INTERACTION PROFILE FOR:
ARSENIC, CADMIUM, CHROMIUM, AND LEAD

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

May 2004

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.

Literature searches for this Interaction Profile were conducted in January 2000. This final version of the document, released in 2004, includes changes based on additional literature searching and analysis of joint action for arsenic and chromium(VI) that were performed in 2002 for an ATSDR health consultation.

SUMMARY

Lead, arsenic, cadmium, and chromium constitute a very frequently occurring quaternary mixture at hazardous waste sites. This mixture was found in soil at 219 sites out of the 1,608 sites for which ATSDR has produced a Public Health Assessment, including waste storage, treatment or disposal, manufacturing and industrial, and government waste sites. The primary route of exposure for this mixture in soil is likely to be oral, and the duration of concern is intermediate and particularly chronic. The profile focuses on inorganic forms of these metals, consistent with the monitoring data, and on chromium(VI), the species of concern for chromium. 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, arsenic, cadmium, and chromium(VI) 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.

An intermediate-duration dietary study of the trinary mixture lead, arsenic, and cadmium in rats indicates that results for the binary submixtures predicted the toxicity of the trinary mixture reasonably well, and that subthreshold doses of two metals can, when administered in combination, result in effects (Fowler and Mahaffey 1978; Mahaffey and Fowler 1977; Mahaffey et al. 1981). An intermediate-duration drinking water study of lead, cadmium, and chromium(VI+III) in diethylnitrosamine-initiated rats gave no evidence that the mixture had promoting activity (Benjamin et al. 1999).

Most of the information regarding joint toxic action for the metals in this mixture is for binary combinations of the metals. Data are voluminous for the lead-cadmium mixture, and fairly extensive for the lead-arsenic mixture. Many of the studies for these two binary mixtures are highly relevant because they employed simultaneous, intermediate or chronic oral exposure, and relevant endpoints of toxicity. Limitations in study design and reporting, and inconsistences in results across studies for the same target organ make it difficult to draw conclusions from these studies. The data for the other binary mixtures are less extensive, and tend to be less relevant in terms of sequence, duration, and route of exposure, as well as endpoints of toxicity. For these reasons, the weight-of-evidence (WOE) approach for the assessment of interactions was used to prepare binary weight-of-evidence determinations (BINWOE) for the binary mixtures (ATSDR 2001a, 2001b). The BINWOE determinations provide conclusions regarding the

expected direction of interaction, and the degree of confidence in these conclusions. BINWOE determinations need to take into account the potential endpoint-specificity of joint toxic action (ATSDR 2001b), particularly as the data for the lead-cadmium and lead-arsenic mixtures indicated that the direction of interaction may not be consistent across endpoints.

Each of the four metals affects a wide range of target organs and endpoints, and there are a number of target organs in common across two or more of the metals. These four metals do not, however, share the same critical effects (i.e., the most sensitive effect that is the basis for the MRL or other health criterion) for long-term oral exposure. For a mixture of this type, the recommended approach is to estimate endpoint-specific hazard indexes, using the target-organ toxicity dose (TTD) modification of the hazard index method (ATSDR 2001a). Uncertainties regarding the impact of interactions are taken into account through application of the qualitative WOE approach (ATSDR 2001a), including the BINWOEs developed for the binary mixtures.

Endpoints of concern for oral exposure to this mixture include the critical effects on which the oral minimal risk levels (MRLs) are based, other sensitive effects, and also endpoints in common that may become significant due to additivity or interactions. 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), and ATSDR (1999b) suggests the use of media-specific slope facts and site-specific environmental monitoring data to predict media-specific contributions to PbB. The critical effect for arsenic is dermal (ATSDR 2000a) and for cadmium is renal (ATSDR 1999a); these effects are the bases for the chronic oral MRLs. The critical effect for chromium(VI) is uncertain; no oral MRLs have been derived, and other health effects guidelines are based on essentiality (because chromium(III) is essential) (ATSDR 2000b) and a free-standing no-observed-adverse-effect level (NOAEL) for chromium(VI) (IRIS 2001). Sensitive effects in common across two or more of these metals include neurological, renal, cardiovascular, and hematological effects. Although less sensitive, testicular effects also are an endpoint of concern because a synergistic interaction has been noted for lead and cadmium, and because chromium(VI) also affects the testes. TTDs and BINWOEs were developed for the endpoints of concern for the four metals using the methods recommended by ATSDR (2001a, 2001b).

The binary mixtures with the most extensive interaction databases are the lead-arsenic mixture and the lead-cadmium mixture. The predicted direction of interaction for the effects of these mixtures is not

consistent across endpoints. This observation is most striking for the effects of cadmium on the toxicity of lead. The predicted direction is greater than additive for the neurological effects (the critical effect) and testicular effects (a less sensitive effect), less than additive for renal and hematological effects, and additive for cardiovascular effects. Confidence in the BINWOE determinations ranges from relatively high for renal and testicular to low for neurological.

The observation of inconsistency in predicted direction of interaction underscores the uncertainty in extrapolating interactions from one endpoint to another. It also suggests the possibility that a less sensitive target organ may have the potential to impact a mixtures health assessment if it is affected synergistically. Concern would be heightened if several chemicals in the mixture affect that target organ, and if confidence in the interaction (as reflected by the BINWOE scores) is high.

The recommendations for assessing the potential hazard to public health of the joint toxic action of lead, arsenic, cadmium, and chromium(VI) is to use the hazard index and TTDs to estimate endpoint-specific hazard indexes for neurological, renal, cardiovascular, hematological, and testicular toxicity of the mixture. This approach is appropriate when hazard quotients of at least two of the components equal or exceed 0.1 (ATSDR 2001a). The hazard quotient for arsenic's dermal toxicity (critical effect for chronic oral MRL) and the cancer risk estimate for arsenic are estimated separately from the other mixture components, because dermal effects are a unique critical effect (oral exposure to the other components does not affect the skin) and because the other components are not carcinogenic by the oral route (ATSDR 2001a). The impact of interactions on the endpoint-specific hazard indexes, unique hazard quotient, and cancer risk, were predicted using the WOE approach (ATSDR 2001a, 2001b), and are summarized below.

Neurological: The predicted direction of joint toxic action for neurological effects, an endpoint common to all four components, is greater than additive for the effect of lead on arsenic (low-moderate confidence), arsenic on lead (moderate confidence), cadmium on lead (low confidence), and chromium(VI) on arsenic (low confidence), and less than additive for the effect of arsenic on chromium(VI). The remaining seven BINWOEs were indeterminate due to a lack of toxicological and mechanistic data. Thus, the potential health hazard may be somewhat greater than estimated by the endpoint-specific hazard index for neurological effects, particularly for waste sites with relatively high hazard quotients for lead and arsenic, and lower hazard quotients for the other components. Given the indeterminate ratings for the majority of the BINWOEs, confidence in this conclusion would be lower for

mixtures where cadmium and chromium(VI) account for a greater portion of the apparent neurological hazard.

Renal: The potential health hazard regarding renal effects is likely to be lower than the additive, endpoint-specific hazard index, because five of the BINWOEs were less than additive, two were additive, and five were indeterminate. Confidence in the less-than-additive and additive BINWOEs ranges from low-moderate to high-moderate. Uncertainty regarding the impact of interactions on this endpoint is less than for neurological toxicity, because more information was available and a greater number of BINWOEs could be determined.

Cardiovascular: The WOE will have little impact on the additive, endpoint-specific hazard index, because the two moderate-confidence BINWOEs for this endpoint (for the effects of cadmium and lead and vice versa) were additive, one low confidence BINWOE (for chromium(VI) on arsenic) was less than additive, six BINWOEs were indeterminate, and three were not applicable (for the effect of the other components on chromium(VI). For mixtures other than those predominated by lead and cadmium, uncertainty is high.

Hematological: The potential health hazard for hematological effects is likely to be lower than indicated by the endpoint-specific hazard index, because six of the BINWOEs were less than additive, one was greater than additive, one was additive, and four were indeterminate. Confidence in the less-than-additive and additive BINWOEs is primarily low-moderate, and confidence in the greater-than-additive BINWOE is low.

Testicular: The potential health hazard may be higher than the endpoint-specific hazard index for testicular effects for mixtures with relatively high hazard quotients for cadmium and lead, because BINWOEs for this pair were greater than additive, with relatively high confidence. The BINWOE scores for arsenic effects on cadmium and chromium(VI) testicular toxicity were less than additive, but the confidence was low and the impact on the hazard index will be low. For the other pairs, BINWOEs were indeterminate (five BINWOEs) or not applicable (three BINWOEs for the effect of the other components on arsenic).

Dermal: Interactions of the other mixture components on the dermal toxicity of arsenic are indeterminate for lead and cadmium, and greater than additive with low confidence for chromium(VI). Thus the

available data do not indicate a significant impact of interactions on the hazard quotient for the unique critical effect of arsenic, but uncertainty is high due to the lack of pertinent information.

Carcinogenic: Data regarding effects of the other mixture components on arsenic carcinogenicity were not available. Mechanistic considerations suggest that the effect of chromium(VI) on arsenic carcinogenicity may be greater than additive, but confidence in this assessment was low. The remaining BINWOEs are indeterminate and will have no impact on the cancer risk estimate for arsenic. Uncertainty regarding interactions is high due to the lack of pertinent information.

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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.

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.

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ACGIH	American Conference of Governmental Industrial Hygienists
ALA	delta-aminolevulinic acid
ALAD	delta-aminolevulinic acid dehydratase
ALAS	delta-aminolevulinic acid synthetase
As	arsenic
ATSDR	Agency for Toxic Substances and Disease Registry
BINWOE	binary weight-of-evidence
BMC	benchmark concentration
Cd	cadmium
CdB	blood cadmium
CDC	Centers for Disease Control
CdMT	cadmium metallothionein
CdU	urinary cadmium
CERCLA	Comprehensive Environmental Response, Compensation, and Recovery Act
Cr	chromium
dL	deciliter
DMA	dimethylarsenite
DNA	deoxyribonucleic acid
DT	Division of Toxicology
EPA	Environmental Protection Agency
FQPA	Food Quality Protection Act
HOME	Home Observation for Measurement of the Environment
IARC	International Agency for Research on Cancer
IRIS	Integrated Risk Information System
kg	kilogram
L	liter
LD_{50}	lethal dose, 50% kill
LOAEL	lowest-observed-adverse-effect level
MCH	mean corpuscular hemoglobin
MCHC	mean corpuscular hemoglobin concentrations
MCV	mean corpuscular volume
mg	milligram
mL	milliliter
MMA	monomethylarsenite
MRL	Minimal Risk Level
MT	metallothionein
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NRC	National Research Council
NTP	National Toxicology Program
Pb	lead
PbB	blood lead
PBPK	physiologically based pharmacokinetic
PBPK/PD	physiologically-based pharmacokinetic pharmacodynamic
ppb	parts per billion
ppm	parts per million
RfC	Reference Concentration
RfD	Reference Dose
RNA	ribonucleic acid
SCE	sister chromatid exchange
SGOT	serum glutamic-oxaloacetic transaminase
TTD	target-organ toxicity dose
U.S.	United States
WOE	weight-of-evidence
ZPP	zinc protoporphyrin

>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
µg	microgram
µmole	micromole