Guidelines/Criteria		
Reference	Rider CV, Furr JR, Wilson VS, Gray LE Jr. 2010. Cumulative effects of in utero administration of mixtures of reproductive toxicants that disrupt common target tissues via diverse mechanisms of toxicity. Int J Androl 33:443-462. This is a review of the work the group has done on antiandrogens. For a description see Rider 2009 (and 2008). However, they also described two original studies which are discussed below.	
***In vivo* Study Type** Route of Administration Species & age of animals	10 mixture study (similar mode of action, different mechanism of toxicity) oral gavage Pregnant Sprague-Dawley rats on gestation day 2	binary mixture (common tissue with different mode of action and different mechanism of toxicity) oral gavage Pregnant Sprague-Dawley rats (adult, 90 day)
Study Duration	until PND 200	until PND 120 of mature F1 males
Type of Mixture Binary >2 components Similar acting or dissimilar What Mode of Action was investigated?	 ten dissimilar disrupt androgen signalling pathway via different mechanisms of toxicity: androgen receptor antagonism in the reproductive tract vs. inhibition of androgen synthesis in the foetal testis	 yes dissimilar disruption of androgen and AhR signalling pathways in the foetal male reproductive tract
Parameters/End points Measured Target organs/Critical effects Pharmacological changes or adverse effects	 androgen signalling pathway disruption: reproductive tract malformations, hypospadias, epididymal agenesis, undescended test adverse effects	 male reproductive tract malformations 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?	 vinclozolin, procymidone, linuron, prochloraz and six phthalates (BBP, DBP, DEHP, DiBP, DiHP, DPP) yes no yes (based on D-R curve)	 di (n-butyl) phthalate (DBP, CAS# 84-74-2) and 98% 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD, CAS# 1746-01-6) yes, in previous D-R studies with these chemicals no 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 (*in vitro*) No. of animals per dose group (*in vivo*)	 six (100, 80, 60, 40, 20, 10% of top dose (=1/7 ED50, see mixtures makeup) The two lowest dose groups contained individual chemicals at or below their NOAELs (data from D-R curves) for inducing male reproductive tract malformations. At the high dose, each chemical was in the mixture at 1/7 of its ED100 for inducing reproductive tract malformations 4 (mixture groups) 6 (control)	 two (100 and 65% of top dose) dose of the chemicals in the mixture were approximately equipotent, based on previous data and D-R curves for the individual compounds 4 per dose group
Observations/Findings	* no maternal toxicity or treatment related pup mortality * reduced BW of male offspring * significant incidence of female-like retained nipples at 20-100% dose groups; most other tissues were significantly affected at 40% of the top dose and above * analysis of the androgen-dependent endpoints revealed that dose-addition models provided estimates of mixture responses that closely approximate the observed responses. Integrated- and response addition models underestimated many of the effects observed	* response addition was exceeded for the epididymal, testicular, vas deferens, hypospadias and liver malformations and for testes and epididymal weights in the 100 and 65% mixture groups * increases in gross liver pathology and malformations of the external genitalia and vas deferens were unexpected as TCDD is not known to induce these malformations, and moreover, the gross liver changes were not seen with either chemical alone It was concluded that mixture responses exceeded those predicted by response addition.
Overall opinion (e.g. sufficient numbers of groups investigated, group sizes adequate, observations reproducible, low dose levels used investigated)	Low doses were tested, observations are reproducible. Good study by an experienced group, belongs to a series of studies (see Rider 2008 and 2009 (review)).	No doses below NOAELs tested, therefore may not be relevant to this report. However, contributes and adds to the series of studies conducted by this group.