

**Comments to the EPA Science Advisory Board Review Meeting for RDX
Submitted by the Office of the Secretary of Defense, Department of Defense
April 6, 2017**

Thank you for the opportunity to provide input to the EPA on the SAB Review of the RDX IRIS Assessment. Please consider the following comments and suggestions:

1. Uncertainty factors (UFs) account, in part, for limited or missing data. A significant amount of new data have been collected since the IRIS assessment in 1988. Therefore, additional data should result in less uncertainty in the composite UF. In this case, the CAAC recommends a larger composite UF when nearly 30 years of exposure based on the current RfD have produced no evidence of adverse human health effects.

- Database insufficiency. The proposed new RfD is based on adult neurotoxicity, and supported with additional, GLP toxicity studies, mechanism of action, and kinetic (PBPK modeling) data. Notwithstanding this additional information, this reevaluation seems to suggest increased uncertainty based on database insufficiency. DoD is unclear as to how can this be justified scientifically, and if the recommendation is retained, would appreciate a discussion of this issue in the report.
- 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 UF_D -- 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 UF_D .
- The draft report (Page 23) suggests use of "a full UF_H of 10." However, this recommendation appears to differ from standard EPA procedures that recognize that the 10-fold UF_H 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.

2. The DoD has concerns about the precedence of setting an RfD based on the response of one animal in one experiment published prior to the original IRIS assessment, especially when there are more recent, higher quality, corroborative data available measuring the same outcome.

- The CAAC recommends basing the RfD on a study (Cholakias et al., 1980) that has multiple issues associated with study quality and applicability. Examples include that the study: (1) was not conducted according to Good Laboratory Practices; (2) used impure RDX as test article; and (3) reported a single seizure incidence in a single animal as a possible LOAEL. This would seem to discount all of the recent, higher quality studies and mechanistic/PBPK analyses since the 1988 evaluation. Use of this study would appear in conflict with regard to the evaluation of cognitive and behavioral effects: the draft report (Page 9) states that an RfD cannot be based on those data because the "the data are not sufficiently robust to evaluate dose-response relationships."

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The DoD suggests the absence of a dose-response relationship is equally applicable to Cholakis et al. (1980).

- DOD suggests that, when multiple studies exist for the same endpoint, weight of evidence with regard to the quality of the study, e.g., demonstration of a robust dose-response relationship and lack of possible confounding due to impurities, be used to select the critical study for quantification of an RfD. Rather than relying on a single study, DoD recommends use of a meta-analytic procedure to evaluate the incidence on when seizure was observed. Such analyses can weight study quality, as well as weighting by the inverse of statistical confidence intervals. Meta-analysis would allow the RfD to be based on more of the available, quantitative data. EPA has performed similar meta-analyses for other substances (e.g., second-hand smoke and potential exposures to ozone) and use of meta-analyses are also recommended in EPA's 2016 draft "Office of Pesticide Programs' Framework for Incorporating Human Epidemiologic & Incident Data in Risk Assessments for Pesticides."