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## **B.5 Derivation of Target-Organ Toxicity Dose (TTD) Values**

A TTD for chronic oral exposure to lead was derived for the primary endpoint of concern for this mixture, i.e., neurological effects in the fetus, infant, and young child from exposure to chlorpyrifos, lead, and methylmercury. Relevant endpoints for another metal mixture, which is the subject of a separate interaction profile, also included hematological, renal, cardiovascular, and testicular. For the sake of completeness, the TTDs derived for those endpoints are retained in this Appendix, but are not recommended for use with the present mixture. The chronic oral TTDs for lead were derived using the methods described in ATSDR (2001a, 2001b). Because ATSDR's approach to the assessment of lead uses media-specific slope factors and site-specific contributions to PbB, the TTDs for lead are derived based on PbB as well (see rationale in Chapter 3 of this profile). The derivations are based on data provided in ATSDR (2005), and particularly Section 3.2 (Health), Chapter 2 (Relevance to Public Health), and Section 3.6 (Biomarkers of Exposure and Effect). The derivation methods used similar reasoning as for the CDC and EPA levels of concern (see neurological effects).

### **Neurological Effects**

A large number of epidemiological studies and case reports indicate that exposure to lead causes neurological effects. Slowing of nerve conduction velocity is associated with PbBs of 30 µg/dL in children and adults. Of greater concern are the inverse linear relationships between IQ and other neurobehavioral measures in children at PbBs extending down through 10 µg/dL or possibly lower. Children appear to be more sensitive to the neurobehavioral toxicity of lead than are adults. Limited data suggest an association between decreased neurobehavioral performance and PbB in aging subjects at relatively low PbBs, indicating that the elderly may be another sensitive population. Although results of

the epidemiological studies in children are not entirely consistent, several meta-analyses have indicated that a highly significant IQ decrement of 1–3 points is associated with a change in PbB from 10 to 20 µg/dL in children (IPCS 1995; Needleman and Gatsonis 1990; Pocock et al. 1994; Schwartz 1994). The CDC (1991) determined that blood lead levels of >10 µg/dL are to be considered elevated in children, based largely on concern for the effects of low-level lead exposure on the central nervous system. EPA defines lead risk as the probability of exceeding a PbB of concern (10 µg/dL) in children or fetuses (EPA 1994a, 1996). The CDC level of concern for lead of 10 µg/dL is adopted as the TTD for neurological effects (TTD<sub>NEURO</sub>).

### **Renal Effects**

Chronic nephropathy is associated with PbB levels of 40–>100 µg/dL in humans exposed to lead occupationally. There are some indications of renal damage in a study of children whose mean PbB was 34.2 µg/dL (increased N-acetyl-β-D-glucosaminidase activity in urine, a sensitive indicator) (Verberk et al. 1996). The value for children, supported by the occupational data, and rounded to 34 µg/dL, is taken as the TTD for renal effects (TTD<sub>RENAL</sub>).

### **Cardiovascular Effects**

At higher levels of exposure, lead produces cardiac lesions and electrocardiographic abnormalities in humans. Many epidemiological studies have reported an association between increases in blood pressure and increases in PbB. The contribution of lead, as compared with other factors, is relatively small, and whether the associations indicate causality is controversial. Animal data demonstrate that oral exposure to lead increases blood pressure ATSDR (2005). The correlation between PbB and blood pressure is apparent at relatively low PbBs extending through 10 µg/dL (e.g., Schwartz 1995). Therefore, the CDC level of concern, 10 µg/dL, is adopted as the TTD for cardiovascular effects (TTD<sub>CARDIO</sub>).

### **Hematological Effects**

Lead interferes with the synthesis of heme. The consequence at higher levels of exposure is a hypochromic, normocytic anemia. The most sensitive indicator of effect on heme synthesis is the inhibition of ALAD. ALAD activity is inversely correlated with PbB through the lowest levels of PbB in the general population. Even in the absence of detectable effects on hemoglobin levels, there is concern that effects on heme synthesis may have far-reach impacts, particularly on children (ATSDR 2005).

Accordingly, the CDC PbB of concern for children, 10 µg/dL (CDC 1991), is selected as the TTD for hematological effects (TTD<sub>HEMATO</sub>).

### **Testicular Effects**

Adverse effects of the testes and sperm have been reported in occupationally exposed men with PbBs of 40–50 µg/dL in some studies, but not in others, and are well-established at higher levels of exposure (PbBs, 66 µg/dL) (ATSDR 2005). The point of departure for increased risk of below normal sperm and total sperm count was 40 µg/dL (Alexander et al. 1996). This value is selected as the TTD for testicular effects (TTD<sub>TESTIC</sub>).

### **Summary (TTDs for Lead)**

TTD<sub>NEURO</sub> = 10 µg/dL PbB = CDC level of concern

TTD<sub>RENAL</sub> = 34 µg/dL PbB

TTD<sub>CARDIO</sub> = 10 µg/dL PbB

TTD<sub>HEMATO</sub> = 10 µg/dL PbB

TTD<sub>TESTIC</sub> = 40 µg/dL PbB

Only the TTD<sub>NEURO</sub> is used in this interaction profile. As explained previously, the other TTDs were derived for endpoints of concern for joint toxic action of a different mixture, which is the subject of a separate interaction profile.

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## Appendix C: Background Information for Mercury and Methylmercury

Mercury exists in the environment as metallic mercury (also called elemental mercury), inorganic mercury compounds (primarily mercuric), and organic mercury compounds (primarily methylmercury). The structure of methylmercury is shown in Appendix D. Metallic and inorganic mercury released into air from mining, smelting, industrial activities, combustion of fossil fuels, and natural processes can be deposited to water and soil, where the mercury is transformed by microorganisms into methylmercury, which bioaccumulates in the food chain, particularly in fish. For the general population, the most important pathway of exposure to mercury is ingestion of methylmercury in foods, with fish, other seafood, and marine mammals containing the highest concentrations (ATSDR 1999). Another source of exposure for the general population is intake 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 (ATSDR 1999). For residents near mercury-contaminated hazardous waste sites, the following information provides insight into important routes of exposure. Exposure analysis of residents near an abandoned industrial site that had produced various inorganic and organic mercury compounds (and was not located near drinking water sources) indicated that the children were exposed to mercury primarily through soil and dust ingestion (Nublien et al. 1995).

### C.1 Toxicokinetics

In humans, approximately 15% of a trace oral dose of inorganic mercury (mercuric nitrate) was absorbed through the gastrointestinal tract (ATSDR 1999). Qualitative information indicates that ingested mercuric chloride and mercuric sulfide also were absorbed through the gastrointestinal tract of humans. Studies in animals indicate gastrointestinal absorption of inorganic mercury is in the 10–30% range, and depends on intestinal pH, compound dissociation, and other factors. Qualitative evidence indicates that the absorption of mercuric sulfide may be less than that of mercuric chloride. Absorption of inorganic mercury tended to be higher in young animals than in adults. Following absorption from the gastrointestinal tract, inorganic mercury distributes to the liver and kidneys, with the highest concentrations in the kidneys. Although concentrations in brain are substantially lower, mercury was retained longer in brain than in other tissues.



















For methylmercury, only the  $MRL_{NEURO}$  is used in this interaction profile. As explained previously, the other TTDs were derived for endpoints of concern for joint toxic action of a different mixture, which is the subject of a separate interaction profile.

## C.6 References

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