1. Introduction

The primary purpose of this Interaction Profile for lead, manganese, zinc, and copper is to evaluate data on the toxicology of the “whole” mixture and the joint toxic action of the chemicals in the mixture in order to recommend approaches for assessing the potential hazard of this mixture to public health. To this end, the profile evaluates the whole mixture data (if available), focusing on the identification of health effects of concern, adequacy of the data as the basis for a mixture MRL, and adequacy and relevance of physiologically-based pharmacokinetic/pharmacodynamic models for the mixture. The profile also evaluates the evidence for joint toxic action-additivity and interactions-among the mixture components. A weight-of-evidence approach is commonly used in these profiles to evaluate the influence of interactions in the overall toxicity of the mixture. The weight-of-evidence evaluations are qualitative in nature, although ATSDR recognizes that observations of toxicological interactions depend greatly on exposure doses and that some interactions appear to have thresholds. Thus, the interactions are evaluated in a qualitative manner to provide a sense of what influence the interactions may have when they do occur. The profile provides environmental health scientists with ATSDR DT’s recommended approaches for the incorporation of the whole mixture data or the concerns for additivity and interactions into an assessment of the potential hazard of this mixture to public health. These approaches can then be used with specific exposure data from hazardous waste sites or other exposure scenarios.

The lead, manganese, zinc, and copper mixture was chosen as the subject for this interaction profile based on an analysis of the most frequently occurring binary mixtures in completed exposure pathways at hazardous waste sites. These metals are commonly found in soil. The primary route of exposure for this mixture is likely to be oral and the durations of concern are intermediate and particularly chronic. The term “metals” is used in this profile for brevity and convenience, and is intended to refer to lead, manganese, zinc, and copper in inorganic compounds or as ions.

Before evaluating the relevance of interactions data for these chemicals, some understanding of the endpoints of concern for oral exposure to this mixture is needed. The endpoints of concern include the critical effects that are the bases for MRLs and other sensitive effects of these metals, and also endpoints in common that may become significant due to additivity or interactions. No MRLs have been derived for lead (Pb) (ATSDR 1999). The critical effect for lead is neurological, particularly in infants and children. Although no MRLs have been derived for lead, the Centers for Disease Control (CDC 1991) has defined a level of concern for lead exposure in children in terms of a blood lead concentration (PbB) of 10 μg/dL, and ATSDR (1999) suggests the use of media-specific slope factors and site-specific environmental monitoring data to predict media-specific contributions to PbB. The critical effect for manganese is neurological. ATSDR (2000) has not derived oral MRLs for manganese (Mn) because no clear threshold level for neurological effects could be determined from the acute and intermediate duration data, and because no firm conclusions were considered possible regarding a critical effect level of chronic intake versus essential dietary levels of manganese. ATSDR (2000) derived a provisional guidance value for total dietary intake of 0.07 mg Mn/kg/day, based on the upper end of the estimated safe and adequate daily dietary intake (ESADDI) range (5 mg/day, divided by 70 kg, the weight of an average adult), to be used in ATSDR human health assessments. ATSDR (1994) derived an intermediate oral MRL of 0.3 mg/kg/day for zinc (Zn) based on hematological effects (decreased hematocrit, serum ferritin, and erythrocyte superoxide dismutase activity) in humans. The hematological effects may be related to disruption of the copper balance. The intermediate oral MRL was adopted as the chronic oral MRL for zinc due to the lack of adequate chronic studies. ATSDR did not derive oral MRLs for copper (Cu) because of the lack of human data, lack of no-observed-adverse-effects level (NOAEL) values in the animal studies, development of tolerance in rats, and because of the essentiality of copper. Nor did ATSDR (1990) suggest a suitable guidance value in this relatively early toxicological profile. If an approach analogous to that for manganese were taken, i.e., to adopt the upper end of the National Research Council (NRC 1989) ESADDI range for copper (3 mg/day for adults, divided by 70 kg, the weight of an adult) as a guidance value for total dietary intake for copper, the resulting value would be 0.04 mg/kg/day. More recently, a Recommended Dietary Allowance (RDA) has been estimated at 0.9 mg/day (≈0.013 mg/kg/day) (Institute of Medicine 2001: prepublication document, final version not published as of December 2001). The critical effect for overexposure to copper was considered to be liver damage, and a tolerable upper intake level (UL) of 10 mg/day (≈0.14 mg/kg/day) of copper was established for adults (≥19 years old). This value, once available in the final published document, may be appropriate as a provisional guidance value.

The bases for the MRLs or guidance value (or health assessment approach in the case of lead), as well as other sensitive effects, are summarized in Table 1. No pertinent studies of the toxicity or interactions of the quaternary mixture were located. Studies of one trinary mixture (lead, zinc, and copper) were located but limitations in study design and relevance of the studied endpoints limit the conclusions that can be drawn. The bulk of the available interactions information is for binary mixtures of these metals. Table 2 summarizes the availability of pertinent data on joint toxic action data by endpoint for the binary mixtures. The table serves as an overview, and shows some data gaps: no relevant studies of joint toxic action for manganese and zinc or for manganese and copper. The lead-zinc mixture has been studied the most extensively.

Table 1. Potential Health Effects of Concern for Intermediate and Chronic Oral Exposure to the Mixture Lead, Manganese, Zinc, and Copper[a]

Lead	Manganese	Zinc	Copper
Neurological Hematological Cardiovascular	**Neurological**	**Hematological**	**Hepatic** Gastrointestinal[b]

[a]The basis for the MRL or health assessment approach is bolded; other sensitive effects are listed in regular typeface.
[b]Particularly for acute exposure to copper in drinking water

Table 2. Availability of Pertinent Joint Toxic Action Data for Pairs of Components

Endpoint	Lead-Manganese	Lead-Zinc	Lead-Copper	Manganese-Zinc	Manganese-Copper	Zinc-Copper
Cardiovascular						
Hematological	X	X	X			
Hepatic			X			X
Renal		X				
Immunological						X
Reproductive (testicular)		X				
Neurological	X	X	X			

X = Some data are available

Potential neurological effects are a particular concern for this mixture. Lead produces neurobehavioral effects in young children (ATSDR 1999), and manganese has the potential to do so, because infants absorb or retain a greater proportion of oral manganese than do adults, and the manganese in breast milk may be more bioavailable than manganese in foods consumed by other age groups (ATSDR 2000). For this reason, the order of discussion of the toxicities of the individual metals and of the binary mixtures starts with lead and manganese.