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Severity scoring of manganese health effects for categorical regression

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ABSTRACT

Characterizing the U-shaped exposure response relationship for manganese (Mn) is necessary for estimating the risk of adverse health from Mn toxicity due to excess or deficiency. Categorical regression has emerged as a powerful tool for exposure-response analysis because of its ability to synthesize relevant information across multiple studies and species into a single integrated analysis of all relevant data. This paper documents the development of a database on Mn toxicity designed to support the application of categorical regression techniques. Specifically, we describe (i) the conduct of a systematic search of the literature on Mn toxicity to gather data appropriate for dose-response assessment; (ii) the establishment of inclusion/exclusion criteria for data to be included in the categorical regression modeling database; (iii) the development of a categorical severity scoring matrix for Mn health effects to permit the inclusion of diverse health outcomes in a single categorical regression analysis using the severity score as the outcome variable; and (iv) the convening of an international expert panel to both review the severity scoring matrix and assign severity scores to health outcomes observed in studies (including case reports, epidemiological investigations, and in vivo experimental studies) selected for inclusion in the categorical regression database. Exposure information including route, concentration, duration, health endpoint(s), and characteristics of the exposed population was abstracted from included studies and stored in a computerized manganese database (*MnDB*), providing a comprehensive repository of exposure-response information with the ability to support categorical regression modeling of oral exposure data.

1. Introduction

Manganese (Mn) is a naturally occurring element and an essential nutrient. Dietary intake of Mn is essential for maintaining a number of important physiological processes, including reproduction and development (e.g., formation of healthy cartilage and bone), energy metabolism (e.g., pyruvate carboxylase), urea cycle (e.g., arginase), and antioxidative capacity (e.g., Mn superoxide dismutase) (Chen et al., 2014). Mn also plays a key role in wound-healing (ATSDR, 2012). Mn is found in nutritional supplements and multivitamin preparations (Santos-Burgoa et al., 2001).

There is a large body of scientific literature on adverse health effects associated with excess or deficient levels of Mn. The toxicity of Mn due to excess or deficiency has been documented in diverse studies including case reports, epidemiological studies of occupational and environmental exposure to Mn, experimental studies in a range of animal models, and in vitro toxicity tests. Krewski et al. (2010) describe an approach to incorporation of data from a diverse

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collection of studies of this nature based on categorical regression of severity scores assigned to the different health outcomes seen in these studies; the utility of this approach was demonstrated by application to a database on copper toxicity, similar to the manganese database (*MnDB*) developed here. This copper database (*CuDB*) was subsequently analyzed by Chambers et al. (2010) to describe the U-shaped exposure response curve for Cu, which, like Mn, is an essential element. Further analyses of the *CuDB* were recently undertaken by Milton et al. (2016a), where they employed new approaches to categorical regression analysis of U-shaped exposure-response curves. In conducting this work, the available data on Cu toxicity due to both excess and deficiency was entered into a computerized database designed to accommodate the collection of information on continuous, dichotomous, categorical or ordinal data which supports both traditional as well as new methods for exposure-response assessment. Further motivation for the use of a systematic approach to the identification and recording of relevant data on Cu toxicity is to avoid unnecessary repetition of reviews of the same literature: without a validated toxicological data storage system, changing regulatory requirements, updating risk assessments, and employing new methods for exposure-response assessment would likely involve unnecessary re-reviews of the same body of literature (Guth and Raymond, 1996).

In the field of health risk assessment, the characterization of exposure-response relationships is important in estimating the risk of adverse health effects of essential elements from toxicity due to either excess or deficiency. Health risk scientists have not yet defined exposure-response curves that simultaneously characterize the risk associated with both Mn deficiency and excess. Historically, regulatory agencies have used benchmarks such as the no-observed-adverse-effects level (NOAEL), corresponding to the level of exposure that does not result in a significant increase in the risk of adverse effects in the exposed group when compared with controls: the NOAEL has served as a point of departure (PoD) on the exposure response curve for establishing a reference dose (RfD) for human exposure through the application of appropriate adjustment factors (Barnes and Dourson, 1988). These benchmarks are typically derived from a single key study that considers one critical effect and rely on weight of evidence assessment for relevant effect in humans and to a considerable extent on expert opinion. This led to differences in human exposure guidelines developed by different regulatory bodies (US EPA, 1993, 1994; Health Canada, 1994; ATSDR, 2000, 2012; WHO, 2000), including occupational exposure guidelines (Deveau et al., 2015). This is illustrated by the disparity of health-based limit values for inhalation of respirable Mn particulate in ambient air (ranging from 0.04 to 0.30 $\mu g/m^3$) derived from the same epidemiological study of battery workers exposed to MnO_2 dust (Roels et al., 1992).

More recently, exposure-response assessment methods have shifted towards more quantitative methods, with health risk assessors exploring more mathematically driven techniques such as the benchmark dose (BMD) (Crump, 1984), and signal-to-noise crossover dose (SNCD) (Sand et al., 2011). Nonetheless, the RfD, SNCD, and BMD approaches all ultimately rely on one critical health effect from a single key study.

Categorical regression addresses this limitation by allowing risk assessors to capture relevant health information across multiple studies and species, including a broad spectrum of health endpoints and exposure levels for exposure-response analysis in an objective and transparent manner. Furthermore, categorical regression also allows the inclusion of multiple independent variables, including level and duration of exposure, and variables that may modify the exposure-response relationship such as age and sex. For these reasons, categorical regression has been advocated as a promising tool to characterize health risk in a comprehensive manner, and has found successful initial application in exposure-response modeling (Gift et al., 2008; Allen et al., 2005; Chambers et al., 2010).

Ten years ago, the US EPA (2006) released a software program called *CatReg*, developed to perform categorical regression modeling and calculate a benchmark level called the extra risk concentration (ERC). Chambers et al. (2010) used *CatReg* to perform an exposure-response analysis on the copper database previously described, creating separate excess and deficiency exposure-response models for oral intake. The authors spliced the excess and deficiency curves together to create a U-Shaped curve, then estimated the exposure level at the trough of the curve. Other *CatReg* applications include hydrogen sulfide (Strickland and Foureman, 2002; Brown and Strickland, 2003; Brown and Foureman, 2005), phosgene (Gift et al., 2008), and acrylamide (Allen et al., 2005), where excess exposure-toxicity curves were fit to exposure-response data. Milton et al. (2016a) used the work by Chambers et al. (2010) as a platform to propose a new method for defining U-Shaped exposure-response curves based on categorical regression. The authors applied their methods to the copper (Cu) toxicity database and obtained a smooth, continuous U-Shaped exposure-response curve that achieves balance between Cu excess and deficiency. The authors identified two potential benchmark levels: the equiprobable crossover point (EPCP), which corresponds to the level of exposure where the risk of toxicity due to excess is equal to the risk of toxicity due to deficiency, and x_{MINDUE}, which corresponds to the level of exposure at the bottom of the U-shaped which minimizes the overall risk due to excess or deficiency (or both). The methodologies used to derive this U-shaped exposure-response curve and the estimation of these two new benchmarks for Mn are discussed in a companion paper (Milton et al., 2016b).

These new approaches to categorical regression modeling developed by Milton et al. (2016a) will be used in the manganese exposure-response assessment. The foundation of categorical regression modeling is the establishment of ordered response categories corresponding to increasingly severe adverse health outcomes and the availability of a comprehensive database which summarizes ordered response categories for manganese toxicity from deficiency or excess.

The purpose of this paper is to: 1) describe the development of the computerized Mn database (*MnDB*) to support the application of categorical regression of Mn toxicity due to excess and deficiency from oral studies; 2) to summarize the development of the severity scoring system for Mn toxicity; 3) to apply the severity scoring system to the scientific literature collected on Mn health effects; and 4) describe the characteristics of the final *MnDB* and its use in categorical regression (Fig. 1).

2. Methods

The development of the categorical regression database took place over the course of two years (2010–2012). Exclusion criteria were defined and relevant scientific publications were identified using a systematic literature search and reviewed to ensure the exclusion criteria were satisfied. A total of 181 eligible studies described in 218 articles were identified (Appendix A). Detailed information including animal species, route of exposure, Mn species, age, sex, study design, dose and duration of exposure, and health outcome was abstracted from these articles and stored in the database. If a study involved different exposure scenarios (e.g., different exposure routes and pathways, different doses and concentrations, different exposure durations, different Mn compounds and basal diets, animal species and strains, sex (male and female subjects)), data for each combination of these parameters were entered as a separate experiment. In total, the present version

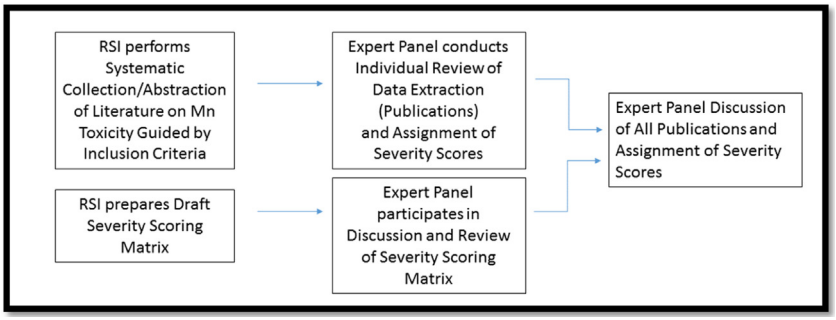

Fig. 1. Work flow diagram of the development and application of the severity scoring matrix to the MnDB.

of the *MnDB* includes data from 272 experiments. There are generally several dose levels within a single experiment, with a separate record created for each dose level. Some studies are described in more than one article: in this event, information from these articles was combined so as to avoid duplication in the *MnDB*.

Upon completion of the *MnDB*, a draft ordinal severity scoring matrix covering the spectrum of health outcomes in the *MnDB* was created. A three-day workshop was held at Risk Sciences International in Ottawa, Canada at the end of January 2013 with participation of experts in epidemiology, toxicology, medicine, veterinary sciences, and risk science. The expert panel was charged to review and modify the ordinal scale of severity scores and apply it to the health outcomes in the computerized database. The expert panel also modified and endorsed the study exclusion criteria specified below in Section 2.1.

2.1. Literature search and exclusion criteria

To develop a robust categorical regression database, it was important to first identify relevant scientific reports for inclusion in the database. To achieve this, the International Manganese Institute (IMnI) electronic library reference list as well as Ovid Medline/Embase and Toxline bibliographic databases were searched. Search terms are provided in Appendix B. No limits were applied to publication date; studies published as early as 1930 and as late as 2013 were included in the analysis. References of identified articles were also searched to identify further relevant publications. Case reports, epidemiological studies and in vivo experimental studies were considered as potentially eligible for inclusion.

The international expert panel also guided the modification of exclusion criteria. For example, it was suggested that studies with transgenic animals with altered metabolic profiles that might be of limited relevance to human health risk assessment be excluded from database until scientific data (e.g., PBPK modeling data) is available to compare dose metrics against conventional animal models. It was also suggested that these studies be retained as a separate group in the *MnDB* for possible use in categorical regression sensitivity analysis. Similarly, arguments for inclusion of metabolic/pharmacokinetic and in vitro studies could be made, as these studies may be useful in elaborating toxicity pathways for Mn. For example, in experiments in which neurotransmitters were evaluated, in vitro studies might be useful in determining severity level of the potential adverse outcomes. However, in the absence of formal criteria for incorporating information from pharmacokinetic and in vitro studies into the assignment of severity scores to support categorical regression, the use of such data was not considered in the present exercise.

The final exclusion criteria reflect the modifications and suggestions provided by the expert panel. The exclusion criteria are:

- exposure to organic manganese (Mn) compounds;
- inadequate information to characterize the dose and/or duration of exposure;
- the information could not be entirely attributed to the effects of manganese alone (due to the presence of possible confounding);
- the exposure route was not relevant for humans;
- exposure occurred in utero;
- exposure occurred by lactation;
- the animal model was not considered suitable for human health risk assessment (ruminant species, non-mammals)
- the study focussed on validation of potential exposure biomarkers (e.g. Mn in blood and urine);
- there was inadequate statistical reporting of data;
- the study focused on pharmacokinetic parameters, or Mn body burden;
- the study was conducted in an in vitro test system (which is difficult to extrapolate to human exposure-response);
- the article was a review rather than original research study.

Exclusion criterion (2) was further developed for application to epidemiologic studies, excluding studies with:

- no “external” measures of exposure (e.g. Mn in air), wherein only biomarkers were used as exposure metrics;
- data on exposure duration were not available;
- exposure estimates were based on modeling rather than measurement;
- it was unclear if the measurements of exposure reported total, inhalable or respirable Mn dust.

2.2. Characteristics of the database

The database was created in Microsoft Access and contains a wide collection of variables, ranging from qualitative inputs related to data abstraction/storage to quantitative inputs associated with exposure. The **identifier variable** is an ID automatically assigned to each record. The **identifier variable** also contains the first author’s last name, publication year, and the full reference. Note that a common study ID is assigned to all experiments within the same study. Characteristics of study subjects, such as **species, strain, sex**, and **life stage** at first exposure (e.g. newborn, weanling, adult, aged) appear in the database. Furthermore, the characteristics of exposure, namely, the **manganese compound, exposure route** (oral or inhalation), **exposure medium** (food, drinking water or gavage for oral exposure; dust or fume for inhalation exposure), **dose of Mn** (mg/kg bw/day or concentration of Mn in air ($\mu g/m^3$)), and **duration of exposure** in days also appear in the database.

Each outcome under investigation was described in a separate text field. An **ordinal severity score** was assigned to each outcome on the basis of a severity system described in the following section. Because neurotoxic effects are “critical” for Mn health risk assessment, each experiment in the database has an indicator of

whether or not this experiment contains at least one neurotoxicity-related outcome. The highest severity score associated with a neurotoxicity-related outcome at each dose level in each experiment was extracted into a separate field. While neurotoxic outcomes are of interest, *CatReg* modeling exercises could consider any and all health outcomes, not only neurotoxicity.

Following complete data abstraction from the scientific publications included in the database, the data was made available to the expert panel for their independent review and assignment of severity scores for each health endpoint measured and included in the database.

2.3. Development of severity scoring template

All relevant animal and human studies on Mn excess and deficiency were identified. Investigators at Risk Sciences International (RSI) with expertise in toxicology, epidemiology, medicine and risk science applied a systematic approach for the examination and differentiation of the reported Mn effects. Using a severity scoring system, these Mn effects were evaluated based on their relevance to humans and the type and magnitude of toxic effects to create a common measure of the physiological and/or pathophysiological response for application across all studies on Mn excess and deficiency. The overall approach for the development of the severity scoring matrix was guided by a similar original scoring exercise for Cu (Krewski et al., 2010; Chambers et al., 2010), with appropriate modifications based on the Mn-specific mechanism of toxicity and target organs. Changes in the Mn toxicokinetic parameters, biochemical and/or cellular changes involved in Mn toxicity pathways, changes in body/organ weight, organ/system impairment or histopathological changes, and reversibility or irreversibility of these changes were used for evaluation of the severity of effect. A severity scoring matrix was created ranging from low to high severity level (from level 0 to level 9 in the excess severity scoring template and from level 0 to level 8 in the deficiency severity scoring template) and was used to rank the severity of all observed effects in animals and humans according to the organ affected and biochemical effects and/or histopathological effects. For example, in the excess severity scoring template, the lower severity level (severity level 0) was associated with exposures with no observed changes compared to controls (effectively the no-observed-adverse-effect level, or NOAEL); severity level 1 corresponded to homeostatic changes in the observed effects of Mn; level 2 was associated with early adaptive systemic changes of unknown clinical significance; level 3 was associated with lowest-observed-adverse-effect level with biochemical and/or cellular changes involved in Mn toxicity pathways (the lowest-observed-adverse-effect-level, or LOAEL); and level 4 reflected a more severe adverse effect level associated with metabolic perturbations. Severity levels 5–9 represented increasingly severe adverse health outcomes. The highest severity levels 7, 8, and 9 were associated with reversible severe clinical signs of toxicity and histopathological changes, irreversible neurotoxic effects and histopathological changes, and death, respectively. The effects observed in animals and humans under conditions of Mn deficiency are different from the effects observed under Mn excess exposure due to a different mechanism of toxicity following inadequate levels of this essential element in the body. The most severe scores for deficiency, −6, −7 and −8 were associated with reversible clinical signs of deficiency and histopathological changes, irreversible histopathological changes and birth defects and death, respectively.

Table 1 presents the 9 severity categories under excess exposure and the 8 severity categories under deficiency exposure and the corresponding adverse health effects associated with each level of severity. As a result of this exercise, all outcomes reported in each single study were categorized and scored consistently across all severity levels. Experts' opinion was used to revise and refine the adopted approach, scoring matrix, and assigned scores to the endpoints extracted from studies on both Mn deficiency and excess to use in the exposure-response analysis.

The experts highlighted important issues in the consideration and interpretation of the severity of adverse health outcomes. Specifically, the need to distinguish between reversible and non-reversible effects for excess and deficiency, and between adverse and non-adverse observed outcomes was noted. It was also suggested that Mn accumulation in target organs (brain and lungs) versus non-target organs and tissues (blood, kidneys, urine) be considered, and that the applicability of histopathological considerations in case of the histological changes without reported statistical significance be evaluated. Consideration of the observed clinical signs as sufficient evidence of an adverse clinical effect, even without data on statistical significance, was also advised.

Advice on assigning severity scores was also provided: despite the fact that some effects were detected by histochemical methods with no statistical data, a severity score was could be assigned when the histopathological lesion demonstrates a direct impact upon target organs. The outcome of fetal death was considered to be equally severe as death, with a severity score 9 and −8. In the case of limited reporting of outcomes by the authors (i.e. lack of quantitative information), behaviour changes with signs of aggressiveness were assigned a severity score of 2 instead of 6. Where local adverse effects were observed it was recognized that they depend on the chemical form of Mn, pH, and exposure pattern (e.g. nasal histopathology in inhalation toxicity studies); in such instances, these portal of entry (local) effects were assigned a score 5. In studies where health effects were scored following a recovery period, severity scores 8 and −7 were assigned when no recovery was observed.

2.4. Dose conversions

Reporting of Mn exposure levels is not uniform across studies pertaining to oral exposure. In some studies, Mn dose was expressed in mg Mn per kg body weight per day, while in others only concentrations in water or food were reported. Because a common dose metric is required for use in categorical regression of multiple studies, all Mn exposures were expressed in mg/kg bw/day. Mn concentrations in food or water were converted into Mn doses based on body weight and food/water consumption. The dose conversions were done as follows:

$$\text{dose in mg/kg bw/day} = \frac{(\text{food intake in grams/day}) * [\text{Mn}]\text{in food in ppm or mg/kg diet})}{(\text{body weight in kg} * 1000)}$$

$$\text{dose in mg/kg bw/day} = \frac{(\text{water in take in mL/day}) * [\text{Mn}]\text{in water in mg/mL}) * 1000}{(\text{body weight in g})}$$

Concentrations of Mn in basal diet were converted to Mn doses using the same approach (US EPA, 2011). Many studies do not report Mn concentrations in basal diet; in such cases, Mn dose from the basal diet was assumed on the basis of existing data. The distribution of existing data on Mn doses from basal diet was examined visually for rats and mice, the two species with the greatest numbers of experiments in the database (Table 3). Due to

Table 1
The 18-point severity scoring matrix developed for application to the MnDB.

Direction of Effect	Severity Score	Description of Adverse Health Effect
Deficiency	**−8**	Death
	−7	Irreversible anatomic pathology
	−6	Clinical signs of deficiency, reversible anatomic pathology
	−5	Functional changes (e.g. alterations in reproductive, hepatic, renal or pancreatic function, changes in activity of pancreatic enzymes). Changes in bone density parameters
	−4	Metabolic perturbations. Changes in Fe, Cu, Zn tissue/biological fluids concentrations. Changes in bone metabolism (e.g. changes in activity of alkaline phosphatase) Changes in body or organ weight
	−3	Biochemical changes involved in pathways of manganese utilization reflecting the deficiency state (e.g. loss of Mn-dependent enzyme function). Decrease in tissue/biofluid Mn concentrations Changes comparable to those seen in category 3 excess
	−2	Changes of unknown clinical significance Changes in gene expression of Mn-dependent enzymes Changes comparable to those seen in category 2 excess
	−1	Decreased Mn excretion; increased gastrointestinal Mn absorption
No Effect	**0**	No Effect
Excess	**1**	Reduced gastrointestinal tract Mn absorption, increased Mn excretion, increase in liver and/or bile Mn concentrations
	2	Changes of unknown clinical significance Changes in gene or protein expression of transport proteins, antioxidant enzymes, neurotransmitter Changes in Mn concentrations in non-target organs/bio-fluids (e.g. kidney, blood, serum, urine) Changes in tissue Se and electrolyte concentrations (e.g. K, Mg, Na, Ca)
	3	Biochemical and/or cellular changes involved in manganese toxicity pathways Increased reactive oxygen species generation, decreased antioxidant enzyme activity Glial activation, increased levels of neuro-inflammatory markers Alteration in the level of neuro-transmitters Mitochondrial dysfunction, altered energy metabolism Increase in brain or lung (inhalation) Mn concentrations
	4	Metabolic perturbations Changes in Fe, Cu, Zn, tissue/biological fluids concentrations Decreased body weight; changes in organ weight Changes in responses to stimuli (e.g. amphetamine, cocaine, electroshock, immunological)
	5	Clinically significant functional changes (e.g. alterations in hepatic, renal, pulmonary, or reproductive function) Portal of entry (e.g. respiratory tract, gastrointestinal, dermal) anatomic pathology or related responses Neurological symptoms (e.g. mood changes, irritability)
	6	Adverse neurofunctional changes (electrophysiological, cognitive, and behavioral)
	7	Overt clinical signs of toxicity (e.g. tremors, seizures, ataxia)
	8	Irreversible anatomic pathology (e.g. neuronal death necrosis and apoptosis) Irreversible adverse neurological effects (e.g. “cock walk”)
	9	Death

Bold values are severity scores used to characterize adverse health effects.

Table 2
Assumptions on Mn in Basal Diet.

Species	Mean Dose (mg/kg bw)	Median Dose (mg/kg bw)	Source(s)	Assumptions
Rat	4.5	4	Calculated from *MnDB*	N/A
Mouse	11	10	Calculated from *MnDB*	N/A
Monkey	3.3	N/A	Schroeter et al. (2012) US EPA (1988)	80 ppm concentration in basal diet 8 kg body weight 330 g/day food intake
Rabbit	3	N/A	http://www.sdsdiets.com/pdfs/rabbit-standard.pdf	90 ppm concentration in basal diet 3.8 kg body weight 120 g/day food intake
Guinea Pig	5	N/A	US EPA (1988)	80 ppm Mn in basal diet 500 g body weight 32 g/day food intake

presence of outliers, the median basal diet Mn concentration is preferable to the mean concentration.

In experiments where data on Mn in the basal diet were unavailable, median doses of Mn from basal diet were assigned according to the values provided below in Table 2.

3. Results

Each observation in the database corresponds to a single dose level from each study, with the severity score(s) corresponding to the adverse health outcome(s) seen at that dose. For each data point, information is provided on the species, sex, age, route of exposure, animal strain, exposure level, and duration of exposure. The database incorporates information from eight different

Table 3
Demographic Characteristics of the MnDB.

Characteristic		Number of studies/ Number of dose groups
Species	*Rattus norvegicus* (rat)	251/658
	Mus musculus (mouse)	73/197
	Monkey[a]	15/33
	Homo sapiens (human)	22/47
	Sus scrofa domestica (domesticated pig)	4/8
	Oryctolagus cuniculus (domesticated rabbit)	10/26
	Mesocrictus auratus (Syrian hamster)	1/2
	Cavia porcellus (domesticated guinea pig)	2/4
Sex	Male	254/640
	Female	72/201
	Both sexes	30/85
	Unknown	22/48
Exposure route	Oral	323/827
	Drinking water	87/198
	Food	138/369
	Gavage	94/253
	Tablet or capsule	4/8
	Inhalation	55/147
Type of study	Experimental	367/954
	Observational	11/20

[a] Rhesus (*Macaca mulatta*), cynomolgus (*Macaca fascicularis*), and squirrel monkeys (*Saimiri scuireus*) were coded as one species (monkey) in the database.

species, males and females of all ages, inhalation and oral exposure routes, as well as experimental and observational studies, providing a comprehensive repository of information for exposure-response assessment.

3.1. Distribution of study characteristics in the MnDB

Table 3 presents the characteristics of these studies by species, sex, exposure route, and study type. The data summarized in this table provides the raw data needed for categorical regression analysis.

Table 3demonstrates the vast majority of studies included in the database were performed on rodents, with males, and via the oral route of exposure. Studies on humans tend to focus on marginal to moderate effects due to both Mn deficiency and excess. In contrast, animal studies tend to focus primarily on more severe effects, with the objective of defining a broad continuum of toxicity. At this time, human data are limited, and may be inadequate for the application of categorical regression, with convergence issues due to complete separation or quasi-separation (Allison, 2004) likely to be encountered as artifacts of a small data set. Complete separation occurs when there is one exposure level, *C*, that perfectly separates the data. In this case, one can ascertain that for exposure levels less than *C*, Y = 0, and for exposure levels greater than *C*, Y = 1. Quasi-separation occurs when exposure level *C* yields Y = 0 and Y = 1; this often occurs when exposure-response data from different studies are combined. As a consequence, human and animal data will likely need to be combined when conducting categorical regression analysis. The *CatReg* software permits model parameters to be stratified by animal species: a categorical regression model can be parametrized so that human data are used to estimate the intercept, while animal data are used to characterize the slope (Haber et al., 2001).

3.2. Distribution of severity scores for oral exposure data

The common response scale was applied to the *MnDB*. In the data abstraction stage, the group size from each experiment was also recorded. In determining the distribution of severity scores, the group level entries were converted to individual level entries, and their distributions are presented above in Table 4, which highlights the extensive data available for excess exposures. By comparison, the information available for deficiency exposure is much more limited. Within the database, it is clear the number of studies on excess exposures to Mn is far greater than the number of studies on deficiency. This reflects the information currently available in the scientific literature, and corresponds to the greater regulatory concern about Mn excess than Mn deficiency.

Table 4
Distribution of severity scores based on oral exposure data in the MnDB.

Excess or Deficiency	Severity Score	Species								
		Humans	*Monkeys*	*Rats*	*Mice*	*Hamsters*	*Guinea Pigs*	*Rabbits*	*Pigs*	Total
Deficiency	−8	0	0	0	0	0	0	0	0	0
	−7	0	0	22	0	0	0	34	26	82
	−6	0	0	8	12	0	0	0	0	20
	−5	0	0	36	0	0	0	0	6	42
	−4	0	0	163	14	0	0	0	0	177
	−3	0	0	217	0	0	0	0	0	217
	−2	0	0	36	0	0	0	0	0	36
	−1	4	0	16	0	0	0	0	0	20
No effect	0	71	16	3382	1112	16	31	116	32	4776
Excess	1	0	0	18	0	0	0	0	0	18
	2	34	0	353	173	0	12	32	0	604
	3	26	0	555	86	0	0	0	16	683
	4	0	4	618	230	0	0	0	0	852
	5	0	0	53	14	0	0	0	0	67
	6	0	16	470	75	0	0	0	0	561
	7	0	0	39	354	0	0	0	0	393
	8	0	4	31	34	0	0	0	0	69
	9	0	0	96	0	0	0	0	0	96
Total		135	36	6113	2104	16	43	182	80	8713

4. Discussion

An important contribution of this work was the development of an 18-point severity scoring matrix designed to standardize health endpoints onto a common scale for the application of categorical regression. This matrix can be adopted as a general template for all metals. Since all metals exhibit different toxicological properties, this general template could be modified to accommodate the characteristics of the metal under study, providing a stepping stone to begin to look at essential elements known to exhibit both health benefits and health risks that may be balanced using categorical regression modeling techniques.

The *MnDB* offers the largest, most current library of data abstracted from relevant Mn studies for exposure-response assessment. The database has proven effective as an organizational tool to synthesize information abstracted from scientific articles. A review of the database reveals considerable diversity among the available studies with regards to species, route of exposure, sex, and age, indicating stratification is an essential aspect in the categorical regression analysis. The database is also useful for identifying gaps in the literature, such as the limited amount of data on Mn toxicity due to deficiency. Future directions for this work include more accurate exposure characterization; one such example is developing biomarkers which can be used to quantitate exposure. As additional information on Mn toxicity due to deficiency accrues in the future, a more complete description of the U-shaped dose response curve for Mn as an essential element demonstrating toxicity due to both excess and deficiency may be possible.

Conflict of interest

None.

Transparency document

The Transparency document associated with this article can be found in the online version.

Appendix A. List of Eligible Articles

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Appendix B. Bibliographical databases searched and search terms

- IMnI electronic library reference list
- Ovid Medline/Embase and Toxline databases
- Ref erence lists of identified articles

Ovid MEDLINE/EMBASE search terms

1) *manganese[1]
2) (manganese adj2 deficiency).ti,de,ab.

TOXLINE search terms

1) Exposure term "manganese" was combined using AND/OR operators with the following terms for health effects:

lung[*1]; pulmonary; fibrosis; asthma; FEV1; bronchi*; alveoli; respiratory; cough; wheeze; rhinitis; sputum; granuloma*; inflammat*; irritation; mutagen*; genotoxic*; mutation; chromosome near/1 aberration[*1]; micronuclei; cancer; neoplasm[*1]; carcinogen*; carcinoma; dermal; skin; contact near/1 dermatitis; hyperreactivity; allergy; hives; immunity; immune; GPMT; sensitization; teratogen*; reproduction; "reproductive toxicity"; toxic*; fertility; ovary; pregnancy; placenta; testes; sperm*; gonad*; prolactin; hormone[*1]; foetus; foetus; neonatal; neonate[*1]; newborn[*1]; infant[*1]; child*; offspring; neurodevelopment*; behaviour*; neurobehavior*; hyperactivity; lactation*; breastfeed*; kidney[*1]; blood; haemotoxic*; hemotoxic*; anaemia; anaemia; bone; skeletal; skeleton; osteoporosis; liver; hepatotoxic*; nephrotoxic*; cardiotox*; heart; endocrine; cytotox*; neurotoxic*; brain; spinal near/1 cord; Parkinson*; tremor*; neuromotor; bradykinesia; cognitive; cognition; intellect*; dementia; memory; learning; neuropathy; biomonitoring; biological near/1 monitoring; absorption; distribution; metabolism; biotransformation; excretion; accumulation; bioavailability; iron

2) Manganese near/2 deficiency.

[1] "In databases with a controlled vocabulary this command focuses the term entered on the command line" (see http://www.ovid.com/site/help/documentation/ospa/en/syntax.htm#operators).

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