

Deriving Toxicity Values for Organophosphate Nerve Agents: A Position Paper in Support of the Procedures and Rationale for Deriving Oral RfDs for Chemical Warfare Nerve Agents

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ABSTRACT

During the process of deriving oral Reference Dose (RfDs) values for chemical warfare agents, several issues arose regarding the identification of adverse effect levels and the application of uncertainty factors. For those agents that function as cholinesterase inhibitors (*e.g.*, agents VX, GA, GB, and GD), these issues included the following: (1) Is the endpoint of blood cholinesterase inhibition an indicator of toxicity or a biomarker of exposure? (2) Can an experimental animal species be more sensitive than humans, thereby eliminating the need for an animal-to-human uncertainty factor? (3) Can the uncertainty factor that is used to extrapolate from a lowest-observed adverse-effect-level (LOAEL) to a no-observed-adverse-effect-level (NOAEL) be less than the default value of 10? (4) Can an oral RfD be derived from non-oral toxicity data? (5) Can an uncertainty factor of less than 10 be used to extrapolate from subchronic to chronic exposure (*i.e.*, is the critical effect adequately described by the subchronic exposure data)? (6) What constitutes an adequate data base for organophosphate cholinesterase inhibitors, and what uncertainty factor should be used for an incomplete data base?

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