

Appendix A11 – Uterotrophic

Uterotrophic	
Purpose	To detect estrogenic chemicals through a simple in vivo assay .
Design	There are two versions of the uterotrophic assay an immature version and an ovariectomized adult version. In both versions, two concentrations of test substance are administered orally or sc to ovariectomized or immature female rats for a minimum of three consecutive days. Estrogenic substances cause a uterotrophic response that is due to the imbibition of water and the growth of cells.
Endpoints	Uterine weight is measured and compared with controls.
Interpretation	A statistical increase in uterine weight compared with controls is a positive result.
Main peer review comments	<ul style="list-style-type: none"> • The rat uterus is biologically relevant for detecting estrogenic effects • Validation program was inadequate in several aspects <ul style="list-style-type: none"> ○ Inadequate number of negative substances tested ○ Phytoestrogen levels need to be addressed ○ Program seriously flawed by not conforming to ICCVAM/ECVAM <p>[These comments were responded to by OECD.]</p> <ul style="list-style-type: none"> • The protocol needs additional refinement <ul style="list-style-type: none"> ○ Dose setting procedure needs to be clarified ○ Definition of what constitutes a positive result <p>[These were clarified in the OECD Test Guideline]</p> <ul style="list-style-type: none"> • The antiestrogen procedure cannot be claimed to be validated because only one strong chemical was tested. [OECD agreed with this point. Finding pure antiestrogens for validation of this MOA is a real problem.]
Strengths (within the context of the proposed battery)	<ul style="list-style-type: none"> • Relatively rapid screen that is quite specific to estrogenic effects (see limitations) • In vivo procedure incorporates metabolism; thus, it can detect chemicals that need activation. • Oral administration will model a primary exposure route and incorporates ADME

Uterotrophic

Limitations
(within the
context of the
proposed battery)

- Uterotrophic response is not due exclusively to estrogenic chemicals, so a uterotrophic response should be confirmed by corroborating information such as ER binding or transcriptional activation.