Investigating Dose Addition and Response Addition for Risk Assessment of Mixtures

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Additivity is a common assumption in the risk assessment of chemical mixtures. The scientific basis for this assumption comes from observing adverse effects in *in vivo* serial dilution studies, where each chemical is present at a dose that is a serial dilution of a dose close to the LOAEL for each chemical. However, an alternative hypothesis is that variability in the LOAELs for each chemical may explain this apparent additivity of effect.

Recent studies by Pham et al. (2020) and Paul Friedman et al. (2023) have investigated the sources of variability in the LOAELs observed in *in vivo* studies[1,2]. Using the findings of Pham et al., 2020 and Paul-Freeman et al., 2023, the Principal Investigator will investigate the potential for inter-study variation to cause "false positive" responses in mixture studies that use the serial dilution study design. A proof-of-concept paper will be published as open access in the peer-reviewed scientific literature. The paper will present the issue of LOAEL uncertainties and will include discussion of areas for future research.

Implications: If apparently additive effects in serial dilutions studies of mixtures are statistical artefacts, then the assumption of additivity for mixtures risk assessment may need to be revisited.

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[1] Ly Pham L, Watford S, Pradeep P, Martin MT, Thomas R, Judson R, Setzer RW, Paul Friedman K. Variability in *in vivo* studies: Defining the upper limit of performance for predictions of systemic effect levels. Comput Toxicol. 2020 Aug 1;15(August 2020):1-100126. doi: 10.1016/j.comtox.2020.100126. PMID: 33426408; PMCID: PMC7787987.
[2] Friedman KP, Foster MJ, Pham LL, Feshuk M, Watford SM, Wambaugh JF, Judson RS, Setzer RW, Thomas RS. Reproducibility of organ-level effects in repeat dose animal studies. Comput Toxicol. 2023 Nov;28:1-17. doi: 10.1016/j.comtox.2023.100287. PMID: 37990691; PMCID: PMC10659077.