

Guidelines/Criteria	
Reference:	Heindel JJ, Chapin RE, Gulati DK, George JD, Price CJ, Marr MC, Myers CB, Barnes LH, Fail PA, Grizzle TB, Schwetz BA, Yang RSH. 1994. Assessment of the reproductive and developmental toxicity of pesticide/fertilizer mixtures based on confirmed pesticide contamination in California and Iowa groundwater. <i>Fundam Appl Toxicol</i> 22:605-621.
In vivo Study Type Route of Administration Species & age of animals	ip C57BL/6 mice, 6 weeks old
Study Duration	4 week (i.p. administration once a week)
Type of Mixture Binary >2 components Similar acting or dissimilar What Mode of Action was investigated?	yes similar action assumed neurotoxicity indicative for Parkinson's disease
Parameters/End points Measured Target organs/Critical effects Pharmacological changes or adverse effects	brain (nigrostriatal dopamine system) Body weight, Locomotor activity, concentrations of dopamine (DA), dihydroxyphenylacetic acid - metabolite of dopamine (DOPAC), homovanillic acid - metabolite of dopamine (HVA) in striatal sections, tyrosine hydroxylase immunoreactivity (TH densimetry) in brain sections, lung histopathology
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?	limited toxicological information given on individual compounds Maneb (Manganese ethylenebisdithiocarbamate) and Paraquat dichloride (N,N'-dimethyl-4,4'-bipyridylium) Yes: individual compounds were administered singly at each two doses for 4 weeks; Paraquat doses: 5/10 mg/kg bw; Maneb doses: 15/30 mg/kg bw (DA, DOPAC and HVA concentrations were only measured in the high dose paraquat and maneb experiment) Dose response was established for TH density in Maneb: 15 mg/kg bw = NOEL, 30 mg/kg bw = LOEL Yes: Administered paraquat doses corresponded the NOEL for locomotor activity, activity counts, and TH density. Administered paraquat dose of 10 mg/kg bw was very close to the NOAEL for Dopamine and Dopamine metabolite (DOPAC, HVA) concentrations. Administered maneb low dose (15 mg/kg bw) corresponded to NOEL for TH density. no
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 (<i>in vitro</i>) No. of animals per dose group (<i>in vivo</i>)	4 dose combinations were administered for 4 weeks: Paraquat/Maneb: 5/15, 5/30, 10/15, 10/30 mg/kg bw Only one compound (paraquat) was administered at a dose below the NOEL (factor 2) for one specific endpoint (TH densimetry). The second compound of the mixture was dosed at the NOAEL or the LOEL level. not applicable 10
Observations/Findings	Effects were observed in combination groups only: decreased locomotor activity, increased levels of dopamine and metabolites, reductions in tyrosine hydroxylase immunoreactivity (in dorsal striatum, not in nucleus accumbens)
Overall opinion (e.g. sufficient numbers of groups investigated, group sizes adequate, observations reproducible, low dose levels used investigated)	Individual and combined doses seem to be relatively high. However no further information on effect and no-effect doses are given, besides LD50 values. LD50 doses of single compounds are only factor 3-12 higher than administered doses. Route of administration was i.p. No information on effect and no-effect doses of single compounds for other related effects. Group sizes seem adequate. No low doses administered.