

Guidelines/Criteria	
Reference:	<p>Constan AA, Yang RSH, Baker DC, Benjamin SA. 1995. A unique pattern of hepatocyte proliferation in F344 rats following long-term exposures to low levels of a chemical mixture of groundwater contaminants. <i>Carcinogenesis</i> 16(2):303-310.</p> <p>Constan AA, Benjamin SA, Tessari JD, Baker DC, Yang RSH. 1996. Increased rate of apoptosis correlates with hepatocellular proliferation in Fischer-344 rats following long-term exposure to a mixture of groundwater contaminants. <i>Toxicol Pathol</i> 24:315-322.</p>
<b>In vivo Study Type</b> Route of Administration Species & age of animals	Drinking water Fischer-344 rats, 60 days
<b>Study Duration</b>	6 months study with 5 examination time points (3 days, 10 days, 1, 3, 6 months)
<b>Type of Mixture</b> Binary >2 components Similar acting or dissimilar What Mode of Action was investigated?	No Yes Dissimilar action assumed Liver toxicity
<b>Parameters/End points Measured</b> Target organs/Critical effects  Pharmacological changes or adverse effects	Liver histopathology, hepatocellular proliferation (BrdU immunohistochemistry), apoptosis (TUNEL assay and morphometric analysis), liver weight, body weight Adverse and non-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?	No Arsenic (arsenic trioxide), benzene, chloroform, chromium (chromium chloride hexahydrate), lead (lead acetate trihydrate), phenol, Trichloroethylene No, a 10-fold increase of the average concentrations of the individual chemicals in the mixture found in groundwater in the vicinity of hazardous waste sites was administered. No Unknown
<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> )	1x and 10x concentrations of the mixture were administered as ppm: Arsenic (arsenic trioxide) 3.1, 31, benzene 5, 50, chloroform 1.5, 50, chromium (chromium chloride hexahydrate) 0.7, 7, lead (lead acetate trihydrate) 3.7, 37, phenol 3.4, 34, Trichloroethylene 3.8, 38; 1x and 10x complete mixtures, 10x inorganic submixture and 10x organic submixture Not applicable 5/time point treated and 5/time point control
<b>Observations/Findings</b>	No effect on body weight gain, final body weights and food consumption, relative liver weights, AST, ALT, liver lesions Decreased water consumption Increased hepatocellular labelling indices at the 10-day and the 1 month time point in the 10x mixture and 10x submixtures dose groups. No changes at 1x Increased apoptotic rates and increased BrdU labeling in liver perivascular areas at the 10x mixture
<b>Overall opinion</b> (e.g. sufficient numbers of groups investigated, group sizes adequate, observations reproducible, low dose levels used investigated)	The rationale for concentration setting of the mixture is unclear. It is said that the chemicals tested are chosen based on environmental relevance, as they are among the most frequently detected in groundwater associated with hazardous waste sites. Only limited endpoints were assessed, as the study was focused on liver toxicity. No effects seen at the 1x concentration (which is considered to represent environmentally relevant concentrations).