Frawley et al, 1957

Guidelines/Criteria	
Reference:	Frawley JP, Fuyat HN, Hagan EC, Blake JR, Fitzhugh OG. 1957. Marked potentiation in mammalian toxicity from simultaneous administration of two anticholinesterase compounds. J Pharmacol Exp Ther 121(1):96-106.
***In vivo* Study Type** Route of Administration Species & age of animals	Dietary study Dietary Adult male albino rats (Osborn-Mendel strain)
Study Duration	16 weeks, including 8 weeks of treatment
Type of Mixture Binary >2 components Similar acting or dissimilar What Mode of Action was investigated?	 Yes Similar AchE inhibition
Parameters/End points Measured Target organs/Critical effects Pharmacological changes or adverse effects	 Whole blood, plasma and erythrocyte cholinesterase activity Phamacological, but adverse if depressed sufficiently
Individual Components Characterisation of individual compounds Name, exact chemical name, CAS no. Were dose responses established for individual components? Were no effect levels established? Were doses below the NO(A)ELs investigated?	 EPN and malathion Yes 5ppm for EPN, 500ppm for malathion Yes for one component
Mixtures Investigated Number of dose levels How does the mixture make-up compare to individual components? (e.g. low dose) equivalents used?) No. of technical replicates per exposure condition (*in vitro*) No. of animals per dose group (*in vivo*)	 Two mixtures tested, of which one was below the NOEL for both components individually Components present at 1x NOEL for EPN and 0.2x NOEL for malathion.
Observations/Findings	No effects seen at the one mixture which was below individual effect levels.
Overall opinion (e.g. sufficient numbers of groups investigated, group sizes adequate, observations reproducible, low dose levels used investigated)	 Dose responses not very well defined, and only a single dose below effect levels was studies, so weak evidence. [A short-term dietary dog study had inadequate group sizes to determine whether effects occurred (1 per sex per group).]