Farrell et al.:

The Use of Categorical Regression in the Assessment of the Risks of Nutrient Deficiency and Excess

Supplementary Data

Application of JMED to manganese risk assessment

Milton et al. (2017) also applied the JMED/IM approach to a comprehensive manganese toxicity database developed by Mattison et al. (2016) using the 18-point severity scoring matrix of deficient and excess exposure to manganese presented in Table S1. The manganese database contained information on a large collection of studies on this substance that used a variety of reporting methods. The information included data on dose level, duration, species, age, sex, and severity of health outcomes from each experiment.

Tab. S1: Eighteen-point severity scoring matrix developed for the Mn toxicity database

Effect	Score (S)	Description of Adverse Health Outcomes
Deficiency	-8	Death (including fetal death).
	-7	Irreversible anatomic pathology, birth defects.
	-6	Clinical signs of deficiency, reversible anatomic pathology.
	-5	Functional changes; changes in bone density parameters.
	-4	Metabolic perturbations; changes in Fe, Cu, Zn tissue/biological fluids concentration; changes in bone metabolism; changes in body/organ weight.
	-3	Biochemical changes involved in pathways of manganese utilization reflecting the deficiency state; decrease in tissue/biofluid Mn concentrations.
	-2	Changes of unknown clinical significance; changes in gene expression of Mn-dependent enzymes; changes comparable to those seen in severity category 2 excess.
	-1	Decreased Mn excretion; increased gastrointestinal Mn absorption.
Homeostasis	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; changes in Mn concentrations in non-target organs/bio-fluids; changes in clinical chemistry or hematological endpoints.
	3	Biochemical and/or cellular changes involved in manganese toxicity pathways; alteration in the levels of neurotransmitters; mitochondrial dysfunction, altered energy metabolism; increase in brain or lung (inhalation) Mn concentrations.
	4	Metabolic perturbations; decreased body weight; changes in organ weight; changes in responses to stimuli.
	5	Clinically significant functional changes; portal of entry anatomic pathology or related responses; neurological symptoms.
	6	Adverse neurofunctional changes (electrophysiological, cognitive and behavioral).
	7	Overt clinical signs of toxicity (e.g., tremors, seizures, ataxia); reversible anatomic pathology changes.
	8	Irreversible anatomic pathology, such as neuronal death (necrosis and apoptosis); Irreversible adverse neurological effects (e.g. “cock walk”)
	9	Death

The severity categories in Table S1 that range from -8 (most severe deficiency) to 9 (most severe excess) were developed by an international panel of investigators with expertise in toxicology, epidemiology, medicine and biostatistics. For simplicity, Milton et al (2017b) dichotomized the 18-point severity scoring system using the absolute value of two as a cut-off point between homeostatic and adverse responses in their analysis. Specifically, letting S_i denote the severity of the response for the i-th subject (or group of subjects, if grouped data is used), $S_i < -2$ or if $S_i > 2$ for the i-th subject was taken to reflect an adverse response (deficiency or excess), while $-2 \leq S_i \leq 2$ was interpreted as a homeostatic outcome.

In the absence of adequate human data for modeling purposes, the JMED/IM analysis was restricted to data from rats. The resulting nonsymmetric joint curve displaying the likelihood of an adverse event for a given dietary manganese intake is presented in Figure S1. The minimum joint probability of an adverse event, denoted $x_{\mathrm{MIN}\,DUE}$, occurs at a daily oral manganese intake of 2.7 mg/kg-bw/day. A 95% bootstrap confidence interval for $x_{\mathrm{MIN}\,DUE}$ is from 2.15 to 3.02 mg/kg-bw/day.

doi:10.14573/altex.2012022s

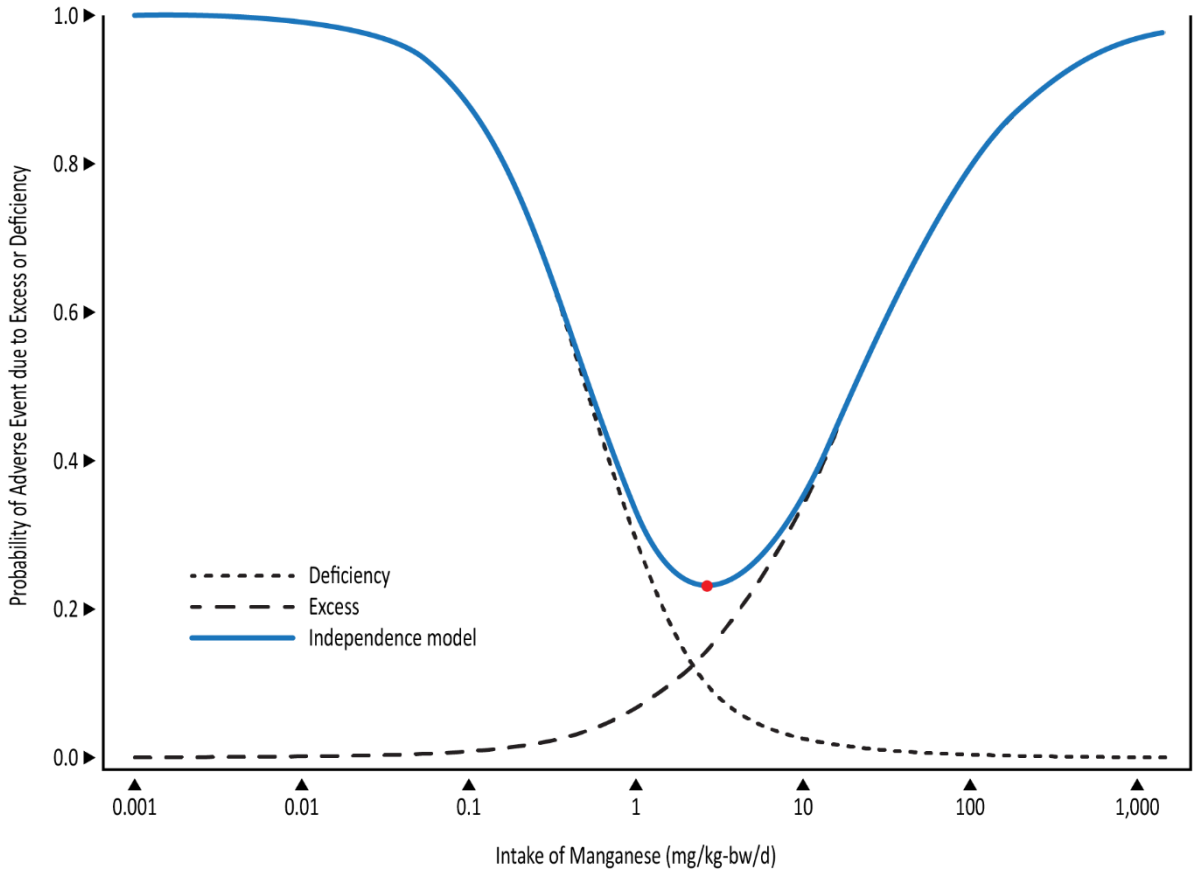

Fig. S1: U-shaped exposure-response curve for manganese based on categorical regression
A nonsymmetric U-shaped exposure-response curve for manganese exposure-response assessment for rats from the JMED and IM models. The underlying JMED curves are shown as dashed black lines. The concentration associated with the red dot gives the value of $x_{\mathrm{MIN}\,DUE}$, the estimated optimal manganese intake for rats (mg/kg-bw/day).

References

Mattison, D., Milton, B., Krewski, D. et al. (2016). Severity scoring of manganese health effects for categorical regression. *Neurotoxicology* 58, 203-216. doi:10.1016/j.neuro.2016.09.001

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