3. Recommendation for Exposure-Based Assessment of Joint Toxic Action of the Mixture

As discussed in the introduction, the mixture of chlorpyrifos, lead, mercury (inorganic), and methylmercury was chosen as the subject for this interaction profile because of concerns for neurological effects in developing children (including fetuses and infants) exposed to these chemicals. The exposure scenario of greatest concern for this mixture is intermediate- to chronic-duration low-level oral exposure.

No adequate epidemiological or toxicological studies and no PBPK models are available for this mixture. Recommendations for exposure-based screening for the potential health hazard of this mixture are based on ATSDR (2001a) guidance, and comprise a component-based approach. This approach is used for the components with hazard quotients that equal or exceed 0.1, when at least two of the mixture components fulfill this criterion. Hazard quotients are the ratios of exposure estimates to noncancer health guidance values, such as MRLs. If only one or if none of the mixture components has a hazard quotient of this magnitude, no further assessment of the joint toxic action is needed because additivity and/or interactions are unlikely to result in significant health hazard. As discussed by ATSDR (1992, 2001a), the exposure-based assessment of potential health hazard is a screening approach, to be used in conjunction with biomedical judgment, community-specific health outcome data, and community health concerns to assess the degree of public health hazard.

Because neurological effects are the critical effects of chlorpyrifos, lead, and methylmercury, the recommended approach (ATSDR 2001a) for these components is to estimate an endpoint-specific hazard index (by summing the hazard quotients for these components) for neurological effects. Estimation of hazard quotients for lead is problematic because of the lack of an oral MRL or RfD. Blood lead is a commonly used index of exposure to lead. The use of media-specific slope factors and site-specific environmental monitoring data has been recommended by ATSDR to predict media-specific contributions to blood lead (ATSDR 2005). The predicted contributions from the individual media are summed to yield a total predicted PbB level. The media-specific slope factors were derived from regression analysis of lead concentrations in water, soil, dust, diet, or air and PbBs for various populations. In order to estimate a hazard quotient, the predicted PbB can be divided by the PbB of 10 μg/dL, the level of concern (CDC 1991), an appropriate guidance value adopted as the target-organ toxicity dose (TTD) for neurological effects of lead (Appendix A).

The hazard index is calculated using the guidance values for neurological effects shown in Table 21, or newer values as they become available. This process is shown in the following equation:

$$HI_{NEURO} = \frac{E_{Cpf}}{MRL_{Cpf\,NEURO}} + \frac{E_{Pb}}{CDCPbB_{\,Pb\,NEURO}} + \frac{E_{MeHg}}{MRL_{\,MeHg\,NEURO}}$$

where HI_{NEURO} is the hazard index for neurological toxicity, E_{Cpf} is the exposure to chlorpyrifos (as the oral intake in mg/kg/day), MRL_{Cpf} is the intermediate oral MRL for chlorpyrifos (in mg/kg/day), E_{Pb} is the exposure to lead (as the predicted PbB in µg/dL), $CDC_{PbB\,NEURO}$ is the CDC PbB of concern (10 µg/dL), E_{MeHg} is the exposure to methylmercury (as the oral intake in mg Hg/kg/day), and MRL_{MeHg} is the chronic oral MRL for methylmercury (in mg Hg/kg/day). For justification of using an intermediate duration guidance value with a chronic one, see section A.5 and C.5.

Table 21. MRLs and TTDs for Intermediate and Chronic Oral Exposure to Chemicals of Concern[a]

	Chemical			
Endpoint	**Chlorpyrifos mg/kg/day**	**Lead PbB µg/dL**	**Mercury (inorganic) mg Hg/kg/day**	**Methylmercury mg Hg/kg/day**
Neurological	0.003[b]	10[c]	NA	$3x1^{-4}$[d]
Renal	NA	NA	0.002[e]	NA

[a]See Appendices A, B, and C for details.
[b]Intermediate oral MRL for chlorpyrifos.
[c]CDC (1991) PbB level of concern, adopted as TTD.
[d]Chronic oral MRL for methylmercury.
[e]Intermediate oral MRL for mercury (inorganic).
NA = not applicable (see text)

Renal endpoints are also relevant to this mixture, but are sensitive effects only of inorganic mercury. Chlorpyrifos does not affect the kidney, and lead affects the kidney at much higher exposure levels than for neurological endpoints in humans. For methylmercury, although some studies in animals provide evidence of renal effects, the MRL for methylmercury is based on human epidemiological studies showing neurological effects, and the human studies do not provide dose-response data for renal effects specific to methylmercury. In addition, the joint action data pertinent to renal effects of these chemicals do not indicate that renal effects of the mixture would become significant due to interactions. Accordingly, the calculation of an endpoint-specific hazard index for renal effects is not recommended. Rather, a separate hazard quotient is recommended for assessing the potential hazard from renal effects of

inorganic mercury. The primary concern for inorganic mercury released to the environment is the conversion of inorganic mercury to methylmercury, which is bioaccumulated in the food chain, particularly fish, and readily absorbed by humans who ingest contaminated organisms.

If the hazard index for neurological effects exceeds 1, it provides preliminary evidence that the mixture may constitute a health hazard due to the joint toxic action of components on that endpoint (ATSDR 2001a). Similar preliminary conclusions apply if the hazard quotient for inorganic mercury's renal effects exceeds 1. The impact of interactions from the WOE analysis also is considered.

The BINWOE predictions for joint toxic action on neurological effects are predominantly less than additive (for lead, mercury, and methylmercury's influence on chlorpyrifos neurotoxicity; and for chlorpyrifos' influence on lead neurotoxicity), with confidence ratings generally in the medium to medium low range. As reflected in several scores, using interaction data for chemical surrogates (instead of chlorpyrifos) increased the uncertainty in interaction assessments. Two BINWOEs are additive (for methylmercury on lead neurotoxicity with medium confidence, and lead on methylmercury neurotoxicity with medium low confidence), and only one is greater than additive (chlorpyrifos on methylmercury neurotoxicity with low confidence). Thus, the predicted impact of interactions on the potential neurological hazard of this mixture is to decrease the hazard, but confidence in this conclusion is only medium to medium low. Therefore, a hazard index for neurological effects that is less than 1 or that is only slightly greater than 1 may not be of concern, but a hazard index that more markedly exceeds 1 will still indicate preliminary evidence of a mixture health hazard. It should be further noted that uncertainty regarding the actual mechanisms of neurodevelopmental toxicity contributes to the lower confidence in the conclusions as they are applied to developing children. The BINWOE predictions for joint toxic action on the renal toxicity of mercury do not significantly alter the conclusions that would be reached from the hazard quotient alone, because the BINWOE for chlorpyrifos on mercury is less than additive with low confidence and for lead on mercury is greater than additive, but also with low confidence.

If this screening procedure indicates preliminary evidence of a mixture health hazard, additional evaluation is needed to assess whether a public health hazard exists (ATSDR 2001a). The additional evaluation includes biomedical judgment, assessment of community-specific health outcome data, and consideration of community health concerns (ATSDR 1992).

Table 22. Matrix of BINWOE Determinations for Intermediate or Chronic Simultaneous Exposure to Chemicals of Concern

	ON TOXICITY OF				
EFFECT OF		Chlorpyrifos	Lead	Mercury	Methylmercury
	Chlorpyrifos		<IIIB n	<IIIC r	>IIIC n
	Lead	<IIB n		>IIIC r	=IIIC n
	Mercury	<IIC n	? n		—
	Methylmercury	<IIIB n	=IIIC n	—	

r = reproductive, n = neurological,

The BINWOE determinations were explained in Section 2.3.

BINWOE scheme from ATSDR (2001a, 2001b):

DIRECTION: = additive; > greater than additive; < less than additive; ? indeterminate

MECHANISTIC UNDERSTANDING:
I: direct and unambiguous mechanistic data to support direction of interaction;
II: mechanistic data on related compounds to infer mechanism(s) and likely direction;
III: mechanistic data do not clearly indicate direction of interaction.

TOXICOLOGIC SIGNIFICANCE:
A: direct demonstration of direction of interaction with toxicologically relevant endpoint ;
B: toxicologic significance of interaction is inferred or has been demonstrated for related chemicals ;
C: toxicologic significance of interaction is unclear .