Appendix 2: Empirical evidence for KER 3487 decreased intratesticular testosterone leading to NR.

The table details datasets considered reliable with or without restriction in the evaluation of methodological reliability.
For the effects on circulating testosterone and NR, ↓*/↑* denotes a statistically significant decrease/increase in the parameter at the given dose.
Both intratesticular and *ex vivo* testosterone were measured after *in utero* exposure to the stressor in the exposure window stated below. Intratesticular testosterone was measured directly in testis homogenates, whereas *ex vivo* testosterone was measured in culture media after culture of exposed testes.
Abbreviations: GD=gestational day; LOAEL=Lowest observed adverse effect level; NOAEL=No observed adverse effect level; NR=nipple retention; Ns= not significant; PND=postnatal day

Study design				**Upstream event (testosterone)**						**Downstream event (NR)**				**Reference**
Substance	**Species**	**Exposure window**	**Doses (mg/kg bw/day)**	**Intratesticular /*ex vivo***	**Method**	**Timepoints**	**Effect (pg/mL)**	**NOAEL (mg/kg bw/day)**	**LOAEL (mg/kg bw/day)**	**Timepoint**	**Effect (NR)[1]**	**NOAEL (mg/kg bw/day)**	**LOAEL (mg/kg bw/day)**	
Butyl benzyl phthalate	Rat	GD14-18	0 500	*Ex vivo* + Intratesticular	Radioimmuno-assay	GD18	↓*	-	500	PND13	Ns	500	-	(Hotchkiss AK et al., 2004)
Dibutyl phthalate	Rat	GD13-21	0 100 500	Intratesticular	Enzyme immunoassay	GD21	Ns ↓*	100	500	PND13	2/18[2] 5/31 7/8*	100	500	(Martino-Andrade AJ et al., 2009)
Diethylhexyl phthalate	Rat	GD7-PND17	0 750	*Ex vivo* + intratesticular	Fluoroimmuno-assay	GD21	↓*	-	750	PND13	↑*	-	750	(Borch J et al., 2004)
Diisonyl phthalate	Rat	GD7-21	0 300 600 750 900	Intratesticular[1]	Fluoroimmuno-assay	GD21	Ns ↓* ns ns	900	600	PND13	1.98±0.83, 2.00±0.64, 2.91±0.69, 3.14±1.21* 3.17±0.92*	600	750	(Boberg et al., 2011)
Linuron	Rat	GD14-18	0 75	*Ex vivo* + Intratesticular	Radioimmuno-assay	GD18	↓*	-	75	PND13	↑*	-	75	(Hotchkiss AK et al., 2004)
Prochloraz	Rat	GD7-PND16	0 50 150	*Ex vivo* + Intratesticular	Fluoroimmuno-assay	GD21	↓* ↓*	-	50	PND13	↑*	-	50	(Laier P et al., 2006)

Prochloraz	Rat	GD7-PND17	0 30	*Ex vivo* + Intratesticular	Fluoroimmuno-assay	GD21	Ex vivo ns; Intratesticular ↓*	-	30	PND13	↑*	-	30	(Vinggaard AM et al., 2005)
Tebuconazole	Rat	GD7-21	0 50 100	Intratesticular[3]	Fluoroimmuno-assay	GD21	1.75 ±0.71 1.25 ±0.40 0.88 ±0.46*	50	100	PND13	2.08±0.6 3.43±0.9* 3.07±2.5*	-	50	(Taxvig C et al., 2007)

*Statistically significant from the control group

[1]Measured as nipples/male

[2]# males with nipples/all males

[3] *Ex vivo* testosterone production was also measured, with no significant decrease