1. Introduction

The primary purpose of this Interaction Profile for lead, arsenic, cadmium, and chromium 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, arsenic, cadmium, and chromium mixture was chosen as the subject for this interaction profile because it is a very frequently occurring quarternary 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. The principal activity at sites with this mixture in soil was waste storage, treatment, or disposal (30%), followed by manufacturing and industrial (23.5%), and government (12.2%), with various other types of site activities accounting for the remainder. The profile is restricted to inorganic forms of these metals, as per the monitoring data. In the case of chromium, although total chromium is often monitored at waste sites, the form of concern is chromium(VI). The primary route of concern for a mixture of these chemicals in soil is likely to be oral, and the duration intermediate to chronic. The term "metals" is used in this profile for brevity and convenience, and is intended to refer to lead, arsenic, cadmium, and chromium(VI) in inorganic compounds or as ions. Arsenic, a metalloid, is usually grouped with metals in terms of its toxicology.

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 minimal risk levels (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 1999b). The effect of concern is neurological. ATSDR (1999b) suggests the use of media-specific slope factors and site-specific environmental monitoring data to predict media-specific contributions to blood lead (PbB). Chronic oral MRLs have been derived for arsenic, based on skin lesions in humans (ATSDR 2000a), and for cadmium (Cd), based on proteinuria (indicator of renal damage) in humans (ATSDR 1999a). No oral MRLs have been derived for chromium(VI) because of insufficient data to define no-observed-adverse-effect levels (NOAELs) for reproductive and developmental effects. Instead, the upper end of the range of the estimated rate and adequate daily dietary intake of 200 µg Cr/kg/day (NRC 1989) was adopted by ATSDR (2000b) as provisional guidance for oral exposure to chromium(VI) and chromium(III). In practice, health assessments may use the reference dose (RfD) for chromium(VI). The RfD is based on a "free-standing" NOAEL that is lower than lowest-observed-adverse-effect levels (LOAELs) for toxic effects, including reproductive and developmental effects, in other studies (IRIS 2001).

The bases for the MRLs (or health assessment approach in the case of lead), as well as other pertinent effects, are summarized in Table 1. No studies were located that investigated the effect of the quaternary mixture on these effects of concern. A few studies have investigated the effect of trinary mixtures of these metals on some of these endpoints, but the bulk of the available interactions information is for binary mixtures of these metals. Table 2 summarizes the availability of pertinent interactions data by endpoint for the binary mixtures. The table serves as an overview, and shows some striking data gaps: no studies of interactions relevant to the critical effect of arsenic (dermal lesions), and no studies on endpoints of concern for oral exposure for the lead-chromium(VI) pair. The lead-cadmium mixture has been studied the most extensively, including in epidemiological studies and in intermediate and chronic simultaneous oral exposure studies in animals.

A point of interest is there appears to be no good animal model for arsenic toxicity in humans. No other species has been found to develop the arsenic effect of greatest concern, cancer in the skin and other organs. Nor have the studied species of animals been found to develop the noncancer skin lesions seen in humans exposed to arsenic. The species most often used in these interactions studies, the rat, is significantly different from humans in terms of arsenic metabolism, distribution, and health effects.

Table 1. Potential Health Effects of Concern for Intermediate and Chronic Oral Exposure to the Mixture Lead, Arsenic, Cadmium, and Chromium(VI)[a]

Lead	Arsenic	Cadmium	Chromium (VI)
Neurological **Hematological** **Cardiovascular** Renal Testicular	***Dermal lesions*** **Cardiovascular** **Hematological** Renal **Neurological** **Cancer**	***Renal (proteinuria*)** Cardiovascular Hematological Hepatic Neurological Testicular	Hematological Hepatic Renal Neurological Testicular

[a]The basis for the MRL or health assessment approach is bolded and italicized; other sensitive effects are bolded; and less sensitive effects in common across two or more metals, or known to be affected synergistically by another metal in the mixture, are listed without bold or italics

Table 2. Availability of Pertinent Interactions Data for Pairs of Components

Endpoint	Lead-Arsenic	Lead-Cadmium	Lead-Chromium(VI)	Arsenic-Cadmium	Arsenic-Chromium(VI)	Cadmium-Chromium(VI)
Cardiovascular		X				
Hematological	X	X		X		
Hepatic	X	X		X		
Renal	X	X		X	X	X
Dermal (for arsenic)						
Immunological		X				
Reproductive (testicular)		X		X		
Neurological	X	X				
Cancer (for arsenic)	X					

X = Some data are available