KER-2133, Appendix 1.

Empirical evidence for KER-2133 is compiled in table 1, which lists chemical stressors shown to antagonise the AR in vitro as well as causing NR in male rat offspring in vivo (Pedersen et al., 2022).

Table 1. List of substances inducing increased nipple/areola retention (NR) in male rat offspring (*in vivo*) and known to antagonize AR *in vitro*. Additional information, including species, strain, exposure period, time of NR measurement as well as the magnitude of NR at the effect dose is presented. * ($p < 0.05$). Abbreviations: SD = Sprague-Dawley; LE = Long Evans; GD = Gestational Day; PD = Pup Day; LOAEL = Lowest Observed Adverse Effect Level; N.D. = Not determined. p,p'-DDE, dichlorodiphenyldichloro ethylene.

Species / Strain	**Stressor**	**Exposure period**	**Time of measurement**	**NOAEL [mg/kg bw/day]**	**LOAEL [mg/kg bw/day]**	**Effect** ***p < 0.05***		**Reference**
						Number of nipples	**% nipples**	
Rat / SD	Fenitrothion	GD 12–21	PD 13 *PD 100*	20 *N.D.*	25 *N.D.*	4.2 * *(0)*	–	Turner et al., 2002
Rat / SD	Flutamide	GD 6–PD 21	PD 14	N.D.	3.5	7 *	–	Schreiber et al., 2020
Rat / SD	Flutamide	GD 0–20	PD 56	2.5	10	3.37 ± 1.34 *	–	Lu et al., 2006
Rat / SD	Flutamide	GD 14–PD 3	PD 12	2.5	10	–	100	Miyata et al., 2002
Rat / SD	Flutamide	GD 12–21	PD 13 *PD 100*	N.D. *N.D.*	6.25 *N.D.*	10.2 * *(8.3 *)*	–	McIntyre et al., 2001
Rat / SD	Flutamide	GD 14–18	PD 13	N.D.	40	6 *	–	You et al., 1998
Rat / SD	Flutamide	GD 12–21	PD 14	N.D.	100	–	100	Mylchreest et al., 1999

Species / Strain	Stressor	Exposure period	Time of measurement	NOAEL [mg/kg bw/day]	LOAEL [mg/kg bw/day]	Effect ** p < 0.05*		Reference
						Number of nipples	% nipples	
Rat / Wistar	Flutamide	GD 6–PD 30	PD 12 *PD 20*	0.025 *N.D.*	0.25 *N.D.*	2.9 * *(0)*	–	Fussell et al., 2015
Rat / Wistar	Flutamide	GD 7–PD 16	PD 13	N.D.	0.77	2.8 *	–	Christiansen et al., 2008; Hass et al., 2007
Rat / LE	Flutamide	GD 14–18	PD 13	N.D.	40	6 *	–	You et al., 1998
Rat / SD	Linuron	GD 14–18	PD 13	N.D.	75	2.16 *	–	Hotchkiss et al., 2004
Rat / SD	Linuron	GD 12–21	PD 13 *PD 35* *PD 56*	N.D. *N.D.* *N.D.*	50 *N.D.* *N.D.*	3.3 ± 0.4 * *(~ 2 *)* *N.D.*	–	McIntyre et al., 2002
Rat / SD	Linuron	GD 12–21	PD 13	25	50	3.7 *	–	McIntyre et al., 2000
Rat / SD	Linuron	GD 14–18	PD 10–13	N.D.	100	2.1 ± 0.7 *	–	Wolf et al., 1999
Rat / Wistar	Mancozeb	GD 7–PD 16	PD 13	6.25	25	0.6 ± 0.6 *	–	Hass et al., 2012
Rat / SD	p,p'-DDE	GD 14–18	PD 10–13	N.D.	100	3.13 ± 0.5 *	–	Wolf et al., 1999
Rat / SD	p,p'-DDE	GD 14–18	PD 13	N.D.	10	1.2 *	–	You et al., 1998
Rat / LE	p,p'-DDE	GD 14–18	PD 10–13	N.D.	100	0.74 ± 0.15 *	–	Wolf et al., 1999
Rat / LE	p,p'-DDE	GD 14–18	PD 13	10	100	3 *	–	You et al., 1998
Rat / Holtzman	p,p'-DDE	GD 14–18	PD 13	50	100	1.76 ± 0.56 *	–	Loeffler & Peterson, 1999

Species / Strain	Stressor	Exposure period	Time of measurement	NOAEL [mg/kg bw/day]	LOAEL [mg/kg bw/day]	Effect ** p < 0.05*		Reference
						Number of nipples	% nipples	
Rat / Wistar	Prochloraz	GD 6–PD 83	PD 12 *PD 20*	0.01 *N.D.*	5 *N.D.*	2.8 * *(0)*	–	Melching-Kollmuss et al., 2017
Rat / Wistar	Prochloraz	GD 7–PD 16	PD 13	8.75	35	1.7 ± 1.2 *	–	Hass et al., 2012
Rat / Wistar	Prochloraz	GD 7–PD 16	PD 13	25	30	3.6 [2.2;5.4] *	–	Christiansen et al., 2009
Rat / Wistar	Prochloraz	GD 7–PD 17	PD 13	N.D.	30	* *(data not shown)*	–	Vinggaard et al., 2006
Rat / Wistar	Procymidone	GD 7–PD 16	PD 13	N.D.	12.5	2.8 ± 1.2 *	–	Hass et al., 2012
Rat / Wistar	Procymidone	GD 7–PD 16	PD 13	N.D.	14.1	2.6 *	–	Christiansen et al., 2008; Hass et al., 2007
Rat / LE	Procymidone	GD 14–PD 3	PD 10–13	N.D.	100	3.75 ± 0.83 *	–	Wolf et al., 1999
Rat / SD	Pyrifluquinazon	GD 14–18	PD 13	12.5	25	4 *	–	Gray et al., 2019
Rat / Wistar	Tebuconazole	GD 7–PD 16	PD 13	12.5	50	1.6 ± 0.4 *	–	Hass et al., 2012
Rat / Wistar	Tebuconazole	GD 7–PD 16	PD 13	N.D.	50	3.43 ± 0.9 *	–	Taxvig et al., 2007
Rat / Wistar	Vinclozolin	GD 7–PD 16	PD 13	5	50	8.4 [6.9;9.6] *	–	Christiansen et al., 2009
Rat / Wistar	Vinclozolin	GD 7–PD 16	PD 13	N.D.	24.5	1.3 *	–	Christiansen et al., 2008; Hass et al., 2007
Rat /LE	Vinclozolin	GD 14–19	PD 13	N.D.	200	9.6 *	–	Wolf et al., 2000
Rat /LE	Vinclozolin	GD 14–15	PD 13	N.D.	400	4.86 ± 0.99 *	–	Wolf et al., 2000

Species / Strain	Stressor	Exposure period	Time of measure ment	NOAEL [mg/kg bw/day]	LOAEL [mg/kg bw/day]	Effect ** p < 0.05*		Reference
						Number of nipples	% nipples	
Rat /LE	Vinclozolin	GD 16–17	PD 13	N.D.	400	8.84 ± 0.68 *	–	Wolf et al., 2000
Rat /LE	Vinclozolin	GD 17–PD 3	PD 13	12.5	50	–	100	(Ostby et al., 1999

Some inconsistencies were observed in the empirical evidence for linuron, fenitrothion and p,p'-DDE, as indicated in table 2, which shows a list of stressors shown to have AR antagonistic properties in vitro or in other in vivo studies, but for which the doses tested in vivo did not produce a significant effect on NR (Pedersen et al., 2022).

Table 2. List of chemicals that caused no significant effect on NR in vivo, albeit being known to have AR antagonistic properties in in vitro studies or previous in vivo experiments. The highest dose tested that led to no significant effect is presented as the NOAEL. Additional information, including species, strain, exposure period, time of NR measurement as well as the magnitude of NR at the NOAEL is presented. Abbreviations: SD = Sprague-Dawley; GD = Gestational Day; PD = Pup Day; NOAEL = No Observed Adverse Effect Level. p,p'-DDE, dichlorodiphenyldichloro ethylene.

Species / Strain	Stressor	Exposure period	Time of measure-ment	Lowest dose tested	NOAEL [mg/kg bw/day]	Effect (number of nipples)	Reference
Rat / SD	Bisphenol C	GD 14–18	PD 13	12.5	200	1.21 (NS)	Gray et al., 2019
Rat / SD	p,p'-DDE	GD 6–PD 20	PD 13	5	50	NS *(data not shown)*	Yamasaki et al., 2009

Rat / Wistar	Epoxiconazole	GD 7–PD 16	PD 13	3.75	15	0.5 ± 1.0 (NS)	Hass et al., 2012
Rat / Wistar	Epoxiconazole	GD 7–PD 16	PD 13	15	50	3.38 (NS) [a]	Taxvig et al., 2007
Rat / SD	Linuron	GD 6–PD 21	PD 14	1.5	12.5	0.6 (NS)	Schreiber et al., 2020
Rat / SD	Fenitrothion	GD 1–PD 21	PD 12	Gestation: 0.62 Lactation: 1.32	Gestation: 3.75 Lactation: 7.75	0.0 ± 0.0	Okahashi et al., 2005

[a] This study had a control group with NR = 2.08, which can explain the non-significance compared to the exposure group despite the high NR value.

For linuron, one study, listed in table 2, did not show effect on NR after *in utero* exposure, whereas 4 studies listed in table 1 did show an effect. A lower dose was used in the study in table 2, which may explain the difference between results. Therefore, the inconsistencies can be explained by dose, and the level of confidence for prenatal linuron exposure resulting in NR in male offspring is judged to be strong.

For fenitrothion, one study listed in table 2 did not show effect on NR after *in utero* exposure, whereas 1 study listed in table 1 did show an effect. A lower dose was used in the study in table 2, which may explain the difference between results. Therefore, the inconsistencies can be explained by dose, and the level of confidence for prenatal fenitrothion exposure resulting in NR in male offspring is judged to be strong.

For p,p'-DDE, one study listed in table 2 did not show effect on NR after *in utero* exposure, whereas 5 studies listed in table 1 did show an effect. 4 of the studies in table 1 used a higher dose than the one in table 2, which may explain the differences between these results. The last study in table 1 used a lower dose than the one not inducing an effect in table 2. Further analysis of differences between these two studies is hindered by lack full reporting of NR results in the publication of the study in table 2. Less weight is therefore put on this study. All in all, the inconsistencies observed can be explained by dose, and the level of confidence for prenatal p,p'-DDE exposure resulting in NR in male offspring is judged to be strong.