

**INTERACTION PROFILE FOR:
LEAD, MANGANESE, ZINC, AND COPPER**

**U.S. Department of Health and Human Services
Public Health Service
Agency for Toxic Substances and Disease Registry**

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PREFACE

The Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA) mandates that the Agency for Toxic Substances and Disease Registry (ATSDR) shall assess whether adequate information on health effects is available for the priority hazardous substances. Where such information is not available or under development, ATSDR shall, in cooperation with the National Toxicology Program, initiate a program of research to determine these health effects. The Act further directs that where feasible, ATSDR shall develop methods to determine the health effects of substances in combination with other substances with which they are commonly found. The Food Quality Protection Act (FQPA) of 1996 requires that factors to be considered in establishing, modifying, or revoking tolerances for pesticide chemical residues shall include the available information concerning the cumulative effects of substances that have a common mechanism of toxicity, and combined exposure levels to the substance and other related substances. The FQPA requires that the Administrator of the Environmental Protection Agency (EPA) consult with the Secretary of the Department of Health and Human Services (which includes ATSDR) in implementing some of the provisions of the act.

To carry out these legislative mandates, ATSDR's Division of Toxicology (DT) has developed and coordinated a mixtures program that includes trend analysis to identify the mixtures most often found in environmental media, *in vivo* and *in vitro* toxicological testing of mixtures, quantitative modeling of joint action, and methodological development for assessment of joint toxicity. These efforts are interrelated. For example, the trend analysis suggests mixtures of concern for which assessments need to be conducted. If data are not available, further research is recommended. The data thus generated often contribute to the design, calibration or validation of the methodology. This pragmatic approach allows identification of pertinent issues and their resolution as well as enhancement of our understanding of the mechanisms of joint toxic action. All the information obtained is thus used to enhance existing or developing methods to assess the joint toxic action of environmental chemicals. Over a number of years, ATSDR scientists in collaboration with mixtures risk assessors and laboratory scientists have developed approaches for the assessment of the joint toxic action of chemical mixtures. As part of the mixtures program a series of documents, Interaction Profiles, are being developed for certain priority mixtures that are of special concern to ATSDR.

The purpose of an Interaction Profile is to evaluate data on the toxicology of the "whole" priority mixture (if available) and on the joint toxic action of the chemicals in the mixture in order to recommend approaches for the exposure-based assessment of the potential hazard to public health. Joint toxic action includes additivity and interactions. A weight-of-evidence approach is commonly used in these documents 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.

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PEER REVIEW

A peer review panel was assembled for this profile. The panel consisted of the following members:

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All reviewers were selected in conformity with the conditions for peer review specified in Section 104(I)(13) of the Comprehensive Environmental Response, Compensation, and Liability Act, as amended.

Scientists from the Agency for Toxic Substances and Disease Registry (ATSDR) have reviewed the peer reviewers' comments and determined which comments will be included in the profile. A listing of the peer reviewers' comments not incorporated in the profile, with a brief explanation of the rationale for their exclusion, exists as part of the administrative record for this compound. A list of databases reviewed and a list of unpublished documents cited are also included in the administrative record.

The citation of the peer review panel should not be understood to imply its approval of the profile's final content. The responsibility for the content of this profile lies with the ATSDR.

SUMMARY

Lead, manganese, zinc, and copper were chosen as the subject mixture 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. Because no pertinent health effects data or physiologically based pharmacokinetic (PBPK) models were located for the quaternary mixture, exposure-based assessment of health hazards for this mixture depends on an evaluation of the health effects data for the individual metals and on the joint toxic action and mechanistic data for various combinations of these metals. This profile discusses and evaluates the evidence for joint toxic action among lead, manganese, zinc, and copper, and recommends how to incorporate concerns regarding possible interactions or additivity into public health assessments of sites where people may be exposed to mixtures of these chemicals.

Although occupational and environmental exposure studies of the trinary mixture of lead, zinc, and copper are available, they are not adequate as the basis for conclusions regarding the toxicity of this mixture due to inconsistencies in results across studies by a single group of investigators and deficiencies in study design. In general, the effects in workers coexposed to lead, zinc, and copper were characteristic of lead toxicity. Whether the coexposure to zinc and copper provided partial protection against these effects cannot be determined from the data. In animals exposed environmentally to lead, zinc, and copper (and cadmium), high bone burdens of lead and low tissue levels of copper were seen, in comparison with unexposed animals. The decreased copper in the tissues may reflect zinc inhibition of copper absorption, but again, no clear conclusions can be drawn from this study.

Most of the data regarding joint toxic action of the components of this mixture are for binary combinations of these metals. Data for the lead-zinc mixture are extensive, and for the lead-manganese, lead-copper, and zinc-copper mixtures are adequate to support some conclusions regarding the mode of joint toxic action. Many of these studies are reasonably relevant because they employed intermediate oral exposure, and investigated endpoints relevant to the critical and sensitive effects of the mixture components. Data for the manganese-zinc and manganese-copper mixtures, however, are inadequate. Based on these data, and on mechanistic data for the individual components, the predicted directions of interaction for the binary mixtures were primarily less than additive or additive, with exception of the

effects of manganese on the toxicity of lead, which were predicted to be greater than additive. Further discussion of the predicted interactions is presented later in this section.

Because no adequate studies or PBPK models for the whole mixture are available, a components-based approach to the exposure-based assessment of the potential hazard to the public is recommended in this profile, consistent with ATSDR (2001a) guidance. The effects of concern for the mixture include the critical effects of the individual components, and effects in common that may become significant due to additivity or interactions. The critical effects of two of the mixture components, lead and manganese, are neurological. The critical effects of zinc are hematological, which is also a sensitive effect of lead. The recommended approach is to estimate endpoint-specific hazard indexes for the neurotoxicity of lead and manganese and for the hematotoxicity of lead and zinc in order to screen for noncancer health hazards from potential additivity. The qualitative weight-of-evidence (WOE) is applied to assess the potential impact of interactions of the mixture components on the neurological and hematological hazard. The critical effect of copper is hepatic. The recommended approach is to use the hazard quotient for copper, with application of the qualitative WOE to assess the potential impact of the other metals on the hepatic toxicity of copper. If an endpoint-specific hazard index or if the hazard quotient for copper is greater than unity, and/or if the qualitative WOE indicates that joint toxic action may be greater than additive, further evaluation is needed (ATSDR 2001a), using biomedical judgment and community-specific health outcome data, and taking into account community health concerns (ATSDR 1992).

Estimation of endpoint-specific hazard indexes and application of the WOE are appropriate when hazard quotients for two or more of the mixture components equal or exceed 0.1 (ATSDR 2001a). If only one or if none of the mixture components has a hazard quotient that equals or exceeds 0.1, further assessment of the joint toxic action is not needed because additivity and/or interactions are unlikely to result in significant health hazard. Appropriate health guidance values for use in estimating hazard quotients and hazard indexes are summarized (Minimal Risk Levels [MRLs]) or derived (target-organ toxicity doses [TTDs]) in this profile.

The WOE method was used to prepare binary weight-of-evidence determinations (BINWOEs) for the binary mixtures (ATSDR 2001a, 2001b). The BINWOEs are predictions of the plausible direction of interactions, when they occur, and the degree of confidence in the prediction (indicated by a numerical score). The BINWOEs are used qualitatively to estimate the impact of interactions on the endpoint-specific hazard indexes for neurological and for hematological effects, and on the unique hazard quotient

for hepatic effects of copper. The BINWOE scores, when summed to give a combined WOE score, provide an overall indication of direction of interaction and confidence.

Neurological: The predicted direction of joint toxic action for neurological effects, an endpoint common to two components, is greater than additive for the effect of manganese on lead, less than additive for the effects of zinc and copper on lead, additive (no effect) for the effect of lead on manganese, and indeterminate for the effects of zinc and copper on manganese. The WOE score indicates that the potential health hazard may be less than estimated by the endpoint-specific hazard index for neurological effects, particularly for waste sites with relatively high hazard quotients for lead, copper, and zinc, and a lower hazard quotient for manganese. The indeterminate ratings for two of the BINWOEs (zinc and copper on manganese) are a source of uncertainty in assessments where manganese accounts for a great portion of the apparent neurological hazard.

Hematological: The potential health hazard for hematological effects is likely to be lower than indicated by the endpoint-specific hazard index for mixtures where lead, zinc, and copper predominate, because three of the BINWOEs for combinations of these metals were less than additive with moderate to high confidence, and the remaining one was additive. The BINWOE for manganese on lead was greater than additive with low-moderate confidence, for lead on manganese was additive, and for manganese on zinc was indeterminate. The WOE score indicates that the potential health hazard may be less than estimated by the endpoint-specific hazard index for hematological effects. The indeterminate BINWOE for manganese on zinc is a source of uncertainty.

Hepatic: The predicted effects of the other mixture components on the hepatic toxicity of copper are less than additive for zinc with high-moderate confidence, additive for lead, and indeterminate for manganese. Thus, the available data indicate the potential health hazard for hepatic effects may be less than predicted by the hazard quotient for mixtures where zinc and copper predominate. There is uncertainty with regard to the potential effect of manganese due to the lack of pertinent information.

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LIST OF ACRONYMS, ABBREVIATIONS, AND SYMBOLS

ACGIH	American Conference of Governmental Industrial Hygienists	mg	milligram
ALA	delta-aminolevulinic acid	Mn	manganese
ALAD	delta-aminolevulinic acid dehydratase	MRL	Minimal Risk Level
ALAS	delta-aminolevulinic acid synthetase	NIH	National Institutes of Health
ATPase	adenosine triphosphatase	NMDA	N-methyl-D-aspartate
ATSDR	Agency for Toxic Substances and Disease Registry	NOAEL	no-observed-adverse-effect level
		NRC	National Research Council
		NTP	National Toxicology Program
BINWOE	binary weight-of-evidence		
BMD	benchmark dose	Pb	lead
BMDL ₁₀	benchmark dose, increased risk of 10%	PbB	blood lead concentration
		PBPK	physiologically based pharmacokinetic
CDC	Centers for Disease Control	PBPK/PD	physiologically-based pharmacokinetic pharmacodynamic
CERCLA	Comprehensive Environmental Response, Compensation, and Recovery Act	ppm	parts per million
CI	confidence interval	RDA	Recommended Dietary Allowance
Cu	copper	RfC	reference concentration
		RfD	reference dose
dL	deciliter	RNA	ribonucleic acid
DNA	deoxyribonucleic acid		
DT	Division of Toxicology	SGOT	serum glutamic-oxaloacetic transaminase
EDTA	calcium disodium ethylenediamine		
EPA	Environmental Protection Agency	TLV	threshold limit value
ESADDI	estimated safe and adequate daily dietary intake	TTD	target-organ toxicity dose
		μg	microgram
FDA	Food and Drug Administration	UL	tolerable upper intake level
FEP	free erythrocyte protoporphyrin	μmole	micromole
FQPA	Food Quality Protection Act	U.S.	United States
GABA	gamma-aminobutyric acid	WOE	weight-of-evidence
GOT	glutamic-oxaloacetic transaminase		
		Zn	Zinc
HDL	high density lipoprotein	ZPP	zinc protoporphyrin
IARC	International Agency for Research on Cancer	>	greater than
IEUBK	Integrated Exposure Uptake Biokinetic	≥	greater than or equal to
		=	equal to
		≈	approximately equal to
i.p.	intraperitoneal	<	less than
IRIS	Integrated Risk Information System	≤	less than or equal to
kg	kilogram		
L	liter		
LOAEL	lowest-observed-adverse-effect level		