

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. Fundam Appl Toxicol 22:605-621.
In vivo Study Type Route of Administration Species & age of animals	drinking water; water control and vehicle control group Sprague-Dawley rats, 10 weeks old
Study Duration	teratogenicity study (GD 6-20)
Type of Mixture Binary >2 components Similar acting or dissimilar What Mode of Action was investigated?	no yes (propylene glycol was added as a vehicle to each mixture to solubilize the pesticides in drinking water) dissimilar action assumed (pesticide/fertilizer mixtures representing up to 100-fold ground water contamination reproduction toxicity (no specific mode of action)
Parameters/End points Measured Target organs/Critical effects Pharmacological changes or adverse effects	body weight, food and water intake, liver and intact uterus weight, corpora lutea counts, number of implantation sites, resorptions, dead and live foetuses, very early resorptions (Salewski stain), foetal body weights, external malformations, visceral and skeletal examinations adverse effects
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?	yes Two mixtures were investigated: 1. Alachlor (15972-60-8), Atrazine (1912-24-9), Cyanazine (21725-46-2), Metolachlor (51218-45-2), Metribuzine (21087-64-9), Ammonium nitrate (6484-52-2), Propylene glycol (57-55-6) 2. Aldicarb (116-06-3), Atrazine (1912-24-9), Dibromochloropropane (96-12-8), 1,2-Dichloropropane (78-87-5), Ethylenedibromide (106-93-4), Simazine (122-34-9), Ammonium nitrate (6484-52-2), Propylene glycol (57-55-6) No, only mixtures at three dose levels were administered Yes: No effects were seen at each dose level 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>)	Each 3 dose groups containing the individual compounds at the following doses (representing 1x, 10x, 100x of observed ground water contamination):: Mixture 1 Alachlor: 0.4 - 42.1 µg/kg bw, Atrazine: 0.06 - 6.4 µg/kg bw, Cyanazine: 0.05 - 5.1 µg/kg bw, Metolachlor: 0.05 - 5.1 µg/kg bw, Metribuzine: 0.07 - 7.4 µg/kg bw, Ammonium nitrate: 1.3 - 132.6 µg/kg bw Mixture 2: Aldicarb: 0.4 - 42.1 µg/kg bw, Aldicarb sulfone: 0.35 - 41.2 µg/kg bw, Aldicarb sulfoxide: 0.35 - 41.1 µg/kg bw, Atrazine: 0.06 - 6.8 µg/kg bw, Dibromochloropropane: 0.001 - 0.1 µg/kg bw, 1,2-Dichloropropane: 0.5 - 62.7 µg/kg bw, Ethylenedibromide: 0.1 - 11.1 µg/kg bw, Simazine: 0.03 - 4.0 µg/kg bw, Ammonium nitrate: 1.2 - 142.5 µg/kg bw Each dose group corresponded most likely to a low dose; not applicable 22-27 animals/group
Observations/Findings	At the 1x mixture 1 two litters with skeletal malformations were observed (one short rib XIII, one bipartite cartilage, bipartite ossification center thoraci centrum) --> as there was no dose-response, these findings are considered to be incidental.
Overall opinion (e.g. sufficient numbers of groups investigated, group sizes adequate, observations reproducible, low dose levels used investigated)	Good study design, sufficient number of animals, relevant endpoints; good documentation. NOELs for long developmental toxicity are partly given in the reference. Low dose levels investigated