## MITIGATION - SCIENCE AND TECHNOLOGY ADVANCES FOR CHEMICAL AND BIOLOGICAL HAZARD MITIGATION

# Towards Accurate Determination Of Short-term Inhalation Chemical Exposure Thresholds: Test Cases Of Phosgene And Tear Gas (cs)

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Phosgene and tear gas (CS, 2-chlorobenzalmalononitrile) are readily available from industrial sources, law enforcement stockpiles, or could be easily obtained through simple laboratory synthesis. These agents have a history of use as chemical weapons and could represent a terrorist threat. In addition, CS is harmful in non-warfare conflicts such as police actions. Mitigation and readiness for such harmful chemical weapon exposures rely on short-term inhalation chemical exposure thresholds, commonly known as MEGs (Military Exposure Guidelines), AEGLs (Acute Exposure Guideline Levels), etc. The toxic load equation establishes threshold concentrations at multiple durations, C^n x t = constant, which Toxic Load Exponent n (TLE or n-value) directly follows from the probit model. Derivation of these thresholds often requires the combined use of multiple independent studies. We published a thorough framework to help accomplish this goal (Prussia, A. J., et al., Regul. Toxicol. Pharmacol. 2020, 115, 104682). In the present work, we applied the framework to reevaluate short-term inhalation thresholds for CS and phosgene using recently published data. CS is an example of a chemical with many studies available: three independent groups studied six species, resulting in 14 datasets. Our framework suggested that the datasets are not parallel in the probit space, deserving either a common effect or random-effects meta-analysis. However, 8 of these datasets either fail statistical goodness-of-fit tests or lead to illogical conclusions (longer durations appear to be more protective). The remaining 6 studies are homogeneous. Therefore, the common-effect meta-analysis was applied, resulting in a TLE for CS of 0.71 (95% CI: 0.64, 0.79). Phosgene is an example of a chemical with conflicting results in the literature. We confirmed the suitability of random-effects model for phosgene by applying our framework to 8 datasets, including two new ones. This work resulted in a TLE for phosgene of 0.78 (95% CI: 0.73, 0.84). This is significantly different from a previous study that found phosgene's TLE to be 1.17 without incorporating a meta-analytical framework. These TLEs for CS and phosgene enable appropriate extrapolation of points-of-departure to any short-term duration required for safeguarding the civilian or military population.