AI/ML AND VIRTUAL HUMAN PLATFORMS FOR THREAT AGENT HAZARD ASSESSMENT AND MEDICAL COUNTERMEASURE DISCOVERY AND DRUG DEVELOPMENT

Towards A Toxicokinetic Model Of Nerve Agent Injuries In Humans

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We describe a novel application of a toxicokinetic/toxicodynamic (TK/TD) model to estimate the probability of injury and mortality due to the inhalation of the nerve agent sarin (GB) in rats and our progress towards humanizing the model for casualty estimation. The model describes uptake, clearance, and the dynamics of GB and acetylcholinesterase with a set of four coupled ordinary differential equations. The model parameters were determined by using recent data on lethal dosage values for rats and mice as well as parameter fitting. This simple model accurately reproduces results from historical data sets and can predict the probability of effects for GB for exposures with arbitrary concentration/time histories. TK/TD model outputs were compared against two implementations of a toxic load model using identical concentration time histories. The results from the two models differ significantly at both long and short exposure times, and we explain this difference in terms of the limitations of the toxic load model in these cases.

We also present our methods for 1) humanizing the parameters in the rat TK/TD model to provide estimates of human injury and fatality that go beyond simple probit analysis, 2) expanding the number of nerve agents in the model, and 3) incorporating a percutaneous component to the model. The result of this effort will be a physiologically based TK/TD model as an alternative for predicting effects over the large range of exposure times and concentration histories likely in realistic exposure scenarios. The model can be used for casualty estimation but focusing on molecular/cellular interactions will make it possible to include models of countermeasure effectiveness.

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