



European Cluster to
Improve Identification
of Endocrine Disruptors



FEMALE REPRODUCTION AND EDCs

The FREIA Project

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These projects have received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No. 825161 (ATHENA), No. 825762 (EDCMET), No. 825759 (ENDpoiNTs), No. 825753 (ERGO), No. 825100 (FREIA), No. 825489 (GOLIATH), No. 825745 (SCREENED), No. 825712 (OBERON). This output reflects only the author's view and the European Union cannot be held responsible for any use that may be made of the information contained therein.

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The FREIA consortium

Amsterdam | October 2019





1 in 6 couples fertility problems

OVULATION DISORDERS account for infertility
in 1 out of 4 infertile couples



BREAST CANCER
1 in 8 women



IRREGULAR
MENSTRUAL CYCLES
50 per 1000 women



POLYCYSTIC OVARY
SYNDROME (PCOS)
5-15% of women



EARLY MENOPAUSE
*1 in 250 women
by age 35 years*



ENDOMETRIOSIS
*10% reproductive-age
women*

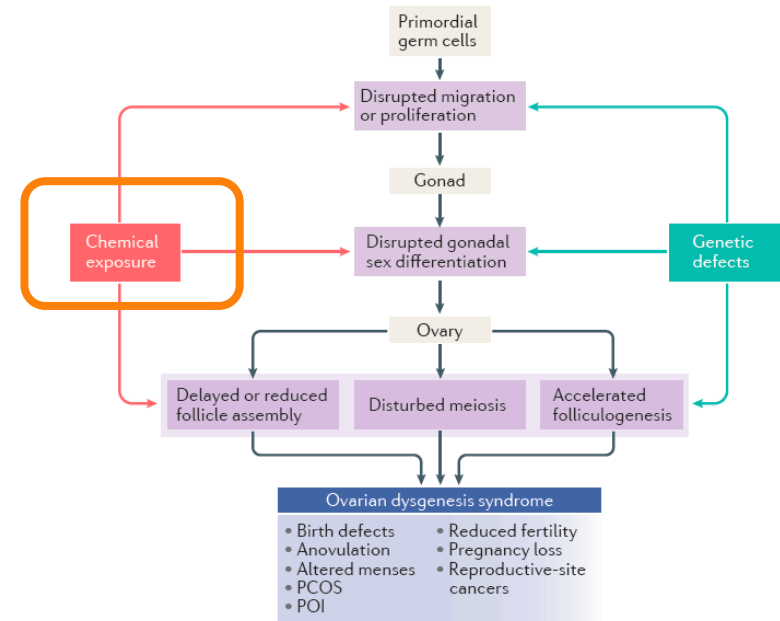
OVARIAN DYSGENESIS SYNDROME (ODS)

“alterations in ovarian structure or function that may manifest as fecundity impairments, gynecologic disorders, gravid diseased or later onset adult diseases”
– Buck Louis 2011

Studies showing clear associations (fetal) EDC and ODS are scarce

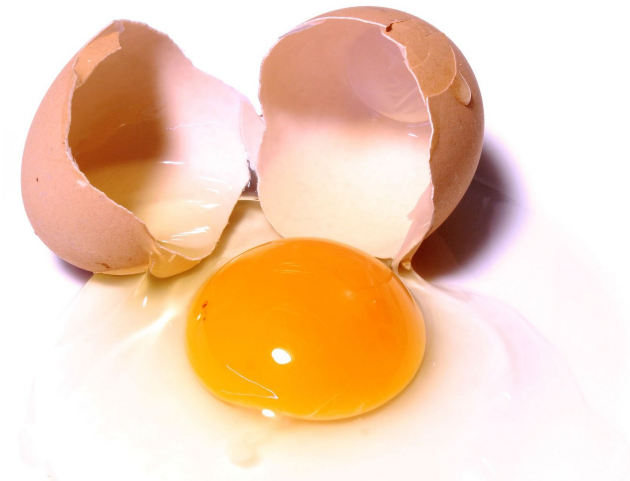
DES associated with impaired fecundity, earlier age at menopause, increased incidence uterine fibroids; **PFOA** delays menarche; **DDT** reduces number of follicles; high serum **BPA** associated with PCOS; **DEHP** associated with endometriosis in humans

Pathological mechanisms are unclear

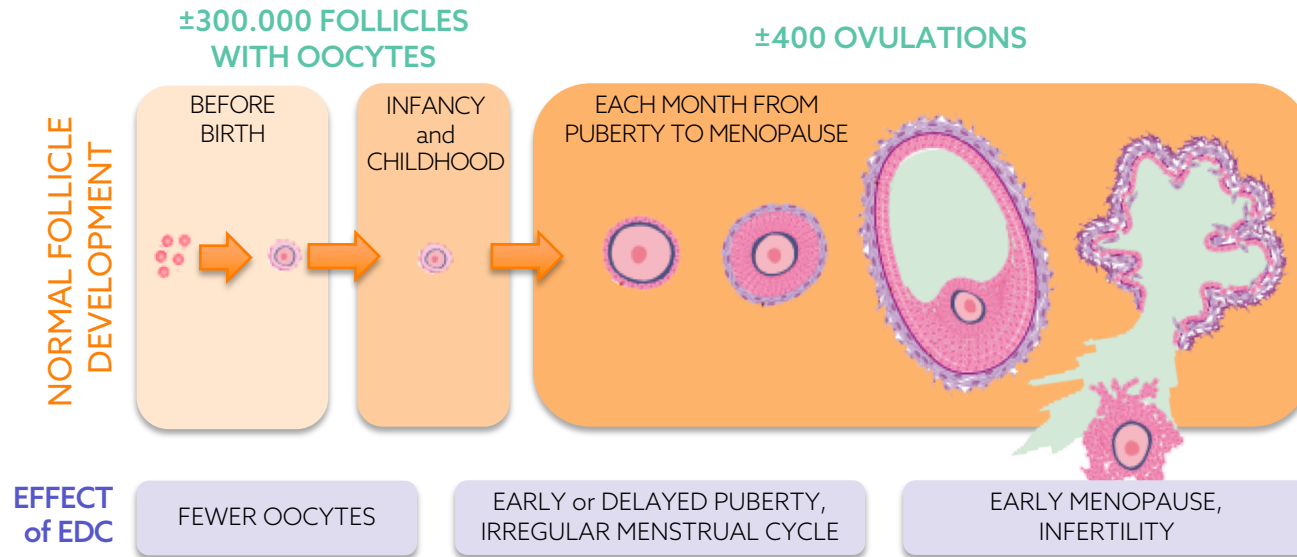


CRACKING THE EGG FACTOR

- Better understanding of biology
- Human-relevant biomarkers
- Sensitive endpoints
- Improve test capabilities

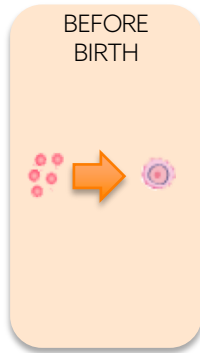


DIFFERENT LIFE STAGES, DIFFERENT EFFECTS

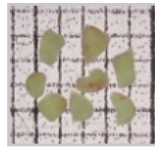


DIFFERENT LIFE STAGES, DIFFERENT EFFECTS

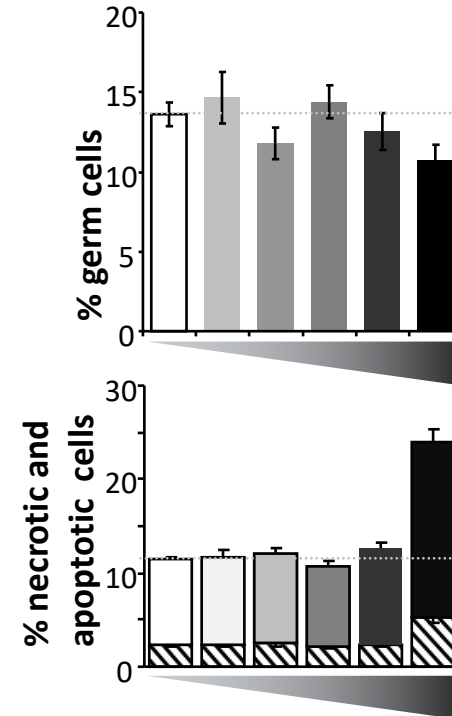
±300.000 FOLLICLES
WITH OOCYTES



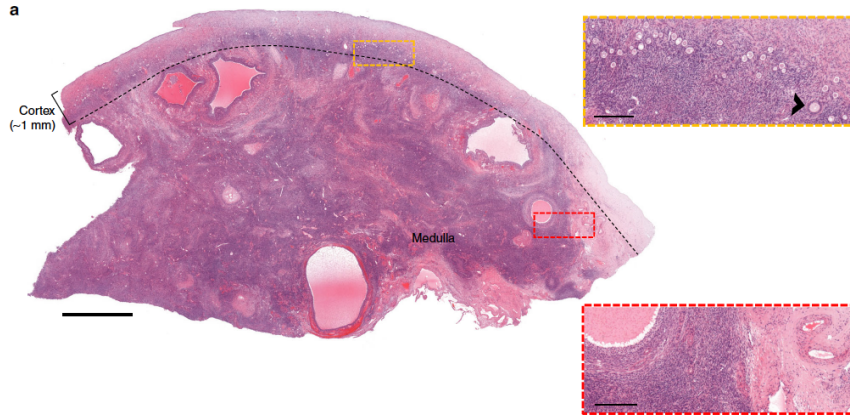
HUMAN FETAL
OVARY
(7-12 DW)



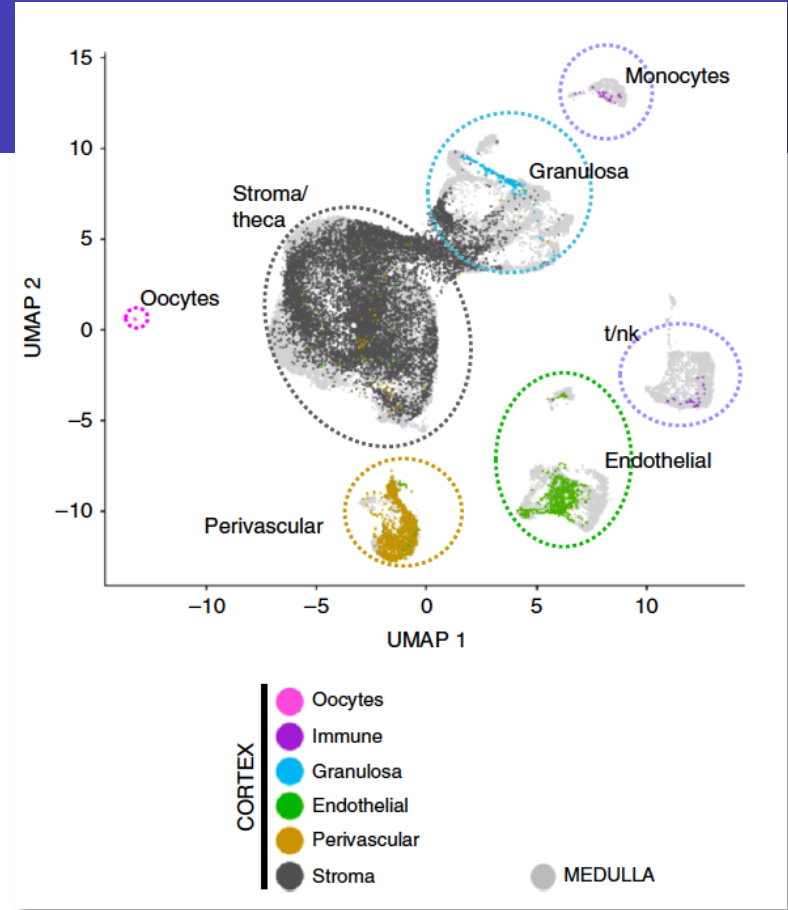
≤ 1 mm³



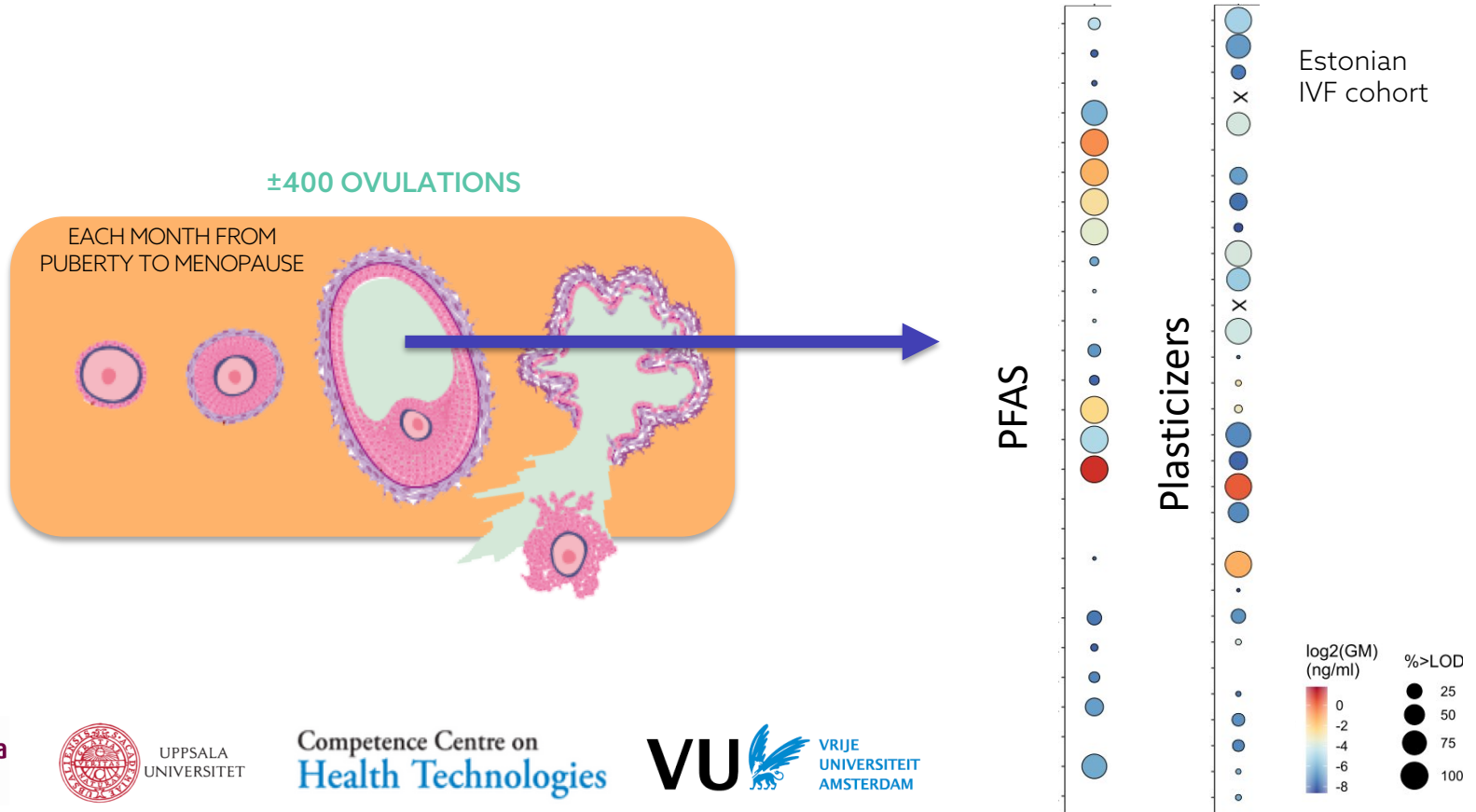
ADULT OVARY



**NO GERMLINE
STEM CELL POPULATION**

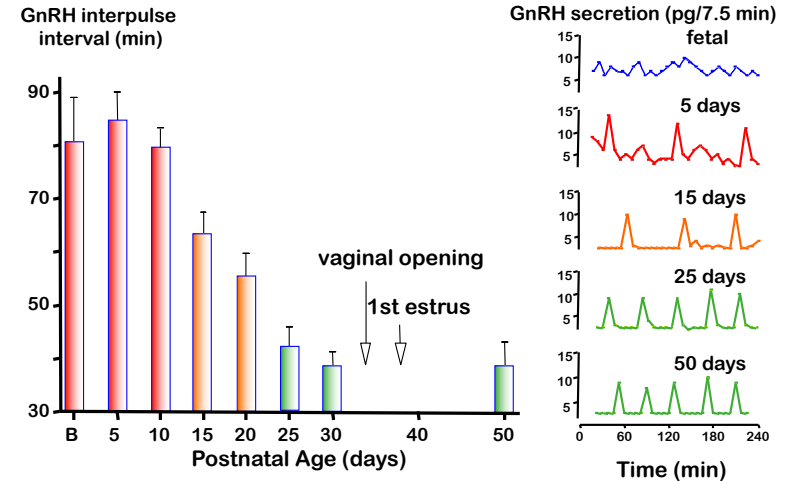
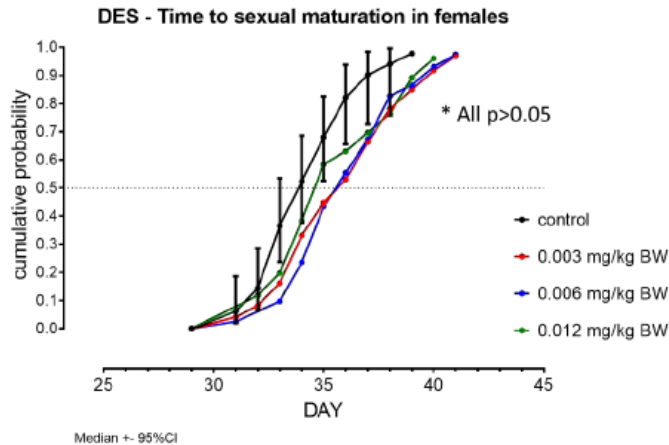


DIFFERENT LIFE STAGES, DIFFERENT EFFECTS



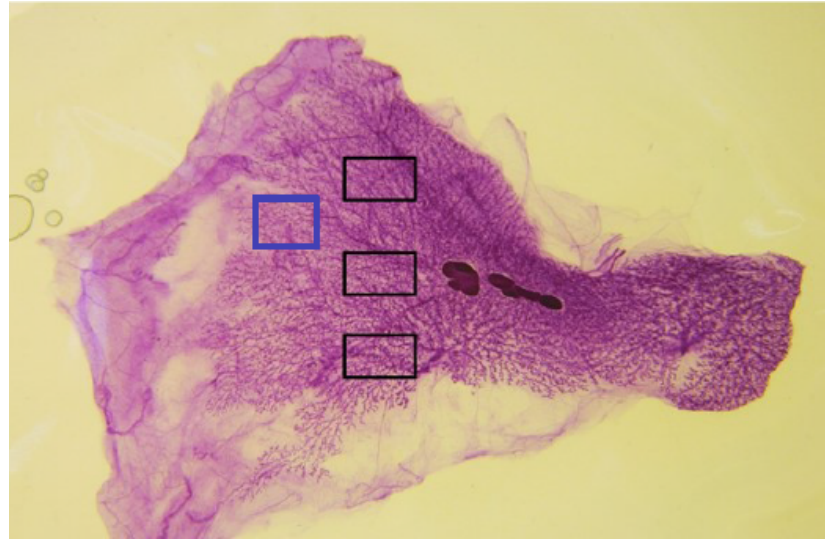
SENSITIVE ENDPOINTS

Onset of puberty



SENSITIVE ENDPOINTS

Mammary gland



IMPROVE UNDERSTANDING

Archives of Toxicology
<https://doi.org/10.1007/s00204-020-02834-y>

REVIEW ARTICLE



Putative adverse outcome pathways for female reproductive disorders to improve testing and regulation of chemicals

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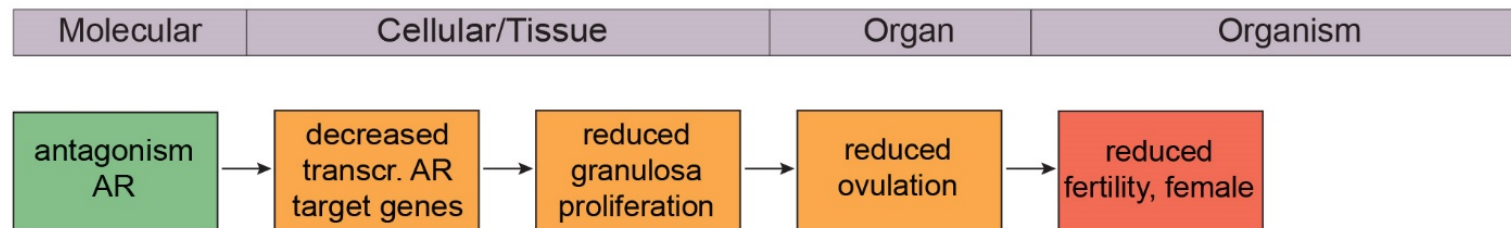
A putative adverse outcome pathway network for disrupted female pubertal onset to improve testing and regulation of endocrine disrupting chemicals

Delphine Franssen^a, Terje Svingen^b, David Lopez Rodriguez^a, Majorie Van Duursen^c, Julie Boberg^b, and Anne-Simone Parent^{a,d}

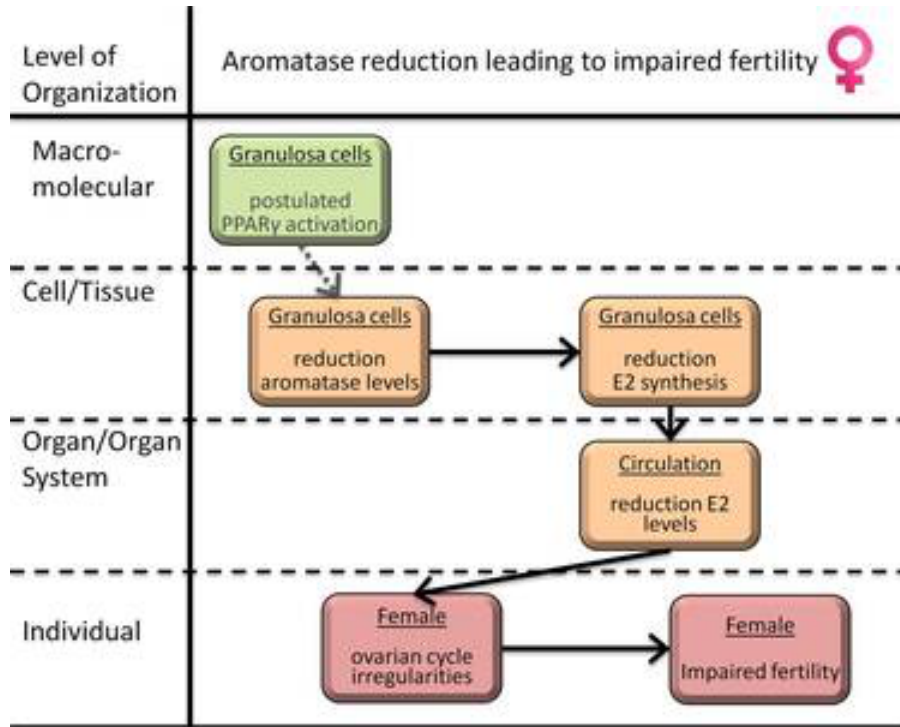
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- Division of Diet, Disease Prevention and Toxicology, National Food Institute, Technical University of Denmark, Kongens Lyngby DK-2800, Denmark
- Department of Environment and Health, Vrije Universiteit Amsterdam, De Boelelaan 1085, NL-1061, The Netherlands
- Department of Pediatrics, CHU de Liège, Rue de Gaillamont 600, B-4032, Belgium

ID 345: AR antagonism leading to reduced fertility, female

AOP 345: "AR antagonism leading to reduced fertility, female"



IMPROVE TEST CAPABILITIES



← QSAR PPARg

← GRANULOSA CELL FUNCTIONING

← OVARIAN SPECIFIC STEROIDOGENESIS

← BOVINE OOCYTE MATURATION & COMPETENCY



<https://aopwiki.org/aops/7>

OPPORTUNITIES

- Use (p)AOPs for better interpretation of *in vivo* findings
 - focus on susceptible windows, including puberty
- Improving existing TGs
 - follicle count, vaginal opening, mammary gland
 - (ovarian) steroidogenesis
- New test methods with clear anchoring in AOPs and test strategies
 - QSAR, screening ER-b, granulosa cell function, oocyte maturation and competency
- Tackling female reproductive toxicity across regulations



Experimental studies...

- Human ovary, adrenal, follicles and follicular fluid
- *In silico* and *in vitro* studies
- Rat studies



...will provide...

- Human-relevant biomarkers
- Adverse Outcome Pathways with focus on sensitive life stages



...for development of:

- Novel or improved *in silico*, *in vitro* and *in vivo* **test methods**
- **Test strategy** to identify EDCs toxic to female reproduction



SAFEGUARDING
WOMEN'S HEALTH
AGAINST ENDOCRINE
DISRUPTORS



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