

Guidelines/Criteria	
Reference:	Jonker D, Woutersen RA, Feron VJ. 1996. Toxicity of mixtures of nephrotoxicants with similar or dissimilar mode of action. Food Chem Toxicol 34:1075-1082.
<b>In vivo Study Type</b>  Route of Administration Species & age of animals	Only the study with nephrotoxicants with similar MoAs is discussed here. For the study on nephrotoxicants with dissimilar MoAs, which was summarized in this paper, see Jonker 1993 oral gavage Wistar rats, 5wk old
<b>Study Duration</b>	32 days
<b>Type of Mixture</b> Binary >2 components Similar acting or dissimilar What Mode of Action was investigated?	four similar nephrotoxicity resulting from the bioactivating pathway (CYP450) following conjugation to glutathione and subsequently $\beta$ -lyase
<b>Parameters/End points Measured</b> Target organs/Critical effects  Pharmacological changes or adverse effects	kidney, clinical observations, haematology and clinical chemistry, urinalysis, pathology and histology adverse effects
<b>Individual Components</b> 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?	tetrachloroethylene (TETRA), trichloroethylene (TRI), hexachlorobutadiene (HCB), 1,1,2-trichloro-3,3,3-trifluoropropene (TCTFP). No CAS numbers were given. range finding study was performed to establish no/lowest-observed-nephrotoxic-level (NONE/LONEL) yes, NONE was established. For each compound, the NONE and LONEL were selected so that the NONE was one-fourth of the LONEL. No
<b>Mixtures Investigated</b> 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 ( <i>in vitro</i> ) No. of animals per dose group ( <i>in vivo</i> )	two four individual compounds and combination of four; one four combination of three compounds were included in the mixture at their individual NONE (1/4 LONEL) and 1/2 LONEL (all four) or 1/3 LONEL (three compounds). Individual compounds were tested at NONE and LONEL.  10 (control) or 5
<b>Observations/Findings</b>	Relative kidney weight was increased to the same extent following exposure to individual compounds at the LONEL, combined exposure to four compounds at the NONE (1/4 LONEL) and to three compounds at 1/3 LONEL. Supports validity of the additivity assumption (dose additivity) for these four nephrotoxicants.
<b>Overall opinion</b> (e.g. sufficient numbers of groups investigated, group sizes adequate, observations reproducible, low dose levels used investigated)	* no doses below NOEL - relevancy? * Dose-additivity was shown based on the application of the same 'toxicity units' for all groups (individual compounds=1TU, four compound mixture=4*1/4=1TU, three compound mixture=3*1/3=1TU) * study is the last in a series of mixtures studies by the same group: mixture with dissimilar MoA/different target organs (Jonker 1990), mixture with dissimilar MoA/same target organ (Jonker 1993 acute and subacute), mixture with similar MoA/same target organ (this study-Jonker 1996)