# 4. Conclusions

No pertinent health effects data or PBPK models were available for the mixture of lead, arsenic, cadmium, and chromium(VI). 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, dermal, renal, cardiovascular, hematological, testicular, and carcinogenic effects. The recommendations for assessing the potential hazard to public health of the joint toxic action of lead, arsenic, cadmium, and chromium(VI) is to use the hazard index and TTDs to estimate endpoint-specific hazard indexes for neurological, renal, cardiovascular, hematological, and testicular toxicity of the mixture. 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 index. The hazard quotient for arsenic's dermal toxicity (critical effect for chronic oral MRL) and the cancer risk estimate for arsenic are estimated separately from the other mixture components, because dermal effects are a unique critical effect (oral exposure to the other components does not affect the skin) and because the other components are not carcinogenic by the oral route (ATSDR 2001a). The impact of interactions on the endpoint-specific hazard indexes, unique hazard quotient, and cancer risk for the mixture are discussed below in terms of the WOE approach.

*Neurological:* The predicted direction of joint toxic action for neurological effects, an endpoint common to all four components, is greater than additive for the effect of lead on arsenic (+0.23), arsenic on lead (+0.50), cadmium on lead (+0.10), and chromium(VI) on arsenic (+0.10); less than additive for arsenic on chromium(VI) (-0.06); and indeterminate (0) for the remaining nine BINWOEs. The combined WOE score is +0.87, indicating that the potential health hazard may be somewhat greater than estimated by the endpoint-specific hazard index for neurological effects, particularly for waste sites with relatively high hazard quotients for lead and arsenic, and lower hazard quotients for the other components. Given the indeterminate ratings for the majority of the BINWOEs, confidence in this conclusion would be lower for mixtures where cadmium and chromium(VI) account for a greater portion of the apparent neurological hazard.

*Renal:* The potential health hazard regarding renal effects is likely to be lower than the additive, endpoint-specific hazard index, because five of the BINWOEs were less than additive, two were additive, and five were indeterminate. The combined WOE score is -1.45. Uncertainty regarding the impact of

interactions on this endpoint is less than for neurological toxicity, because more information was available and a greater number of BINWOEs could be determined.

*Cardiovascular:* The WOE will have little impact on the additive, endpoint-specific hazard index, because the two moderate confidence BINWOEs that could be determined for this endpoint (for the effects of cadmium and lead and vice versa) were additive, one low confidence BINWOE was greater than additive (+0.10), six BINWOEs were indeterminate, and three were not applicable for the effect on chromium(VI). Thus, the combine WOE score is +0.10. For mixtures other than those predominated by lead and cadmium, uncertainty is high.

*Hematological:* The potential health hazard for hematological effects is likely to be lower than indicated by the endpoint-specific hazard index, because six of the BINWOEs were less than additive, one was greater than additive, and four were indeterminate. The combined WOE score is -1.21.

*Testicular:* The potential health hazard may be higher than the endpoint-specific hazard index for testicular effects for mixtures with relatively high hazard quotients for cadmium and lead, because BINWOEs for this pair were greater than additive, with relatively high confidence (>IIA) and correspondingly high numerical scores (+0.71 for each). The BINWOE scores for arsenic effects on cadmium and chromium(VI) testicular toxicity were less than additive, but the confidence was low (IIIB2ii, -0.14, and <IIC2ii, -0.06) and the impact on the hazard index will be low. For the other pairs, BINWOEs were indeterminate (5 BINWOEs) or not applicable (3 BINWOEs for the effect on arsenic). The combined WOE score is +1.22.

*Dermal:* Interactions of the other mixture components on the dermal toxicity of arsenic are indeterminate (0) for lead and cadmium, and greater than additive with low confidence (+0.10) for chromium(VI). Thus, the available data do not indicate a significant impact of interactions, but uncertainty is high due to the lack of pertinent information.

*Carcinogenic:* Data regarding effects of the other mixture components on arsenic carcinogenicity were not available. Mechanistic considerations suggest that the effect of chromium(VI) on arsenic carcinogenicity may be greater than additive, but confidence in this assessment is low (+0.10). The remaining BINWOEs are indeterminate (0) and will have no impact on the cancer risk estimate for arsenic. Uncertainty regarding interactions is high due to the lack of pertinent information.