

4. Conclusions

ATSDR recommends a component-based HI approach (modified with TTDs) that assumes additive joint toxic action to assess possible endocrine, neurobehavioral, and developmental health hazards from oral exposure to mixtures of CDDs, PBDEs, and phthalates. No *in vivo* studies were located that examined endocrine, neurobehavioral, or developmental endpoints following exposure to trinary mixtures of CDDs, PBDEs, and phthalates, thereby precluding the derivation of any “whole mixture” MRLs. However, the available toxicity information for chemicals from each of the chemical classes of concern indicates that joint toxic action is plausible with regard to thyroid disruption (2,3,7,8-TCDD, PBDEs, DEHP, DNOP, and DBP), neurodevelopmental effects (2,3,7,8-TCDD and PBDEs), and developmental endocrine effects (i.e., disruption of male or female reproductive function following perinatal exposure [2,3,7,8-TCDD, PBDEs, and DEHP or DBP] or disruption of thyroid functioning, which may influence neurological development [PBDEs and CDDs]). Based on the available toxicity information, separate chemical-specific TTDs have been derived for the most sensitive endpoints encompassing developmental neurobehavioral effects (PBDEs and TCDD), developmental endocrine effects (TCDD, PBDEs, and phthalates), and thyroid disruption in adults (TCDD, PBDEs, and phthalates). For TCDD, the TTD for neurodevelopmental effects is the chronic MRL. ATSDR recommends using these TTDs in screening-level assessments (using the HI approach) for the protection of public health from increased risks for these effects from chronic oral exposure to mixtures of CDDs, PBDEs, and phthalates.

Weight-of-evidence analyses of available data on the joint toxic action of binary mixtures of these components indicate that scientific evidence for greater-than-additive or less-than-additive interactions between TCDD and phthalates and between phthalates and PBDEs is lacking or inadequate to characterize the possible modes of joint action on endocrine disruption, neurobehavioral toxicity, and developmental toxicity. *In vitro* mechanistic evidence indicates that PBDEs may antagonize TCDD-related toxic effects mediated through the AhR signal transduction pathway, but there are no studies that address possible joint action of PBDEs and TCDD on any toxicity endpoint. Furthermore, the mechanistic evidence suggesting possible antagonism is offset by thyroid toxicity data for TCDD alone and PBDEs alone that suggest the possibility of joint additivity on the basis of a common non-AhR-mediated mode of action (i.e., inhibition of T₄ binding by hydroxylated intermediates). Based on these considerations, ATSDR recommends that additivity be assumed in exposure-based screening assessments for the protection of public health from oral exposure to mixtures of these components. When the screening assessment indicates a potential hazard, further evaluation is needed, using biomedical judgment, community-specific health outcome data, and taking into account community health concerns.