ON ENVIRONMENTAL QUALITY
Toxicology Division

Development Support Document for Manganese and Inorganic Manganese Compounds

(Proposed August 16, 2017)

Comments of the Manganese Interest Group (MIG)

November 16, 2017

Submitted Electronically to:
Texas Commission on Environmental Quality
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Comments of the Manganese Interest Group (MIG)

The Manganese Interest Group (MIG) [1] submits the following comments regarding the Texas Commission on Environmental Quality's ("TCEQ") proposed "Development Support Document" for Manganese and Inorganic Manganese Compounds (hereinafter "DS Document"). MIG very much appreciates the opportunity to provide comments on the TCEQ's proposed toxicity factor for manganese in air. MIG has two brief comments.

First, MIG applauds the TCEQ's focus upon the most up-to-date scientific publications concerning manganese and, in particular, the TCEQ's reliance upon various studies that have applied validated, human physiologically-based pharmacokinetic models (PBPK) for manganese. As the TCEQ notes in the DS Document, the most recent PBPK derived science demonstrates that tissue manganese concentrations are not "linearly-related to ambient air concentration, particularly at lower air concentrations." To that end, Gentry et al., 2017 clearly shows that the maximum biologically plausible uncertainty factor that can be applied in the case of manganese is approximately 10. Application of a ten-fold uncertainty factor to derive the chronic ReV for manganese (rather than the 60-fold factor proposed by TCEQ) generates a chronic ReV of 5 $\mu g/m^3$. MIG respectfully requests that the TCEQ consider reducing the total uncertainty factor for derivation of the chronic ReV for manganese from 60 to 10.

Second, the adoption of a chronic ReV for manganese of 5 $\mu g/m^3$ is not unprecedented. In 2011, the scientific importance of the human manganese PBPK models was also recognized as part of the Toxicology Excellence for Risk Assessment (TERA) /International Toxicity Estimates for Risk (ITER) peer review process. The purpose of the ITER database is to provide risk assessors and managers with the latest human health risk values from organizations around the world. ITER includes chronic human health risk data from the Agency for Toxic Substances Disease Registry (ATSDR), Health Canada, the International Agency for Research on Cancer, the National Institute of Public Health and the Environment (RIVM) – The Netherlands, the U.S. Environmental Protection Agency (EPA), *and independent parties whose risk values have undergone peer review*.[2] Because the peer-reviewed literature contains many more risk values that may be of value to

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1 MIG is an *ad hoc* coalition of trade associations and companies interested in the scientifically sound evaluation and regulation of manganese. Membership is comprised of steel producers, metalworkers, chemical manufacturers, ferroalloy producers, and other similar stakeholders, including: 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, Cliffs Natural Resources, Eramet Marietta, Inc., Felman Production, Inc., New Castle Stainless Plate LLC, Nucor Steel, and S.H. Bell Company.

2 The ITER database can be found at www.tera.org/iter/.

risk practitioners, TERA developed a process to include these peer-reviewed, "literature-based" values on the ITER database.[3]

The publication reviewed in the TERA/ITER peer review process in 2011 proposed a safe manganese reference value in the range of 2-7 μg/m^3.[4] Following the standard TERA/ITER peer review process, the proposed RfC range was added to the ITER database. As reflected in the TERA/ITER meeting report, the reviewers relied upon the human PBPK models for manganese for much of the technical justification for the proposed manganese reference value range.[5] As the peer reviewers ultimately noted, "[t]his proposed range of values is fairly different from values already loaded on ITER, but it uses the most recent epidemiology studies and PBPK models" and therefore "is likely to be valuable to the risk assessment community as well."[6] For this reason as well, MIG respectfully recommends that TCEQ increase the chronic ReV for manganese to 5 μg/m^3.

* * * * *

MIG appreciates the opportunity to submit these comments for consideration by TCEQ, and would be happy to provide further information or address any questions the Department may have about the appropriate risk threshold for manganese to use in the permitting process. Please contact Joseph Green, counsel to MIG, at 202.342.8849 or JGreen@KelleyDrye.com for further information.

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[3] In order to be considered for inclusion in ITER, "literature-based" values must meet the following criteria: (1) a manuscript that includes derivation of a risk assessment value has been published in a peer-reviewed journal; (2) the assessment follows an identified, commonly used methodology (*e.g.,* U.S. EPA, IPCS, Health Canada); and (3) the manuscript's acknowledgment clearly states the source of funding for the work, or the authors provide this source of funding at the review meeting for full disclosure to the panel on ITER.

[4] *See* Bailey, L.A., *et al*., "Proposal for a revised Reference Concentration (RfC) for manganese based on recent epidemiological studies," Regul. Toxicol. Pharmacol. 55: 330-339 (2009).

[5] *See* "Report of the ITER Review Meeting on Literature Risk Values for Manganese Oxide (June 29, 2011)(hereinafter "ITER Review Meeting Report"), pp. 13-18. A copy of the ITER Review Meeting Report is appended to these comments.

[6] *Id.*, p. 18.

International Manganese Institute
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November 16, 2017

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Comments of the International Manganese Institute (IMnI)

The International Manganese Institute (IMnI) wishes to express our gratitude for the excellent work by TCEQ to focus on the most up-to-date scientific publications concerning manganese and, in particular, TCEQ's reliance upon validated, human physiologically-based pharmacokinetic models (PBPK) for manganese. As such, we wish to highlight that tissue manganese concentrations are not "linearly-related to ambient air concentration, particularly at lower air concentrations" and that Gentry et al., 2017, clearly shows that the maximum biologically plausible uncertainty factor that can be applied in the case of manganese is approximately 10; thus, generating a chronic ReV of 5 $\mu g/m^3$.[1] In this regard, the IMnI respectfully asks that TCEQ reduce the total uncertainty factor for derivation of the chronic ReV for manganese from 60 to 10.

IMnI would also like to emphasize that in 2011 the Toxicology Excellence for Risk Assessment (TERA) / International Toxicity Estimates for Risk (ITER) peer review process put forth a safe manganese reference value in the range 2-7 $\mu g/m^3$.[2] ITER includes chronic human health risk data from the Agency for Toxic Substances Disease Registry (ATSDR), Health Canada, the International Agency for Research on Cancer, the National Institute of Public Health and the Environment (RIVM) – The Netherlands, the U.S. Environmental Protection Agency (EPA), *and independent parties whose risk values have undergone peer review*.[3] Because the peer-reviewed literature contains many more risk values that may be of value to risk practitioners, TERA developed a process to include these peer-reviewed, "literature-based" values on the ITER database.[4]

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1. 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. Toxicol. Appl. Pharmacol. 322, 27–40 (2017).

2. *See* Bailey, L.A., et al., "Proposal for a revised Reference Concentration (RfC) for manganese based on recent epidemiological studies," Regul. Toxicol. Pharmacol. 55: 330-339 (2009).

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As with TCEQ, the TERA / ITER reviewers relied upon the human PBPK models for manganese for much of the technical justification for the proposed manganese reference value range[5] and they subsequently noted, "This proposed range of values is fairly different from values already loaded on ITER, but it uses the most recent epidemiology studies and PBPK models" and therefore "is likely to be valuable to the risk assessment community as well."[6] In addition to our statement above, IMnI respectfully recommends that TCEQ increase the chronic ReV for manganese to 5 $\mu g/m^3$.

Sincerely,

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5 *See* "Report of the ITER Review Meeting on Literature Risk Values for Manganese Oxide (June 29, 2011) (hereinafter "ITER Review Meeting Report"), pp. 13-18. A copy of the ITER Review Meeting Report is appended to these comments.

6 *Id.*, p. 18.