

1. Introduction

The primary purpose of this Interaction Profile for chlorpyrifos, mercury, methylmercury, and lead 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 Minimal Risk Level (MRL), and adequacy and relevance of physiologically-based pharmacokinetic/pharmacodynamic (PBPK/PD) 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 (WOE) 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 the Agency for Toxic Substances and Disease Registry (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 Division of Toxicology’s (DT) 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 chlorpyrifos, lead, mercury/methylmercury mixture was chosen as the subject for this interaction profile based on a concern for neurological effects in children co-exposed to these chemicals. Chlorpyrifos is an organophosphorus insecticide. It is one of the most widely used insecticides for agricultural applications and indoor and outdoor residential applications in the United States (ATSDR 1997; EPA 2000a). Children may have been exposed to chlorpyrifos through the diet, drinking water, and exposure in the home, yard, schools, and parks where the chlorpyrifos may have been applied to lawns or indoor cracks and crevices, and used for whole-building termite treatments. A study of a small number of households in the Lower Rio Grande Valley concluded that indoor dust and air were the primary exposure media for the residents of those households, based on monitoring of those media, as well as outdoor soil and air, food, and a characteristic urinary metabolite of chlorpyrifos (used as a biomarker of exposure) (Buckley et al. 1997). Thus, exposure pathways in this limited study are likely to have been ingestion and

inhalation. A study of urinary pesticide metabolites during the third trimester in 386 pregnant women from East Harlem indicated that exposure to chlorpyrifos was prevalent (42% of the women had detectable levels of the chlorpyrifos metabolite). The study further showed that the exposure was higher than the median in National Health and Nutrition Examination Survey (NHANES) III, did not show seasonal variation, and did not change during the time period of the study (1998–2001) (Berkowitz et al. 2003). The exposure of these women was thought to be primarily indoor, due to household pesticide use and exterminator application, and also dietary. Under the Food Quality Protection Act (FQPA), the Environmental Protection Agency (EPA) and chlorpyrifos registrants have agreed to phase out or reduce many uses of chlorpyrifos that contribute to children's exposure (EPA 2000a, 2002a). In June of 2000, EPA announced an agreement with chlorpyrifos registrants to eliminate certain uses of this pesticide (EPA 2000a, 2002a). Uses on foods frequently eaten by children (apples, grapes, tomatoes), uses by homeowners (except for ant baits in child resistant containers), and uses in settings such as schools and parks where children may be exposed, are being canceled, or phased out, or limited to minimize exposure. Residential uses by licensed applicators are being phased out or limited to lower application concentrations or rates. Reduced application rates for other agricultural uses and golf courses also are being instituted to protect workers and wildlife.

Lead is present in the environment primarily as divalent lead compounds (ATSDR 2005). Mercury exists in the environment as metallic mercury, inorganic mercury compounds (primarily mercuric), and organic mercury compounds (primarily methylmercury) (ATSDR 1999). Mercury and lead co-occur in completed exposure pathways at hazardous waste sites, most commonly from soil or water. The exposure pathway of concern from these media is oral.

Metallic and inorganic mercury also are released into the environment (primarily into air) from mining, smelting, industrial activities, combustion of fossil fuels, and natural processes (ATSDR 1999). The metallic and inorganic mercury in air can be deposited to water and soil, where they are transformed by microorganisms into methylmercury, as are metallic and inorganic mercury from hazardous waste sites. Methylmercury bioaccumulates in the food chain, particularly in fish. For the general population, and particularly for subsistence fishers and hunters, the most important pathway of exposure to mercury is ingestion of methylmercury in foods, with fish (including tuna, a food commonly eaten by children), other seafood, and marine mammals containing the highest concentrations. Another source of exposure for the general population is the release of metallic mercury from dental amalgams. Infants can be exposed to inorganic mercury and methylmercury from breast milk, and the developing fetus can be exposed through transplacental transfer of metallic mercury and methylmercury.

Lead also is released into the environment from mining, smelting, and industrial activities (ATSDR 2005). In addition, children are exposed to lead from deteriorating lead paint, which contaminates soil and house dust with lead, and from the historical use of lead in gasoline, which has contaminated the soil, particularly in urban areas. Lead can be transferred to the fetus through the placenta and to infants through breast milk.

Before evaluating the relevance of joint toxic action data for these chemicals, some understanding of 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 or other health guidance values, and any other endpoints that may become significant because they are shared targets of toxicity or due to interactions (ATSDR 2001a).

Chlorpyrifos' critical effect, which is the basis of ATSDR (1996) MRLs and EPA (2000c; IRIS 2004) reference doses (RfDs), is neurological, due to inhibition of acetylcholinesterase.

The critical effect for lead is neurological. Although no MRLs have been derived for lead (Pb) (ATSDR 2005), the Centers for Disease Control and Prevention (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. ATSDR (2005) suggests the use of media-specific slope factors and site-specific environmental monitoring data to predict media-specific contributions to PbB.

The critical effect of methylmercury also is neurological (ATSDR 1999). Metallic mercury also causes neurological effects when inhaled, but not when ingested (due to lack of absorption from the gastrointestinal tract); exposures of concern for inhalation of metallic mercury are generally occupational rather than environmental. The concern from environmental release of metallic mercury is its conversion to methylmercury. Metallic mercury in dental amalgam appears to be absorbed, possibly after volatilization from fillings, but reliable evidence of adverse effects from this source of exposure is lacking. Therefore, methylmercury and inorganic (mercuric) mercury are the forms of mercury discussed further in this interaction profile.

Sensitive subpopulations for chlorpyrifos, lead, and methylmercury are fetuses, infants, and young children. These conclusions are based on human data for lead (ATSDR 2005) and methylmercury (ATSDR 1999), or are predicted on the basis of animal studies for chlorpyrifos (ATSDR 1997; EPA 2000b).

Although inorganic mercury can cause neurological effects, these effects are not sensitive effects, but rather are seen primarily at very high acute doses, probably because inorganic mercury does not pass the blood-brain and placental barriers readily, in contrast to methylmercury (ATSDR 1999). A major concern from environmental release of inorganic mercury, however, is its conversion to methylmercury, which does have neurological effects. The critical effect of inorganic mercury is renal tubular damage (ATSDR 1999), and also renal glomerular damage, which may be mediated through autoimmune responses (IRIS 2004). Methylmercury and lead also cause renal damage, but at much higher exposure levels than those that cause neurological effects, and chlorpyrifos is not known to damage the kidney.

Carcinogenic effects are not a particular concern for the components of this mixture. Chlorpyrifos was evaluated for carcinogenicity in 2-year feeding studies in rats, mice, and dogs; results were negative (ATSDR 1997; EPA 2000b). A few lead compounds, mercuric chloride, and methylmercury have produced some evidence of carcinogenicity in animal studies, but the relevance to human exposures has been questioned, and the main concern for these chemicals is noncancer health effects (see appendices for details).

Thus, the primary endpoint of concern for this mixture is neurological, and the subpopulation of concern is developing children. Renal endpoints are also relevant, but are sensitive effects only of inorganic mercury. In addition, the interaction data for renal effects of these chemicals are conflicting, and the available studies are poor models, in terms of route and duration, for human exposure. Accordingly, this interaction profile will focus on the joint toxic action of the mixture on neurological effects. Effects of the other mixture components on the renal toxicity of inorganic mercury also will be assessed.