

## 4. Conclusions

No pertinent health effects data or PBPK models were available for the mixture of lead, manganese, zinc, and copper. Endpoints of concern for this mixture include the critical effects of the individual components, and toxicity targets in common that may become significant due to additivity or interactions. These endpoints are neurological, hematological, and hepatic effects. The recommendations for assessing the potential hazard to public health of the joint toxic action of this mixture include the estimation of endpoint-specific hazard indexes for neurological effects of lead and manganese and for hematological effects of lead and zinc. This approach is appropriate when hazard quotients of at least two of the components equal or exceed 0.1 (ATSDR 2001a). The qualitative WOE approach is then used to predict the impact of interactions on the endpoint-specific hazard indexes. The hazard quotient for copper's hepatic toxicity (critical effect for oral exposure) is estimated separately and the qualitative WOE is used to predict the impact of interactions on this hazard quotient. The impact of interactions on the endpoint-specific hazard indexes and the copper hazard quotient are discussed below in terms of the WOE approach.

*Neurological:* The predicted direction of joint toxic action for neurological effects, an endpoint common to two components, is greater than additive for the effect of manganese on lead, less than additive for the effects of zinc and copper on lead, additive (no effect) for the effect of lead on manganese, and indeterminate for the effects of zinc and copper on manganese. The combined WOE score (sum of the BINWOE scores) is  $-0.78$ , indicating that the potential health hazard may be less than estimated by the endpoint-specific hazard index for neurological effects, particularly for waste sites with relatively high hazard quotients for lead, copper, and zinc, and a lower hazard quotient for manganese. The indeterminate ratings for two of the BINWOEs (zinc and copper on manganese) are a source of uncertainty in assessments where manganese accounts for a great portion of the apparent neurological hazard.

*Hematological:* The potential health hazard for hematological effects is likely to be lower than indicated by the endpoint-specific hazard index for mixtures where lead, zinc, and copper predominate, because three of the BINWOEs for combinations of these metals were less than additive with moderate to high confidence, and the remaining one was additive. The BINWOE for manganese on lead was greater than additive with low-moderate confidence, for lead on manganese was additive, and for manganese on zinc was indeterminate. The combined WOE score is  $-2.11$ .

*Hepatic:* The predicted effects of the other mixture components on the hepatic toxicity of copper are less than additive for zinc with high-moderate confidence (-0.71), additive for lead (0), and indeterminate (0) for manganese. Thus, the available data indicate the potential health hazard for hepatic effects may be less than predicted by the hazard quotient for mixtures where zinc and copper predominate. There is uncertainty with regard to the potential effect of manganese due to the lack of pertinent information.