DOD Question to SAB CAAC to explain basis for recommendation for a UF_H of 10

- 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.

Rationale and points for discussion

Much of the human data on RDX exposure outcomes are derived from descriptive clinical case outcomes reported with virtually no exposure data. The outcomes for the most part focus on acute seizure-like activity and the onset and persistence of convulsions after purported exposure(s) occurred. The majority of the human RDX data is from adult exposure situations. Indeed, the CAAC pointed to several examples in clinical case reports and the Ma and Li epidemiological study (1993) that adverse outcomes can manifest in the absence of frank convulsions, and can persist for some time after exposure. Without exposure measurements and control of confounding factors, one cannot define the dose-response relationship for RDX exposures that cause neurological impairments without frank convulsions from the human literature. Likewise, the available data from animal studies with RDX considered by the panel provide clear evidence that exposure to sufficiently high doses of the chemical elicits convulsions. However, data on the influence of low-level exposure(s) of RDX either through adult life stages, or most importantly, during the highly susceptible perinatal period, on more subtle, yet no less important, behavioral, psychomotor, and cognitive outcomes are missing. It is generally agreed that the balance/imbalance of neuronal network excitation/inhibition during the perinatal and post-weaning periods of development have profound and measurable influences on the functional and anatomical integrity of developing neuronal networks not only impacts behavioral, psychomotor, and cognitive outcomes throughout the lifespan, and can also promote significantly greater susceptibility to subsequent seizurogenic chemical and physical triggers (Lein 2013; Lee 2016; Meunier 2017). There is a wealth of peer-reviewed experimental evidence showing that even modest impairments in the excitation/inhibition balance of developing neuronal circuits, whether originating from genetic mutations, chemical exposures, or the combination can affect long-lived (possibly permanent) changes in behavioral, psychomotor, and cognitive outcomes. This is particularly important for chemicals that interfere with GABAergic neurotransmission. It is also important to emphasize the developmental transition of $GABA_A$ receptor from excitatory to inhibitory neurotransmission during the perinatal/postnatal period, which adds additional complexity to the how dose and timing of RDX exposures alters neurological outcomes. This is especially important since RDX has been shown to interact in a competitive manner with picrotoxin at $GABA_A$ receptors of BLA, but once it alters their function its actions are poorly reversible (Williams 2013).

Clearly there are major gaps in our knowledge about exposures to sub-convulsive doses of RDX and their possible neurological ramifications, especially during the perinatal and early weaning periods of development. Clearly such exposures are possible and relevant, and could have consequences not only to individuals directly exposed to RDX but also those exposed through transplacentally and/or during lactation.

Is there biological plausibility to support a more stringent full UFH of 10 for RDX? There are no low-dose developmental exposure studies with RDX that focus on neurological outcomes that measure behavioral, psychomotor, and cognitive outcomes in the F1. However, there is a rich literature demonstrating *in vivo* and *in vitro* that developmental exposure to seizurogenic chemicals that alter the balance of neural network excitation/inhibition, albeit through distinct molecular mechanisms, have potent influences on outcomes relevant to developmental neurotoxicity at concentrations below those that elicit convulsions, but influence behavioral, psychomotor, and cognitive outcomes. Examples relevant to RDX include the $GABA_A$ receptor antagonist bicuculline (Salari 2017; Nasehi 2017; Grasso 2016), and domoic acid (Marriott 2016; Doucette 2016; Hiolski 2016; Mills 2016; Zuloaga 2016; Costa, 2010; Grant 2010).

Finally, Zhang and Pan (2008) provided strong evidence that adult mice fed RDX at a sub-convulsive dose of 5mg/kg for 28 days resulted in significant changes in key miRNA brain transcripts related to not only neurological and metabolic functions, but also were changed in a tissue-specific manner. It is not unreasonable to conclude that such effects are likely could have long-lived consequences on brain development should they be elicited in the perinatal period (Hu 2017).

New citations

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