

## **DoD comment #1 regarding UFs and with respect to the EPA DDEF Guidance:**

DoD Comment: The Chemical Assessment Advisory Committee (CAAC) recommends use of data on chemicals with the same MOA to complement the database. The DoD concurs with such an approach. We assume that using surrogate data on sensitivity for developmental neurotoxicity would reduce or eliminate the UFD -- this would be expected from EPA's 2014 "Guidance for Applying Quantitative Data to Develop Data-Derived Extrapolation Factors for Interspecies and Intraspecies Extrapolation". If the CAAC agrees, we suggest adding a discussion of how use of surrogate data would reduce uncertainty for UFD.

**Response:** It is not clear what the commenter means by "surrogate data," but appears to refer to data for chemicals (other than RDX) with the same MOA as RDX. Referencing the EPA's DDEF Guidance (2014), the commenter states "We assume that using surrogate data on sensitivity for developmental neurotoxicity would reduce or eliminate the UFD..." In fact, the referenced guidance outlines approaches for developing subfactors for INTERspecies and INTRAspecies extrapolation, based on toxicokinetic and/or toxicodynamic data for a particular chemical (or group of chemicals that share a mode or mechanism of action or TK characteristics). Uncertainty factors for database deficiencies are not addressed within the DDEF guidance. The term "surrogates" in the context of the DDEF guidance, refers to surrogate tissues (i.e., tissue other than the critical target tissue), surrogate measures (e.g., use of glomerular filtration rate as a surrogate for clearance), and surrogate dose metrics (e.g., concentration of parent compound as a surrogate for concentration of active metabolite). The term "surrogates" in this context does not refer to chemical surrogates (i.e., other substances having a similar toxic MOA).

DoD Comment: The draft report (Page 23) suggests use of "a full UFH of 10." However, this recommendation appears to differ from standard EPA procedures that recognize that the 10-fold UFH is a composite of kinetic and dynamic influences. Furthermore, since brain RDX concentrations at observation of seizure in swine, quail, and rats are very similar (~20 ppm), and GABA is phylogenetically conserved across species, that this would support a reduction in the potential for RDX to act differently within humans as well as other species. Current protocols for investigating neurodevelopmental effects are likely inadequate. If the CAAC retains this recommendation, DoD would appreciate a discussion of what studies would be sufficient to address this uncertainty.

**Response:** The commenter is correct the the 10-fold UFh is a composite of kinetic and dynamic influences. To quantify human variability, data would be needed to characterize population distributions of the relevant kinetic parameter or effective dose in the general population and sensitive subpopulations. Since there are not sufficient data to inform either the kinetic influences of RDX in humans (e.g., inter subject variability in absorption and clearance), nor the dynamic influences (e.g., inter subject variability in receptor binding and response), the default 10-fold UFh is appropriate. It is worth noting that very few DDEF for human variability have been adopted in regulatory assessments to date, and none for the toxicodynamic subfactor, since human data are rarely available or sufficient for this purpose.

Information regarding the brain RDX concentrations at observation of seizure in various species, and the phylogenetic conservation of GABA receptor across species could potentially be the basis for developing a DDEF for INTERspecies toxicodynamics. However, it is unclear that the relevant quantitative data are available and sufficient. If such data exist, they should be addressed within the Draft Toxicological Assessment of RDX. Absent this information, it is appropriate that the toxicodynamic portion of the interspecies UF is currently set at the default of 3x.