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ENDpoiNTs

Role of Metabolomics in Test Development

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Why metabolomics?

What is possible

What appears to be happening

What makes it happen

What actually happens

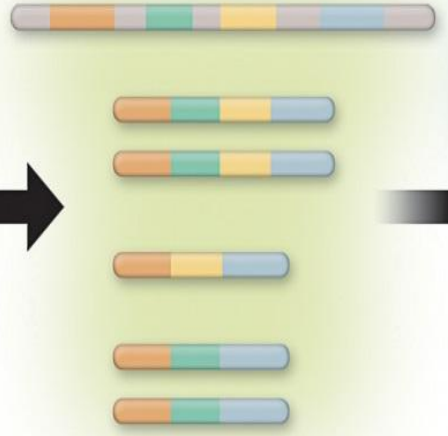
Genomics

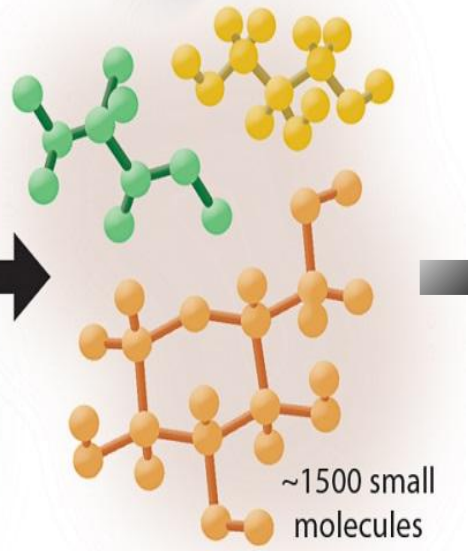
Transcriptomics

Proteomics

Metabolomics

Phenotype
Behaviour
Development
….





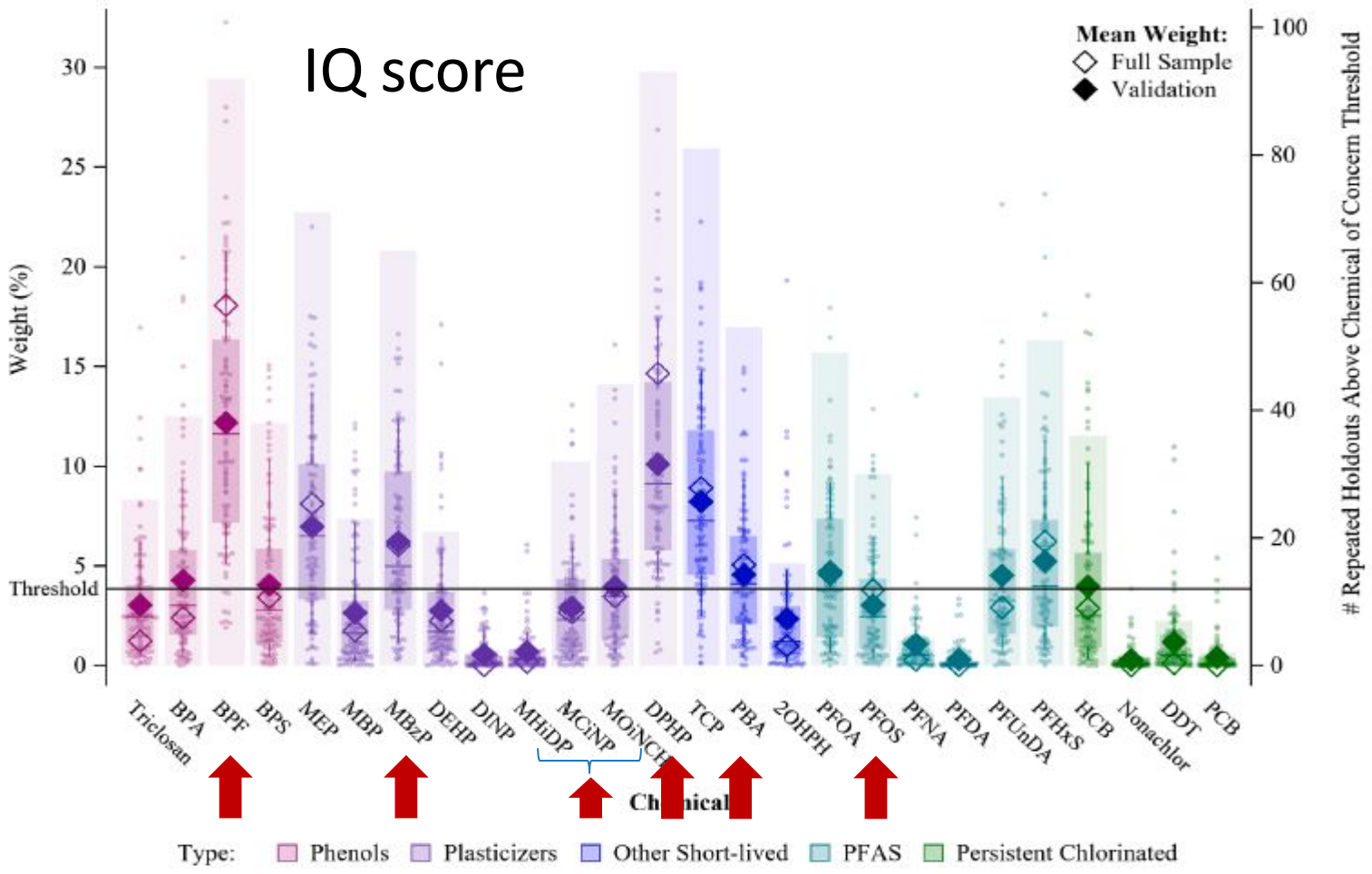
DNA

RNA

Protein

Metabolites

Selection of EDCs for rat studies



Tanner et al., 2020, Environ. Int

Rat studies

BPF: Bisphenol F
PMT: Permethrin
TPHP: Triphenyl phosphate
PFOS: Perfluorooctane sulfonic acid
BBzP: Benzyl butyl phthalate
DINCH: cyclohexane-1,2-dicarboxylic acid-diisononyl ester

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GREEN TOX

Group for Reproductive, Endocrine and Environmental Toxicology

Rat studies

BPF: 0.036 & 3.6 mg/kg
PMT: 0.36 & 3.6 mg/kg
TPHP: 2& 20 mg/kg
PFOS: 0.3 & 0.75 mg/kg
BBzP: 20 & 200 mg/kg
DINCH: 30 & 300 mg/kg

Butylbenzylphthalate

Bisphenol F

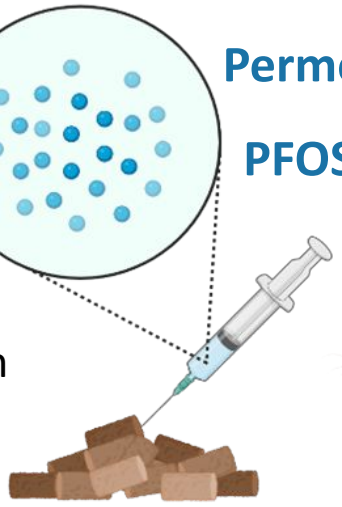
Permethrin

DINCH

PFOS

Triphenylphosphate

Selection based on human epidemiology



EDCs Exposure

F0 generation

F0 + F1 generation

pre-mating/mating

pregnacy &lactation

Metabolomics

Transcriptomics

Epigenomics

Tissue collection

F0 - 12/14 weeks

F1 - PND6

Behavioural tests in adults

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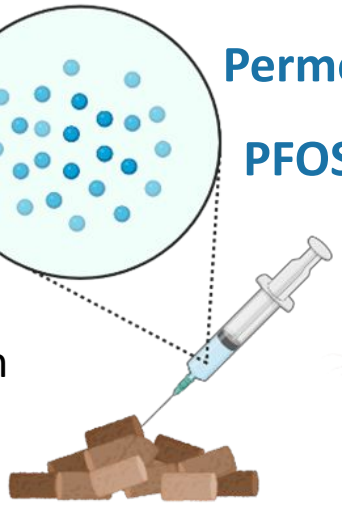
Butylbenzylphthalate

Bisphenol F **Permethrin**

DINCH **PFOS**

Triphenylphosphate

Selection based on human epidemiology



EDCs Exposure

F0 generation

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Metabolomics

Transcriptomics

Tissue collection

Epigenomics

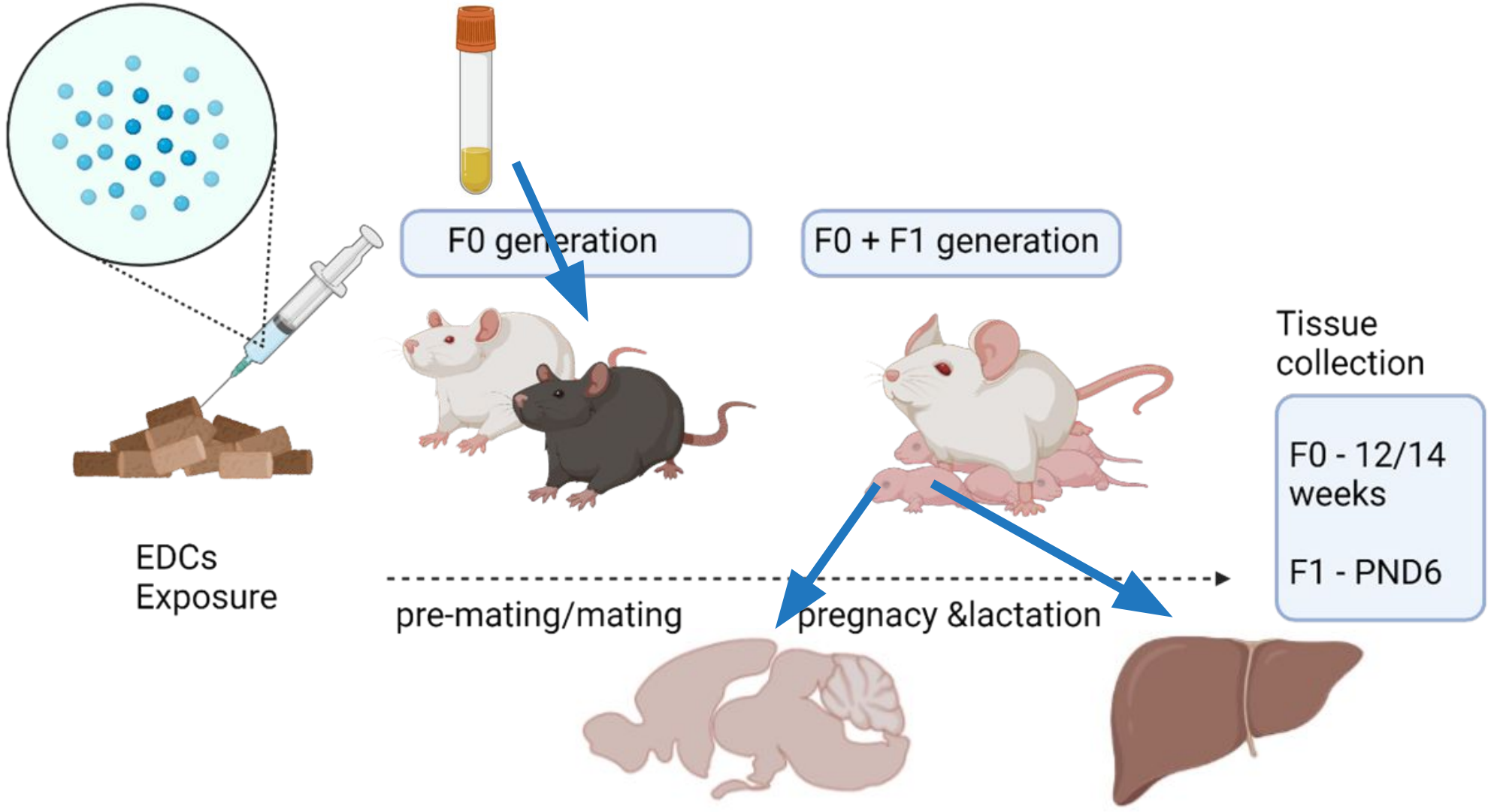
F0 - 12/14 weeks

F1 - PND6

Behavioural tests in adults

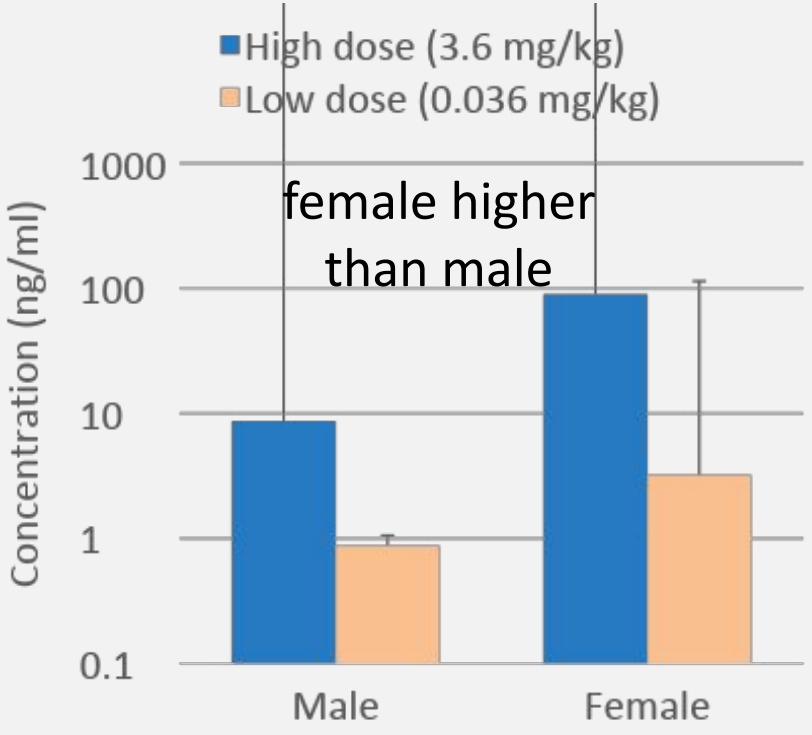
PND6

Samples for internal concentration and omics analysis

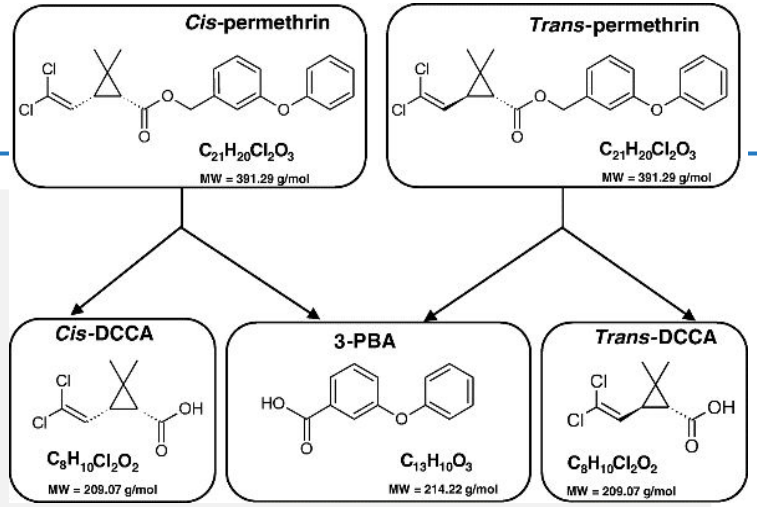


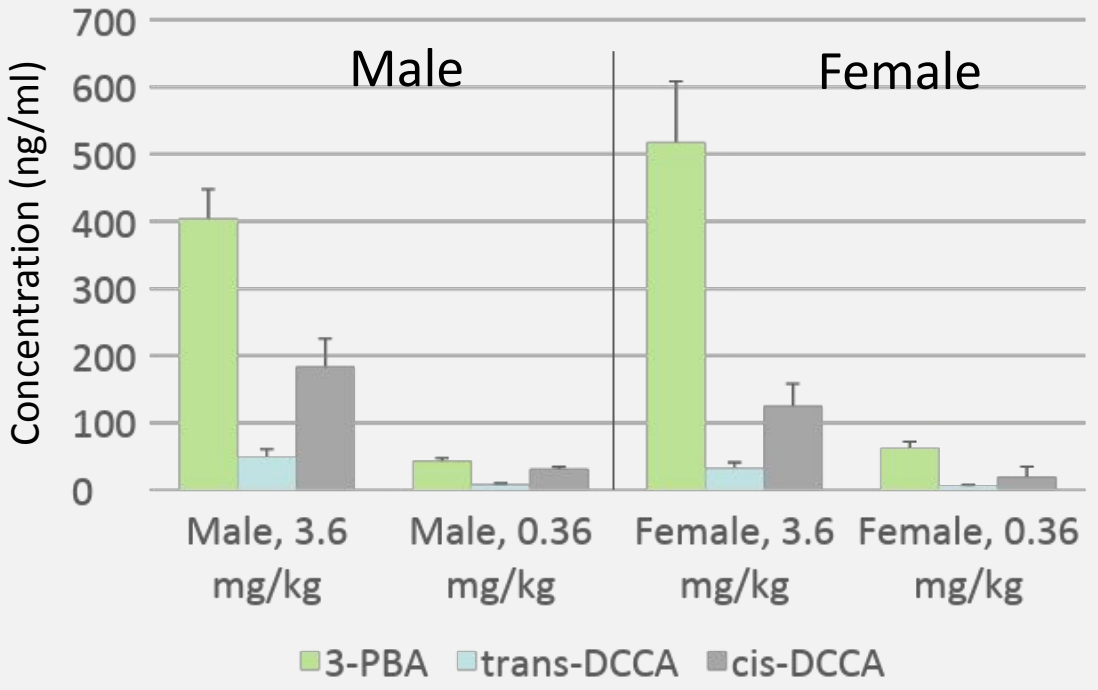
Internal concentrations BPF and permethrin in adult rat plasma

BPF



Permethrin





Steroid hormone synthesis pathway

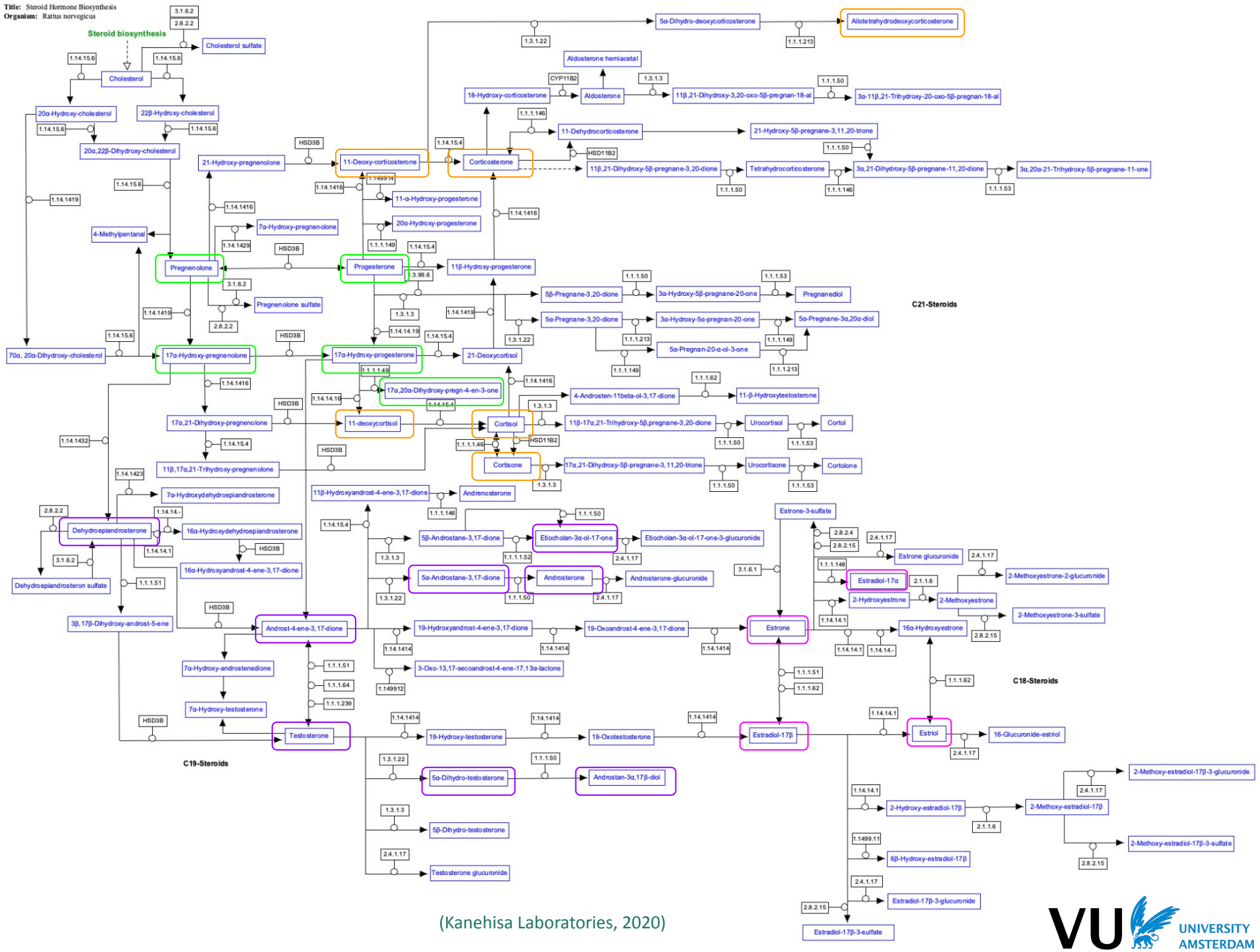
Corticoids*

Progestogens*

Androgens*

Estrogens*

** only steroids present in the method of this study are colored*



(Kanehisa Laboratories, 2020)

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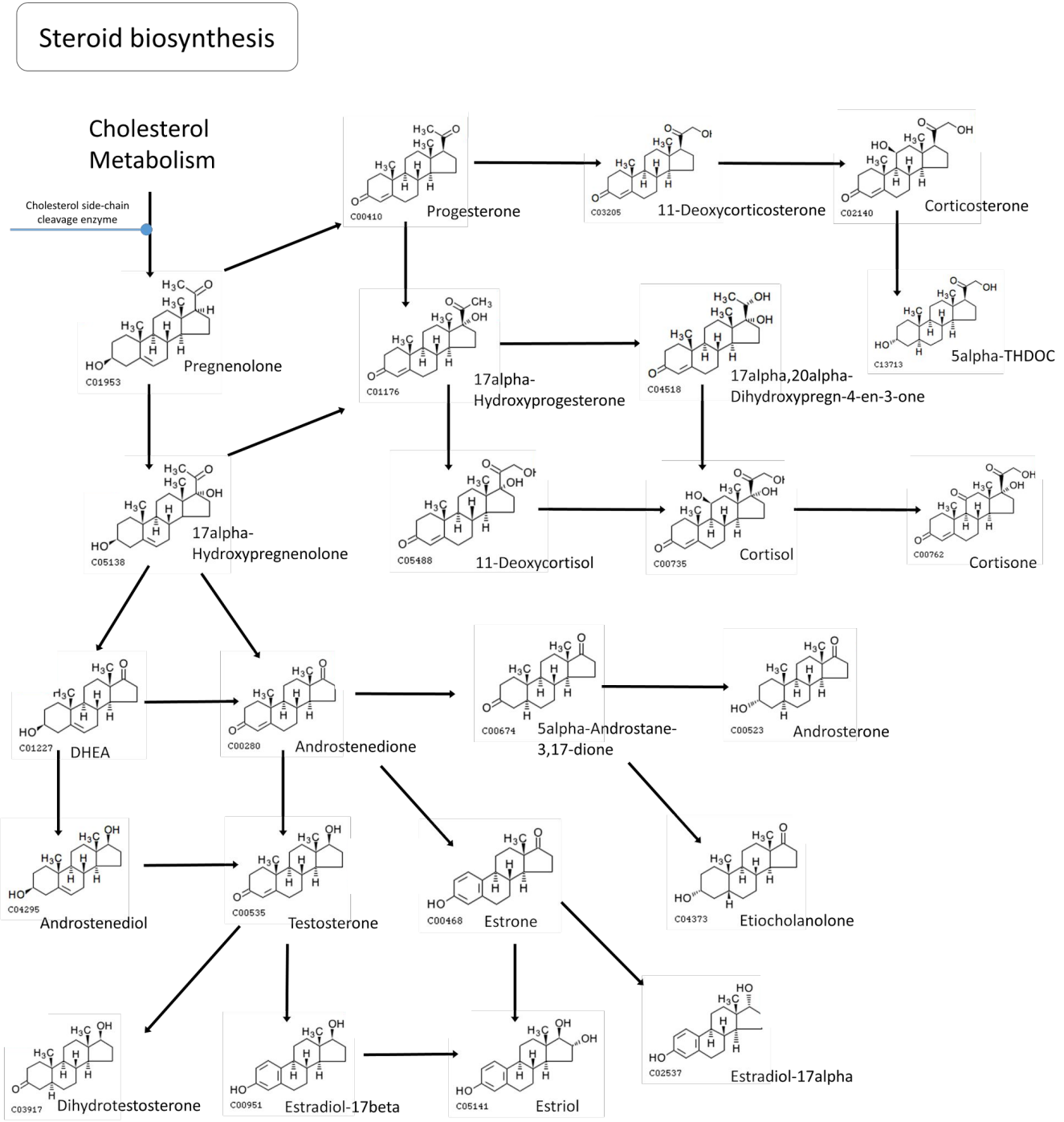
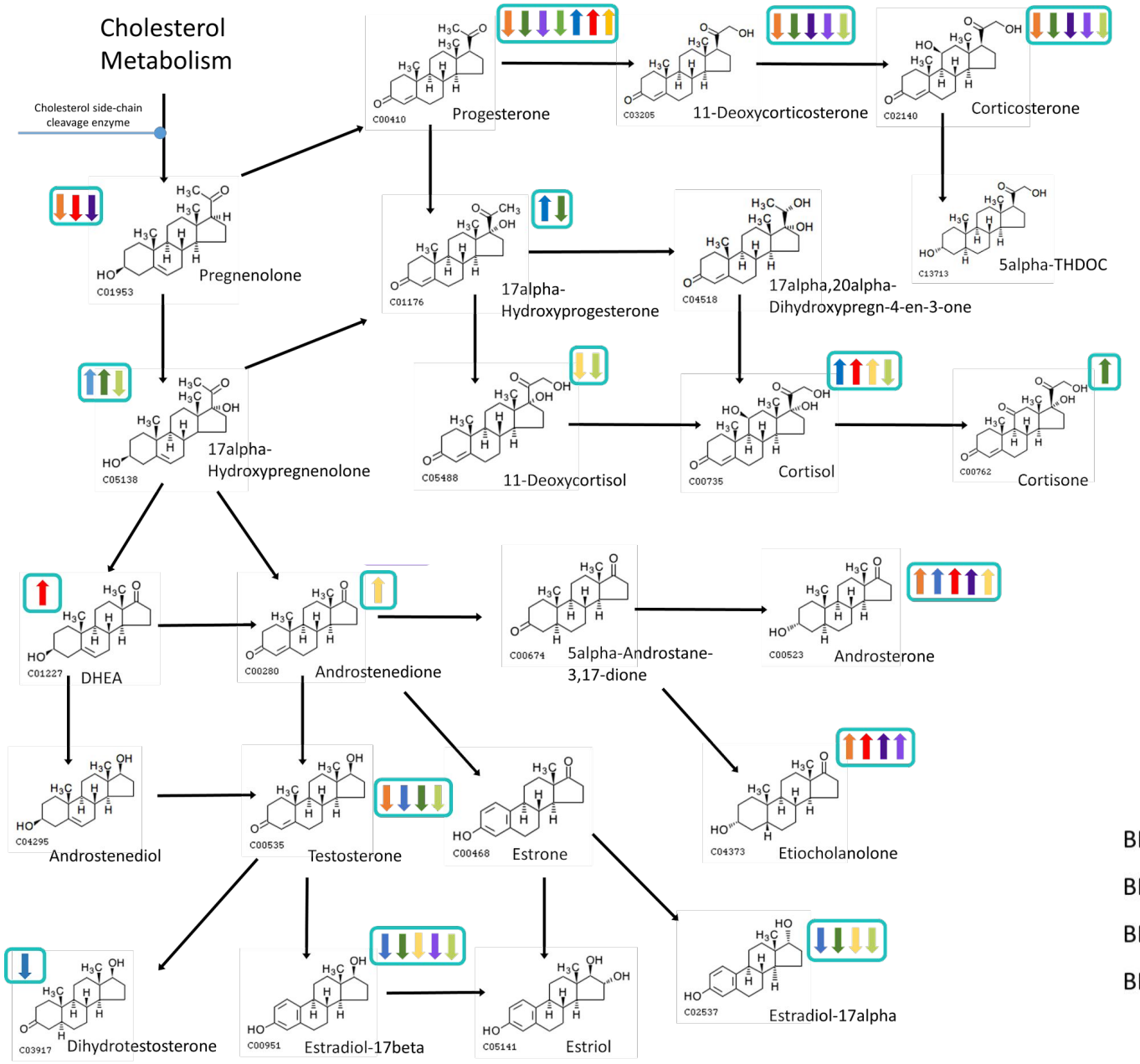
Determined steroids



Effects of **BPF** and **permethrin** on

- **plasma adult**

Steroid biosynthesis



Plasma adult

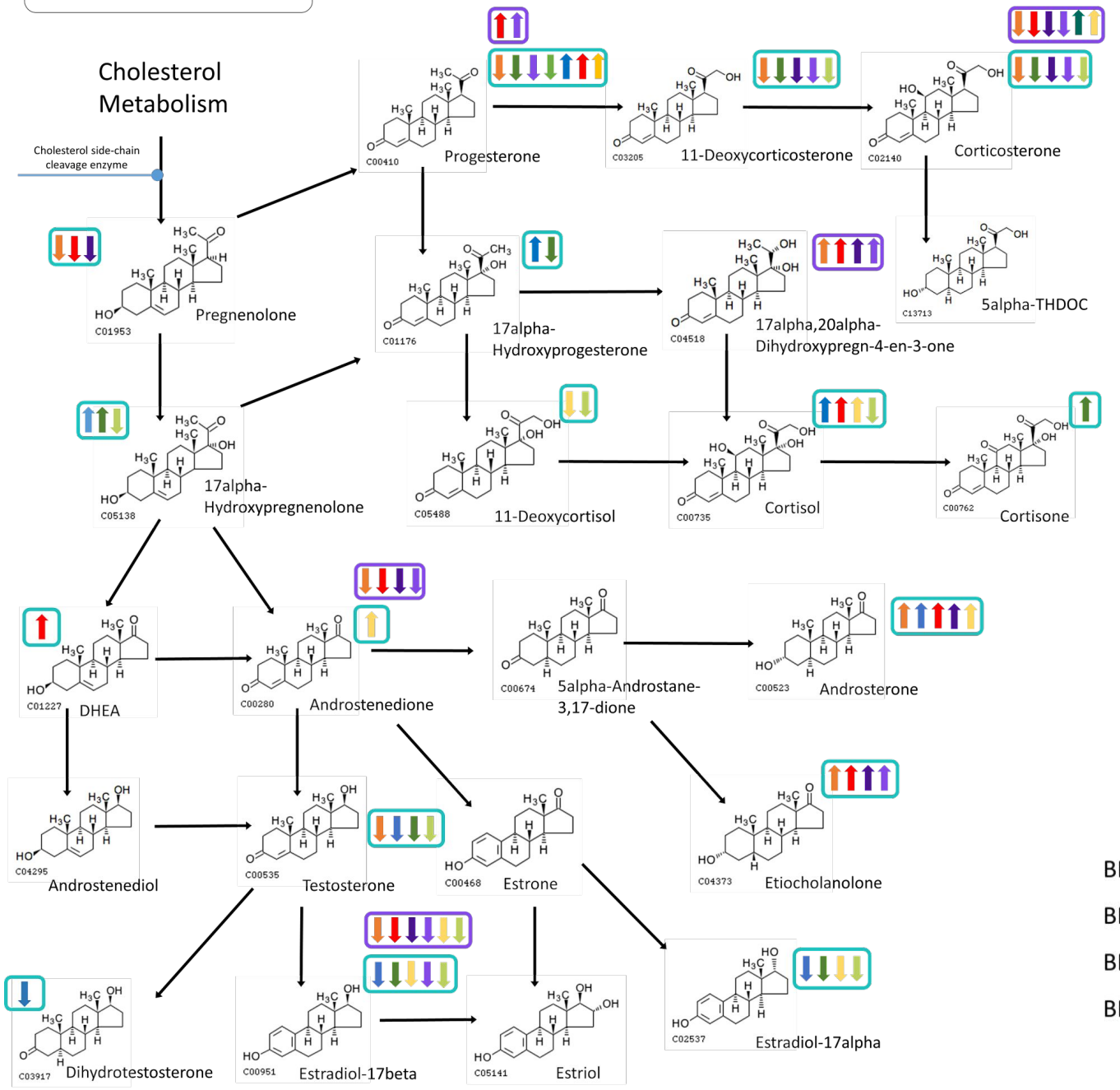
BPF 0.036 F
BPF 0.036 M
BPF 3.6 F
BPF 3.6 M

PMT 0.36 F
PMT 0.36 M
PMT 3.6 F
PMT 3.6 M

Effects of **BPF** and **permethrin** on

- **plasma adult**
- **PND6 liver**

Steroid biosynthesis



PND6 liver

Plasma adult

BPF 0.036 F

BPF 0.036 M

BPF 3.6 F

BPF 3.6 M

PMT 0.36 F

PMT 0.36 M

PMT 3.6 F

PMT 3.6 M

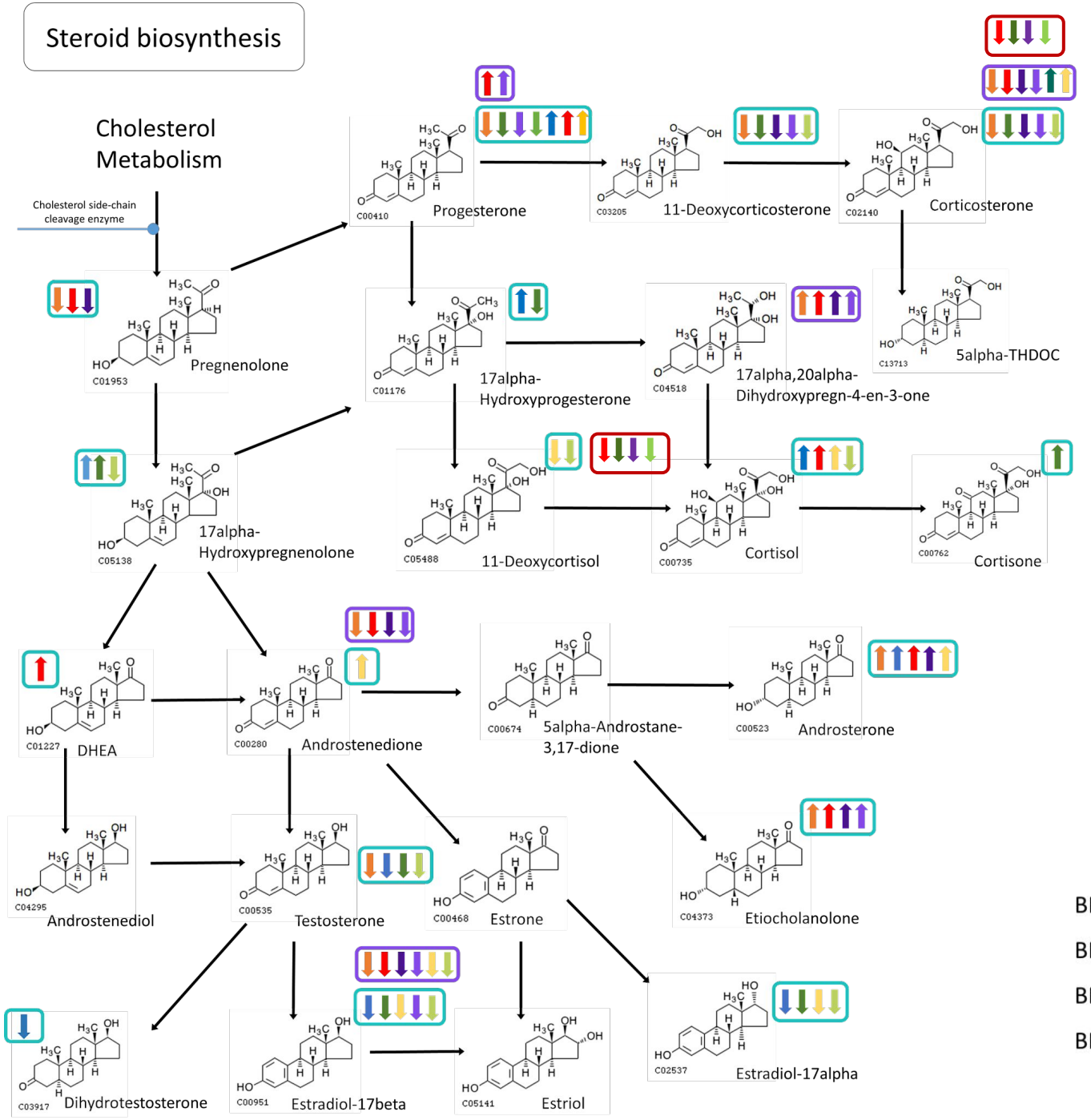
Effects of **BPF** and **permethrin** on

- **plasma adult**
- **PND6 liver**
- **PND6 hippocampus**

Steroid biosynthesis

Cholesterol Metabolism

Cholesterol side-chain cleavage enzyme



PND6 hippocampus

PND6 liver

Plasma adult

BPF 0.036 F

BPF 0.036 M

BPF 3.6 F

BPF 3.6 M

PMT 0.36 F

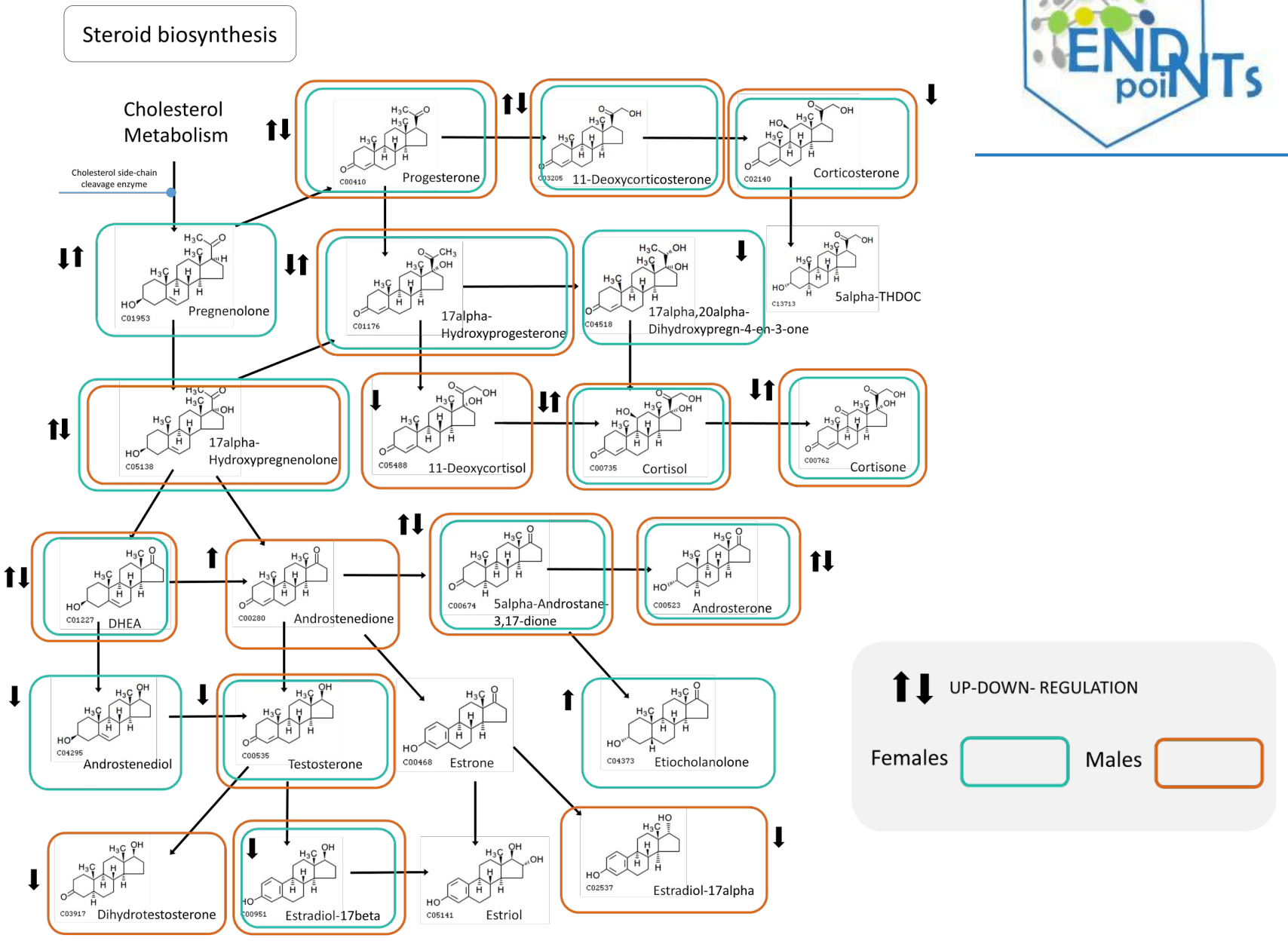
PMT 0.36 M

PMT 3.6 F

PMT 3.6 M

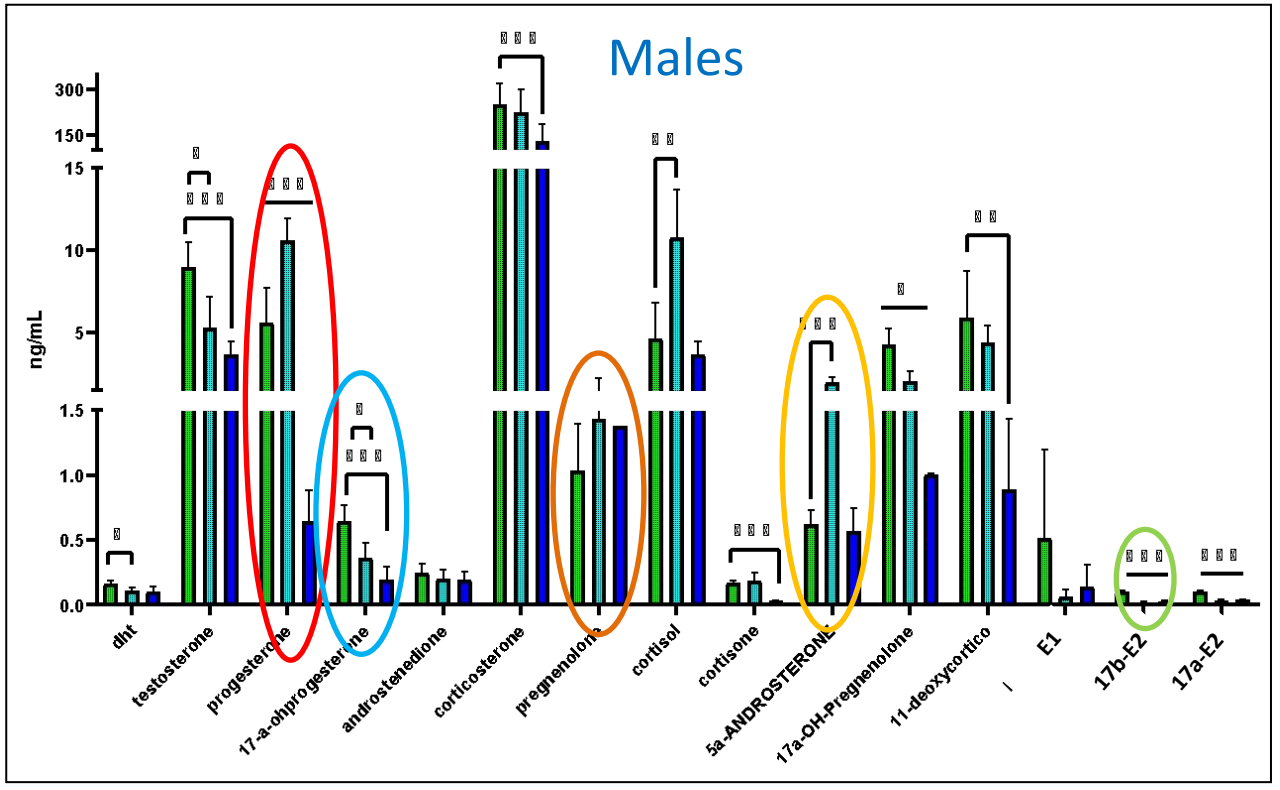
Sex-specific effects of steroids in adult rat **plasma** by BPF, PMT, BBzP, PFOS

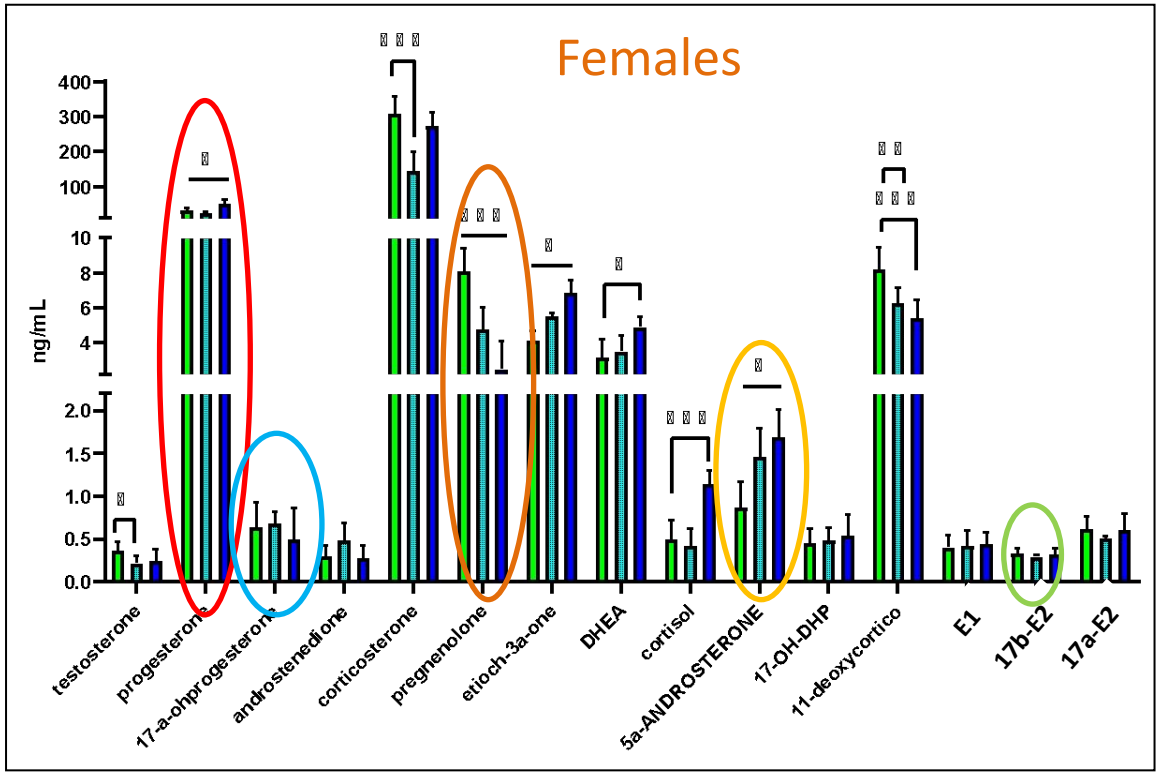
- Many steroids are affected by EDCs
- Colored boxes significantly up-down regulated ($p < 0.05$)
- Sex-specific effects
- 20/23 steroids affected by at least one EDC



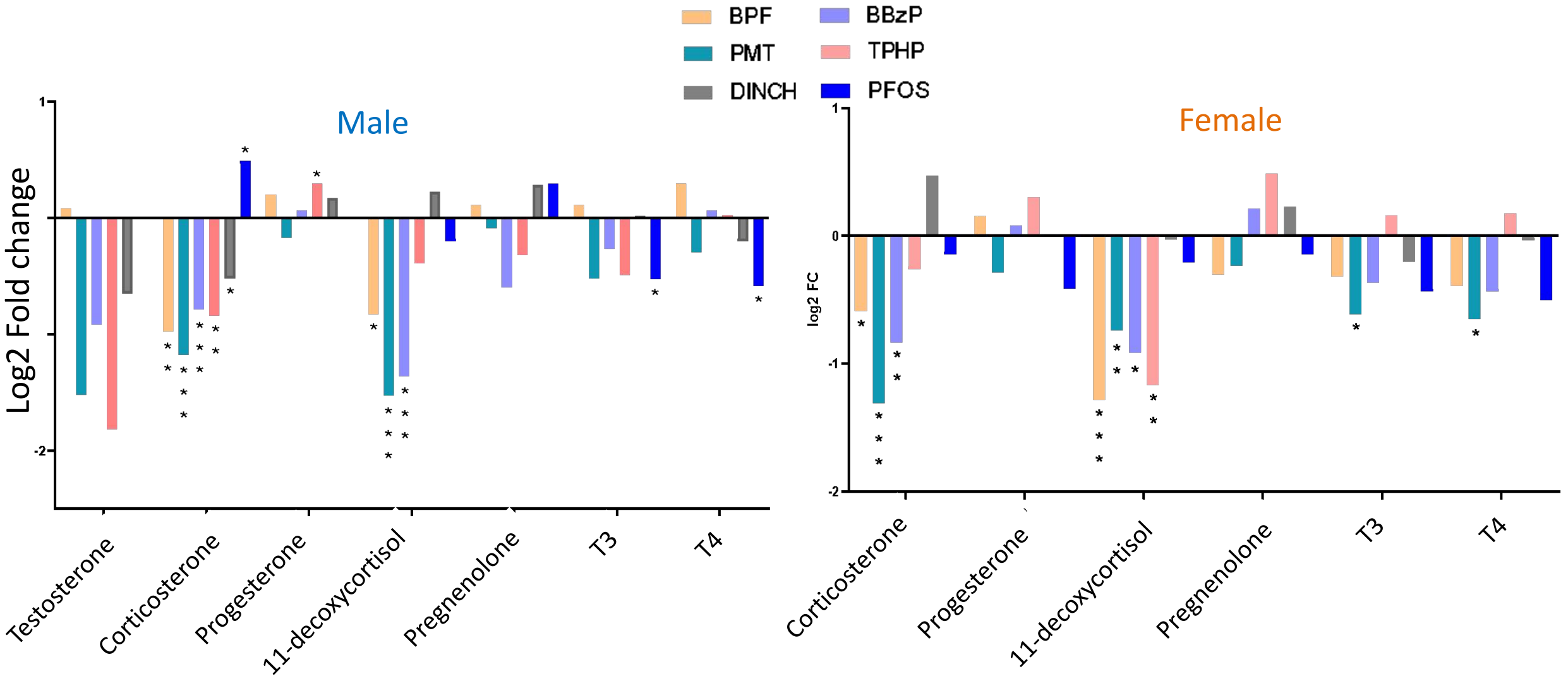
Sex-specific effects of BPF in adult plasma

Control BPF 0.036 mg/kg bw BPF 3.6 mg/kg bw

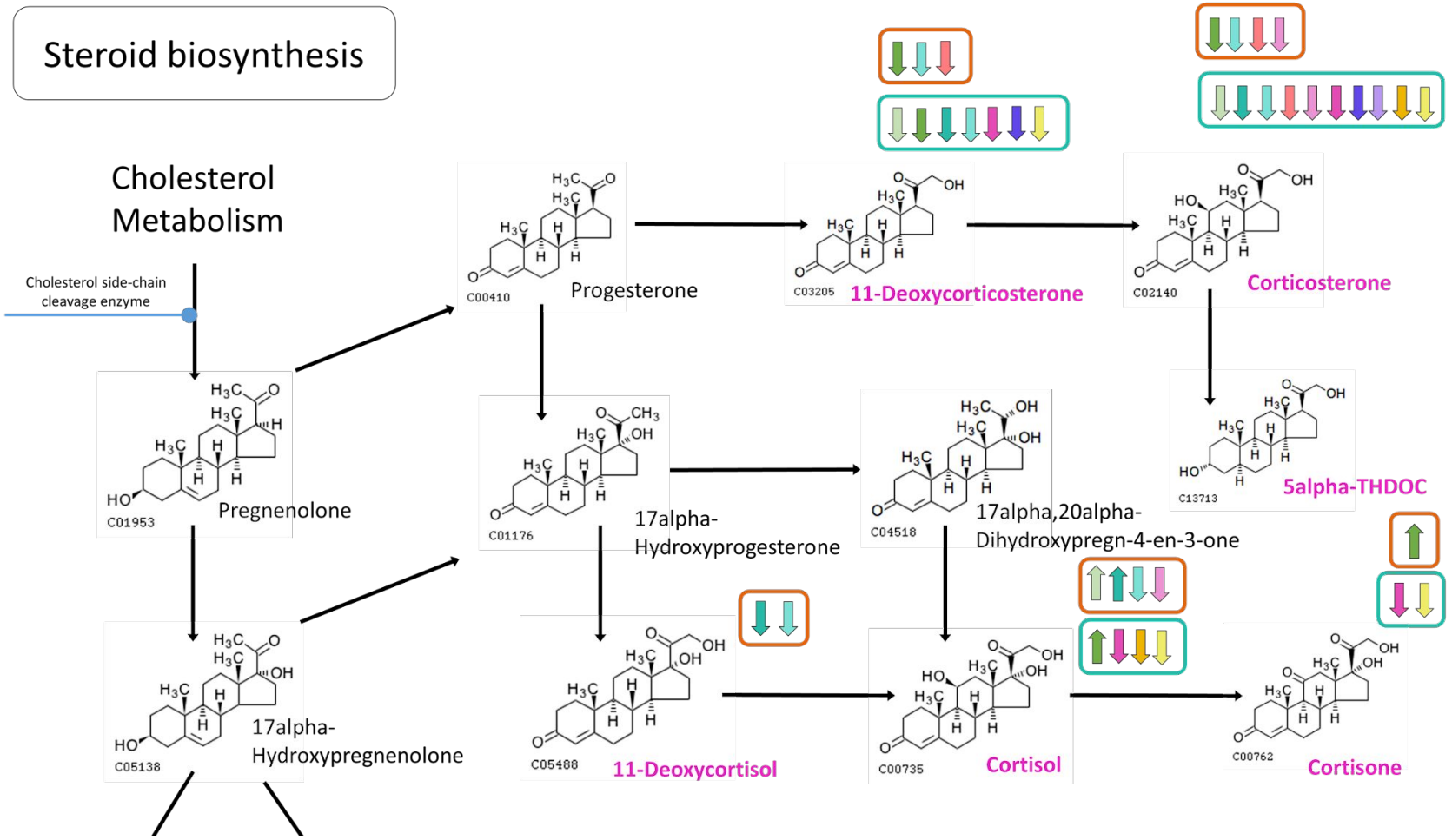




Sex-specific effects on PND6 rat hippocampus



Glucocorticoids disruption by PMT, BPF, BBzP, TPHP & DINCH in adult plasma



UP-DOWN- REGULATION

Glucocorticoids

Females

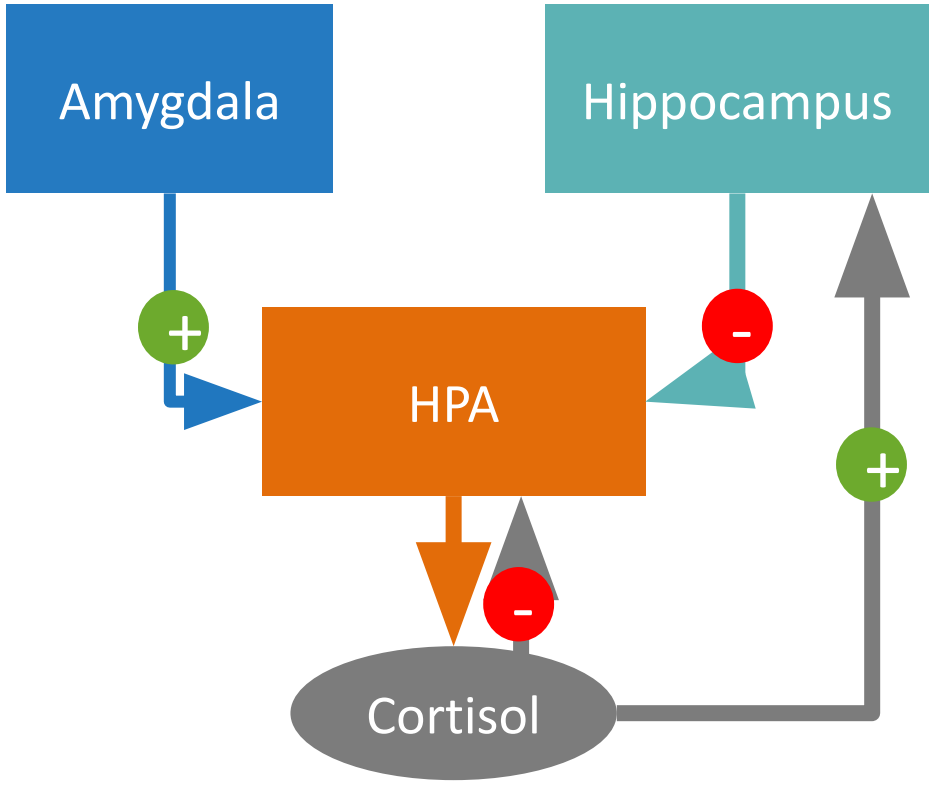
Males

Exposure:

BPF 0.036	PFOS 0.3
BPF 3.6	PFOS 0.75
PMT 0.36	TPhP 2
PMT 3.6	TPhP 20
BBzP 20	DINCH 30
	DINCH 300

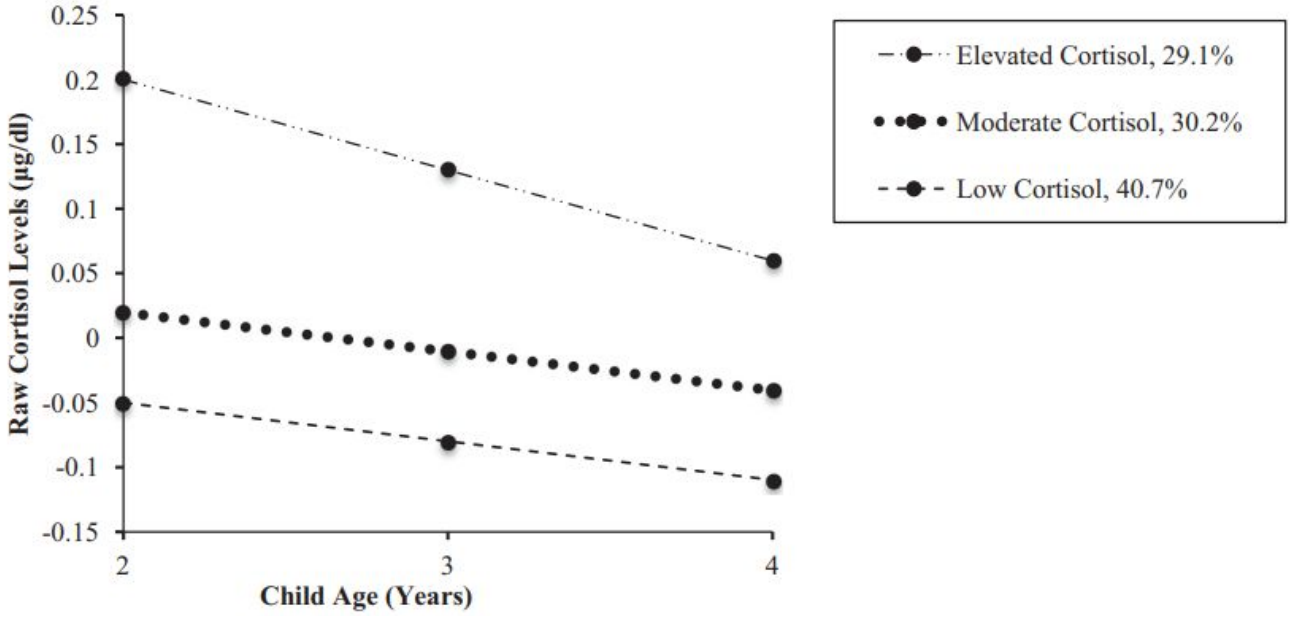
Glucocorticoids (corticosterone)

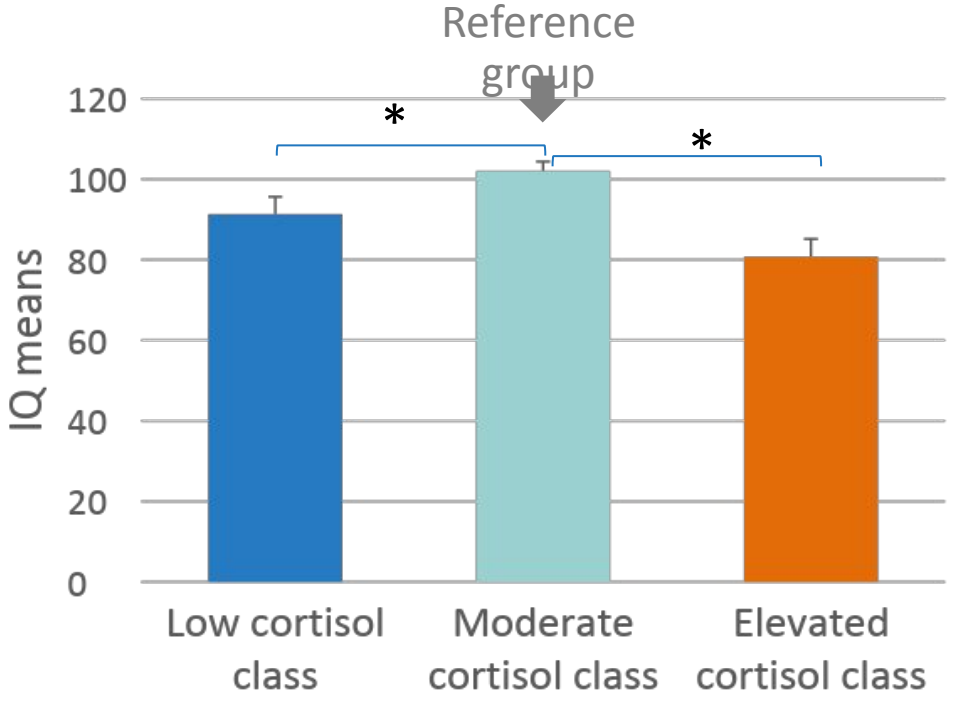
- Adrenal GC production regulated by Hypothalamic–pituitary–adrenal (HPA) axis
- Corticosterone/cortisol regulates neuropeptides and neurotransmitters thus affecting functional brain systems
- Imbalance of glucocorticoids with the two corticosteroid-receptor types?
- Inverted U-shape relation between glucocorticoids and cognitive functioning



Associations between cortisol and cognitive function in childhood

- Children assessed at ages 2, 3, and 4 years
- Three basal cortisol classes (low, elevated, moderate)





Suor et al., 2015, Child Development, 86, 1142–1158

Role of Metabolomics in Test Development

- Improve our understanding between the endocrine system (ED) and developmental neurotoxicity (DNT) outcomes
- Provide metabolite profiles for test systems that link the ED system with DNT outcomes (e.g. corticosterone and neurotransmitters profiles, sex-specific)

Acknowledgement

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GREEN TOX

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Margret Schlumpf

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