

# Heindel et al, 1995mice

Guidelines/Criteria	
Reference:	Heindel JJ, Chapin RE, George J, Gulati DK, Fail PA, Barnes LH, Yang RSH. 1995. Assessment of the reproductive toxicity of a complex mixture of 25 groundwater contaminants in mice and rats. Fundam Appl Toxicol 25:9-19.
<b>In vivo Study Type</b> Route of Administration Species & age of animals	drinking water, water control group Swiss CD-1 mice (11 week of age)
<b>Study Duration</b>	reproductive assessment by continuous breeding (7 days pre mating, 98 days breeding in breeding pairs, pairs are separated, selected F1 pups are reared in same sex groups for 74 days +/- 10 days of age, cohabitation for 7 days, housed singly until delivery of F2 generation
<b>Type of Mixture</b> Binary >2 components Similar acting or dissimilar  What Mode of Action was investigated?	no yes dissimilar action assumed (chemicals mix to simulate groundwater supplies near hazardous dumps) reproduction toxicity (no specific mode of action)
<b>Parameters/End points Measured</b> Target organs/Critical effects   Pharmacological changes or adverse effects	Clinical signs, parental body weight, fertility (number producing a litter/number of breeding pairs), litters per pair, live pups per litter, proportion of pups born alive, sex of live pups, pup body weights within 24 hr after birth, feed and water consumption, organ weight determination and histopathology of selected F1 organs, spermatology adverse effects
<b>Individual Components</b> Characterisation of individual compounds Name, exact chemical name, CAS no.	yes One mixture was investigated: Acetone, Aroclor 1260, Arsenic trioxide, Benzene, Cadmium acetate trihydrate, Carbon tetrachloride, Chloroform, Chlorobenzene, Chromium chloride hexahydrate, 1,1-Dichloroethane, 1,1-Dichloroethylene, 1,2-Dichloroethane, 1,2-t-Dichloroethylene, Di(2-ethylhexyl)phthalate, Ethylbenzene, Lead acetate trihydrate, Mercuric chloride, Methylene chloride, Nickel acetate tetrahydrate, Phenol, Tetrachloroethylene, Toluene, 1,1,1-Trichloroethane, Trichloroethylen, Xylenes
Were dose responses established for individual components?	No, only mixtures at three dose levels were administered
Were no effect levels established?	Yes
Were doses below the NO(A)ELs investigated?	Yes

<p><b>Mixtures Investigated</b> Number of dose levels</p>	<p>Each 3 dose groups containing the individual compounds at 1, 5, 10% of a stock solution: Acetone: 5.3, 26.5, 53 ppm, Aroclor 1260: 0.001, 0.005, 0.01 ppm, Arsenic trioxide: 0.9, 4.5, 9.0 ppm, Benzene: 1.25, 6.25, 12.5 ppm, Cadmium acetate trihydrate: 5.1, 25.5, 51.0 ppm, Carbon tetrachloride: 0.04, 0.20, 0.40 ppm, Chloroform: 0.7, 3.5, 7.0 ppm, Chlorobenzene: 0.01, 0.05, 0.10 ppm, Chromium chloride hexahydrate: 3.6, 18.0, 36.0 ppm 1,1-Dichloroethane: 0.14, 0.7, 1.4 ppm, 1,1-Dichloroethylene: 0.05, 0.25, 0.5 ppm, 1,2-Dichloroethane: 4.0, 20.0, 40.0 ppm, 1,2-t-Dichloroethylene: 0.25, 1.25, 2.5 ppm, Di-2-ethylhexyl)-phthalate: 0.0015, 0.0075, 0.015 ppm, Ethylbenzene: 0.03, 0.15, 0.3 ppm, Lead acetate trihydrate: 7.0, 35.0, 70.0 ppm, Mercuric chloride: 0.05, 0.25, 0.50 ppm, Methylene chloride: 3.75, 18.75, 37.5 ppm, Nickel acetate tetrahydrate: 0.68, 3.4, 6.80 ppm, Phenol: 2.9, 14.5, 29.0 ppm, Tetrachloroethylene: 0.34, 1.7, 3.40 ppm, Toluene: 0.7, 3.5, 7.0 ppm, 1,1,1-Trichloroethane: 0.2, 1.0, 2.0 ppm, Trichloroethylen: 0.65, 3.25, 6.50 ppm, Xylenes: 0.16, 0.8, 1.60 ppm</p> <p>Actual doses administered at the 10% concentrations are: Acetone: F0: 6190 µg/kg bw , F1: 8056 µg/kg bw, Aroclor 1260: F0: 1 µg/kg bw F1: 2 µg/kg bw, Arsenic trioxide: F0: 1051 µg/kg bw F1: 1368 µg/kg bw, Benzene: F0: 1460 µg/kg bw F1: 1900 µg/kg bw, Cadmium acetate trihydrate: F0: 5957 µg/kg bw F1: 7752 µg/kg bw, Carbon tetrachloride: F0: 4.7 µg/kg bw F1: 61 µg/kg bw, Chloroform: F0: 818 µg/kg bw F1: 1064 µg/kg bw, Chlorobenzene: F0: 12 µg/kg bw F1: 15 µg/kg bw, Chromium chloride hexahydrate: F0: 4204 µg/kg bw F1: 5472 µg/kg bw, 1,1-Dichloroethane: F0: 164 µg/kg bw F1: 213 µg/kg bw, 1,1-Dichloroethylene: F0: 58 µg/kg bw F1: 76 µg/kg bw, 1,2-Dichloroethane: F0: 4672 µg/kg bw F1: 6080 µg/kg bw, 1,2-t-Dichloroethylene: F0: 292 µg/kg bw F1: 380 µg/kg bw, Di-2-ethylhexyl)-phthalate: F0: 2 µg/kg bw F1: 2 µg/kg bw, Ethylbenzene: F0: 35 µg/kg bw F1: 46 µg/kg bw, Lead acetate trihydrate: F0: 8176 µg/kg bw F1: 10640 µg/kg bw, Mercuric chloride: F0: 58 µg/kg bw F1: 76 µg/kg bw, Methylene chloride: F0: 4380 µg/kg bw F1: 5700 µg/kg bw, Nickel acetate tetrahydrate: F0: 794 µg/kg bw F1: 1033 µg/kg bw, Phenol: F0: 3387 µg/kg bw F1: 4408 µg/kg bw, Tetrachloroethylene: F0: 397 µg/kg bw F1: 517 µg/kg bw, Toluene: F0: 818 µg/kg bw F1: 1064 µg/kg bw, 1,1,1-Trichloroethane: F0: 233 µg/kg bw F1: 304 µg/kg bw, Trichloroethylen: F0: 759 µg/kg bw F1: 988 µg/kg bw, Xylenes: F0: 186 µg/kg bw F1: 243 µg/kg bw</p> <p>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>)</p>
<p><b>Observations/Findings</b></p>	<p>&gt;= 5%: Water consumption was decreased (presumably due to taste); Reproduction F0: number of female pups/litter decreased (6.9/7.0/6.2/5.7) 10%: F1 generation: increased liver inflammation (f), increased abs. kidney/adrenal weight (f), increased incidence of nephropathy (m+f). Reproduction F0: Number of live pups/litter slightly decreased. Reproduction F1: Number of live pups/litter slightly decreased (not statistically significant), adjusted live pup weight decreased, decreased no. of copulatory plugs/no. cohabitated = mating index (14/19 compared to 16/20 in the control group = is considered a no-effect by the authors of the study), sperm concentration decreased, spermatid head counts decreased. No effects observed at 1% mixture.</p>
<p><b>Overall opinion</b> (e.g. sufficient numbers of groups investigated, group sizes adequate, observations reproducible, low dose levels used investigated)</p>	<p>Good study design, sufficient number of animals, relevant endpoints; NOAELs of individual compounds should be evaluated and compared to the actual doses administered.</p>