Hazard profiling of persistent and mobile substances using new approach methodologies

Maxim Carlier – Vrije Universiteit Amsterdam

ZeroPM prioritization workshop

September 20th, 2024

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WP6

ZeroPM – Phase-1 compounds (n=36)

Triazole (n=16)	Triazine (n=9)	PFAS (n=11)
Tetraconazole	Cyromazine	TFMSA
Bitertanol	Atrazine	PFBS
Fenbuconazole	Ametryn	PFHxS
Tebuconazole	Benzoguanamine	PFOS
Difenoconazole	Melamine	TFA
Paclobutrazol	Cyanuric acid	PFPrA
Triadimenol	Deethyl-atrazine	PFBA
Cyproconazole	Ammeline	PFHxA
Propiconazole	Ammelide	PFOA
Pyroxsulam		GenX
Benzotriazole		PFEtS
4-Methylbenzotriazole		
5-Methylbenzotriazole		
1,2,4 triazole		
Triazole acetic acid		
Triazole alanine		

ZeroPM – bioassay test battery selection

- **Endocrine disruption**
  - All three chemical classes
  - EATS modalities
- **(Neuro-)developmental toxicity**
  - All three chemical classes
  - Zebrafish: embryotoxicity and light/dark behavior
  - Nematode: developmental toxicity, mobility and reproductive toxicity
- **Immunotoxicity**
  - Mainly PFAS
  - Zebrafish embryo immunotoxicity test (newly developed)
- **Liver toxicity**
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  - HepaRG cell functioning, mitochondrial activity, oxidative stress, lipid accumulation

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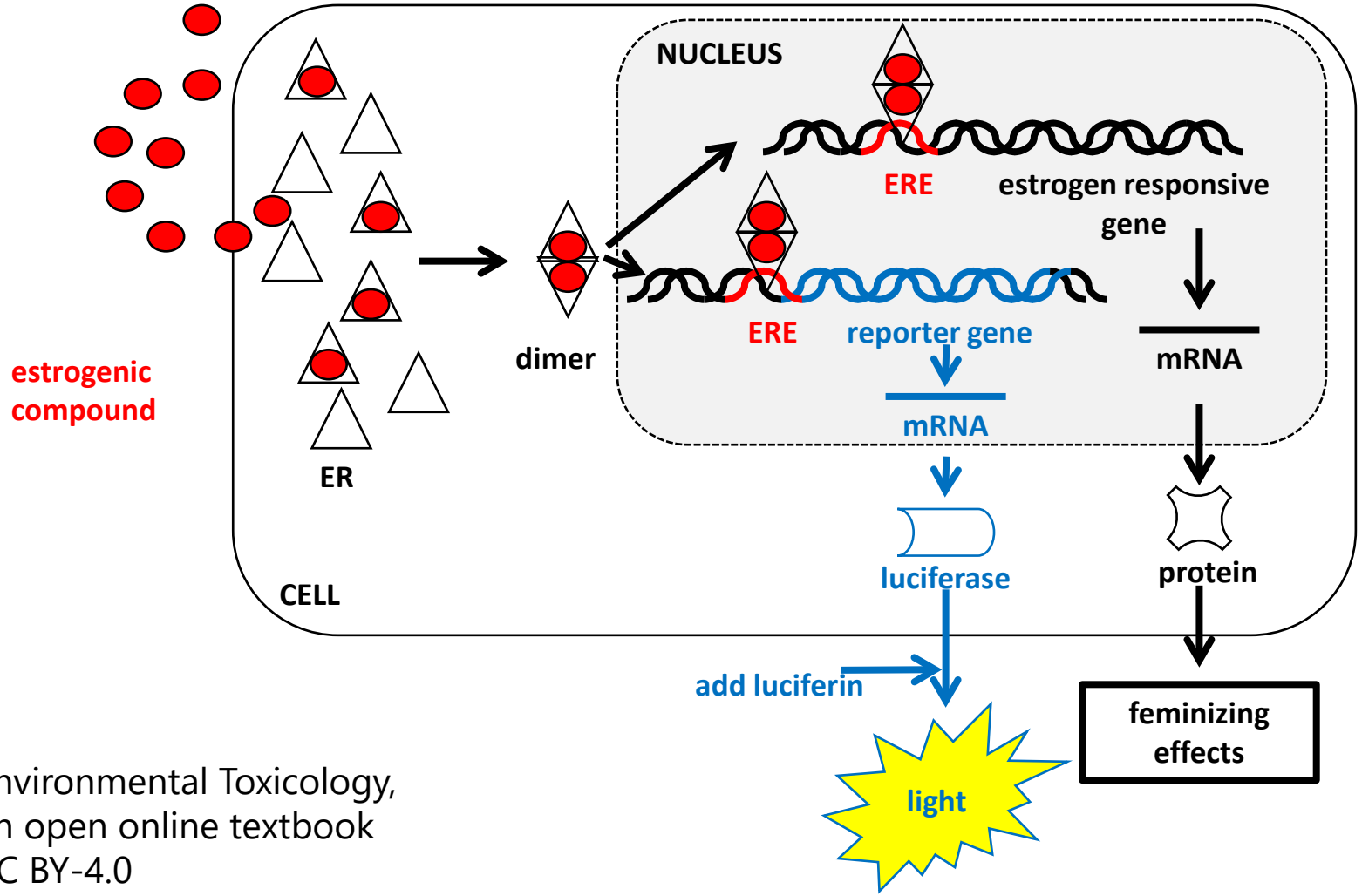
Endocrine disruption

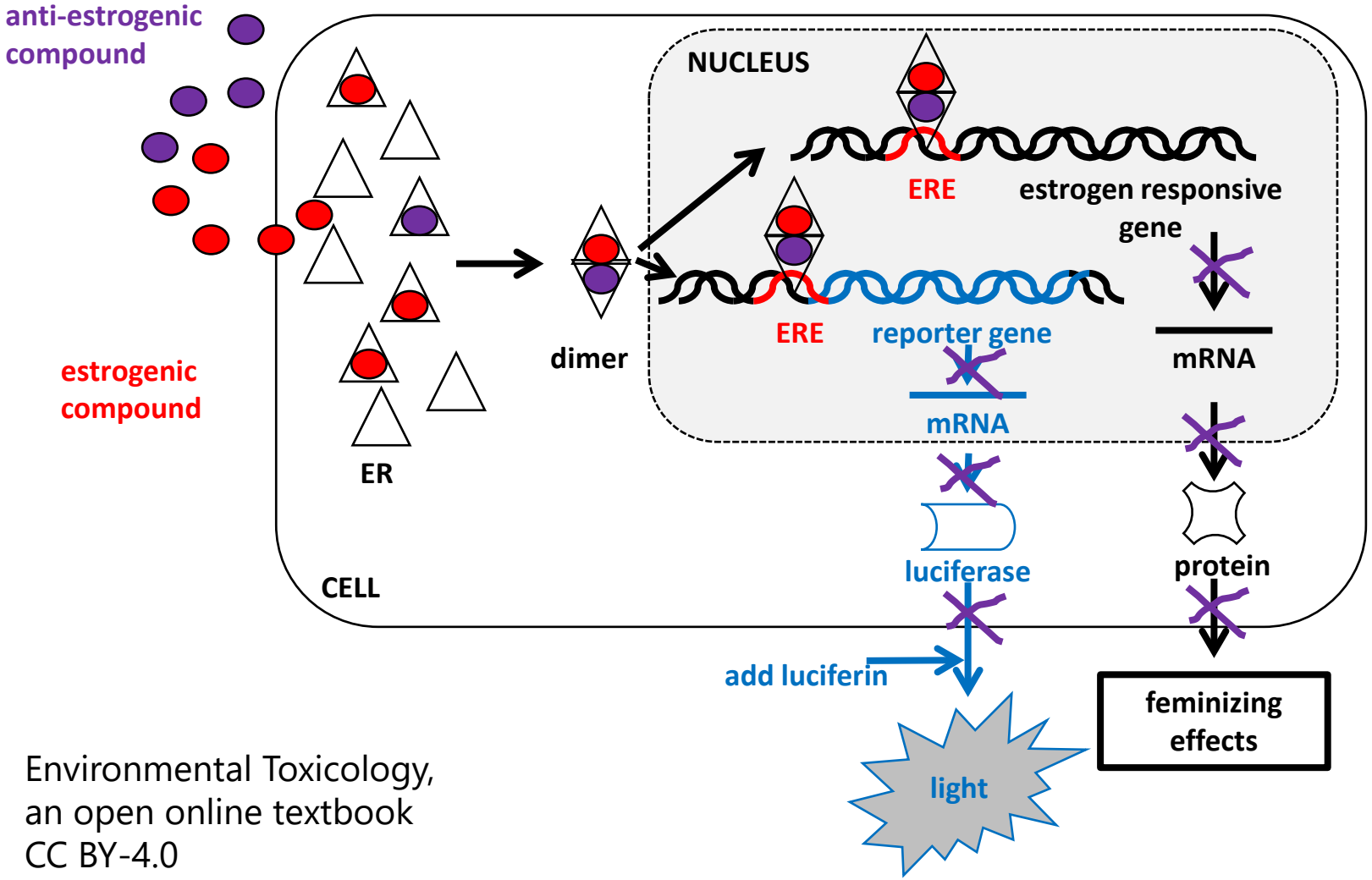
- **E**strogen
  - agonism/antagonism towards estrogen receptor
- **A**ndrogen
  - agonism/antagonism towards androgen receptor
- **T**hyroid hormones
  - agonism/antagonism towards thyroid hormone receptor
  - displacement of thyroid hormone from transthyretin
- **S**teroidogenesis
  - increased/decreased production of 13 steroid hormones

Hormone receptor activation
(reporter gene assay)



- Precocious puberty
- Effects on menstrual cycle
- Breast cancer
- Male infertility

Hormone receptor inactivation
(reporter gene assay)



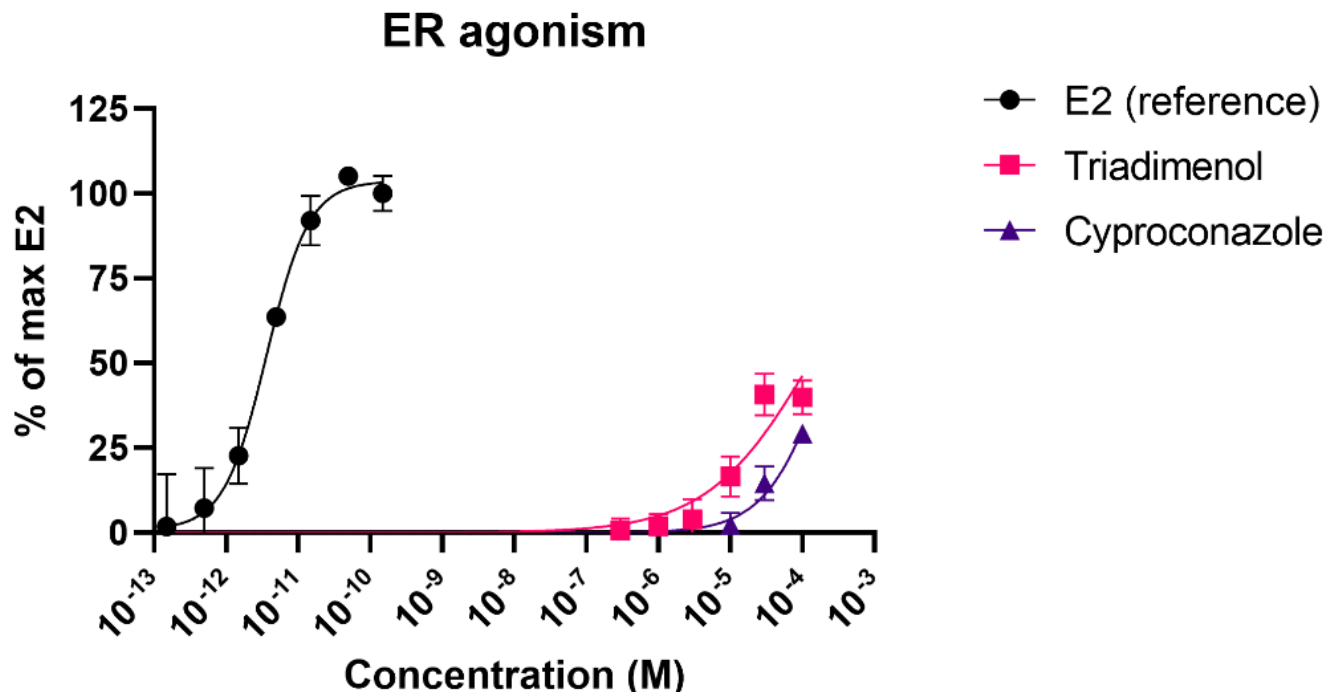
- Delayed puberty
- Effects on menstrual cycle
- Female infertility

Androgen receptor (AR) and thyroid hormone receptor (TR)

- AR agonism effects: a.o. female infertility
- AR antagonism effects: a.o. male infertility
- TR agonism effects: hyperactivity, developmental neurotoxicity
- TR antagonism effects: hypoactivity, depression, developmental neurotoxicity

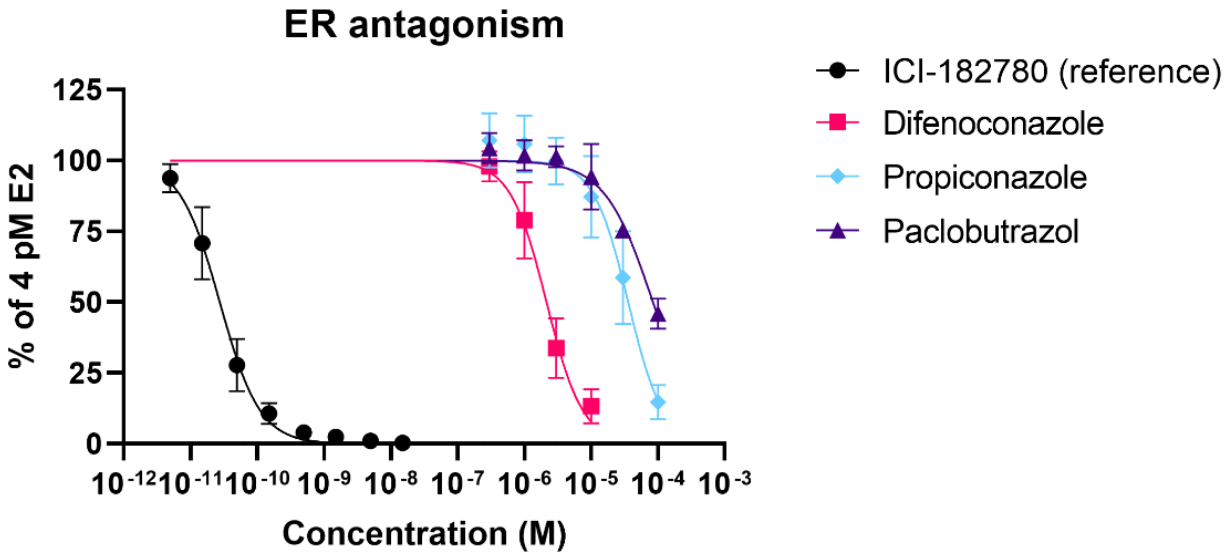
ER agonism

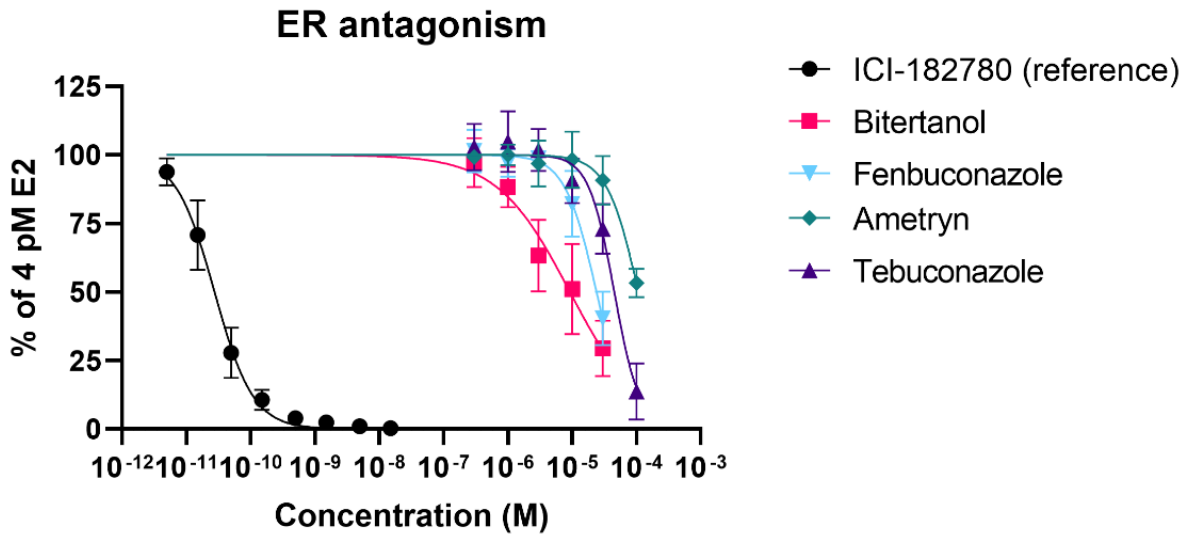
- Only triadimenol and cyproconazole showed ER agonism



ER antagonism

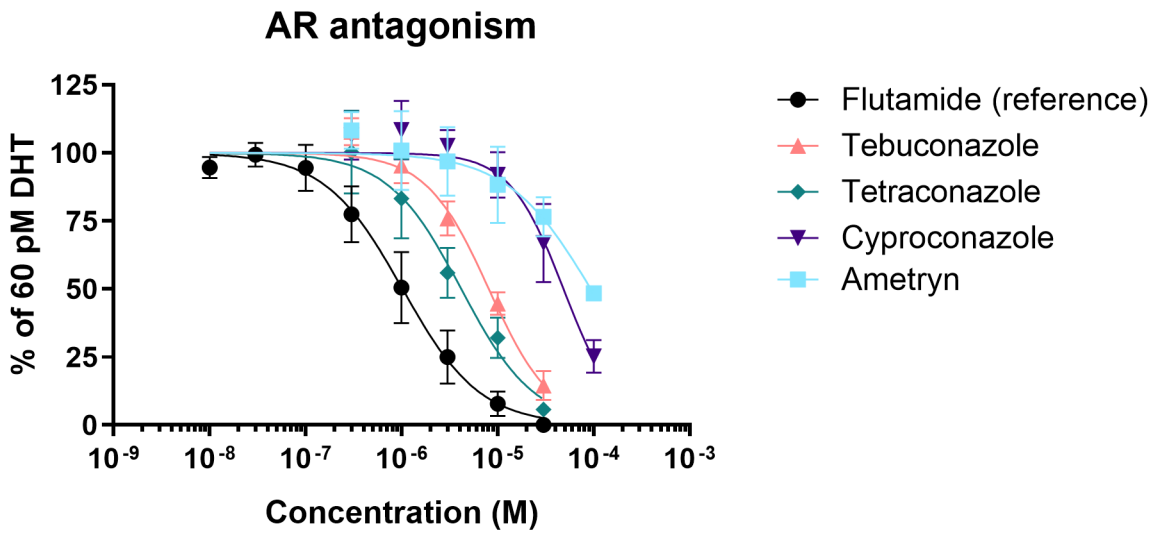
- Some triazole fungicides, and the triazine ametryn showed ER antagonism

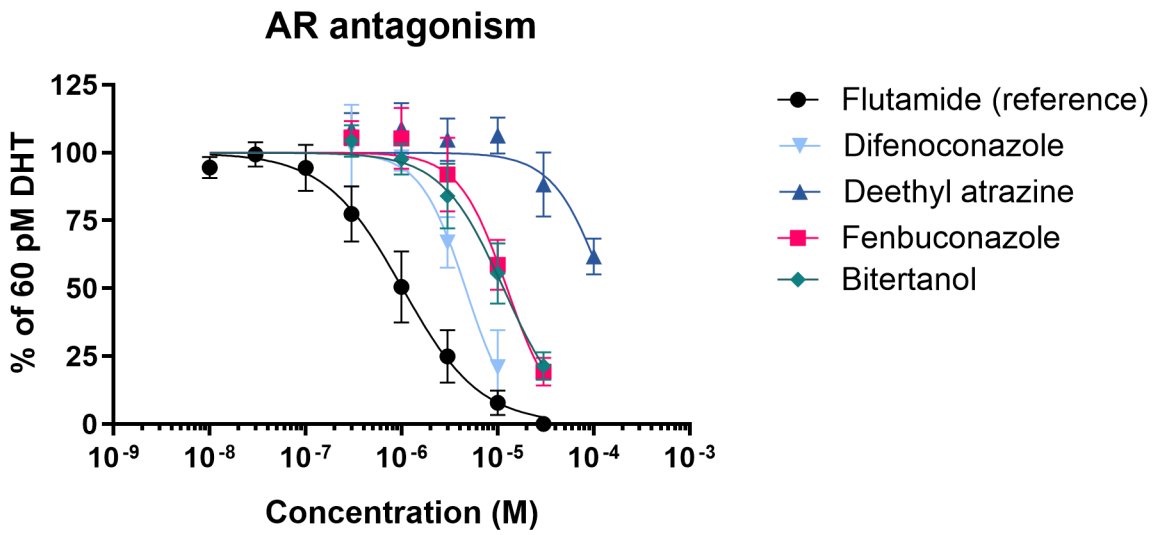




AR antagonism

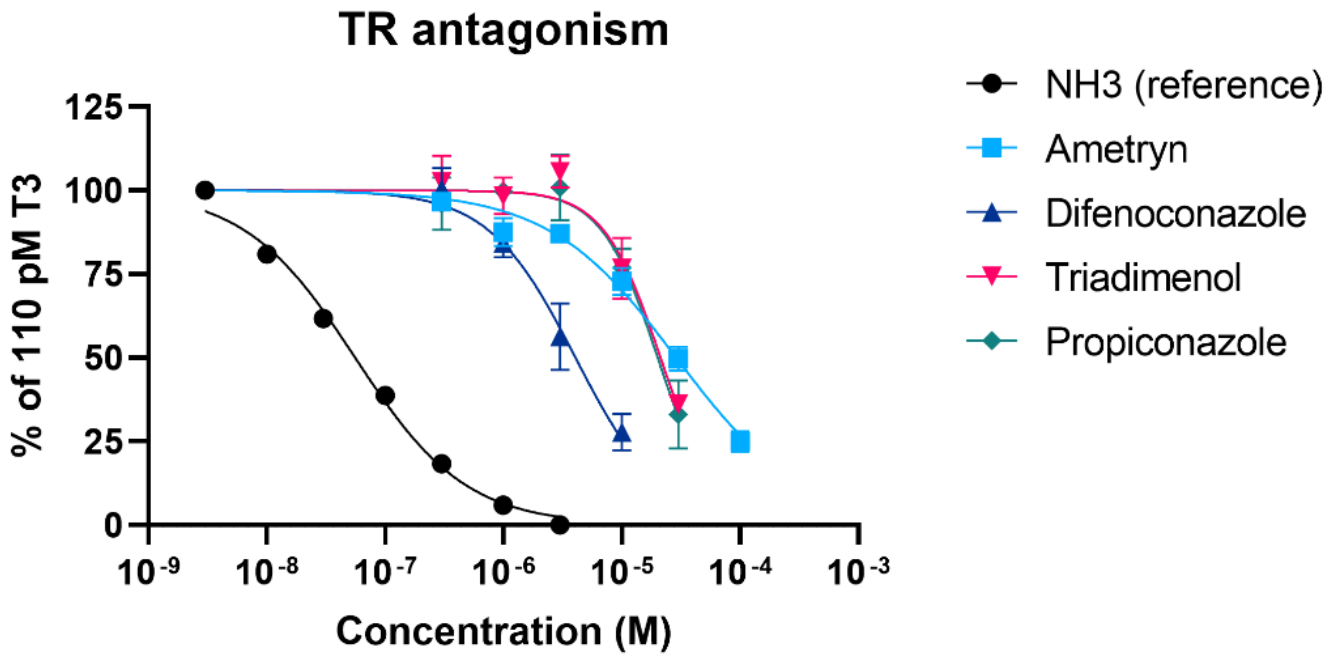
- Some triazole fungicides, and the triazines ametryn and deethyl atrazine showed ER antagonism (flutamide dezelfde kleur geven)





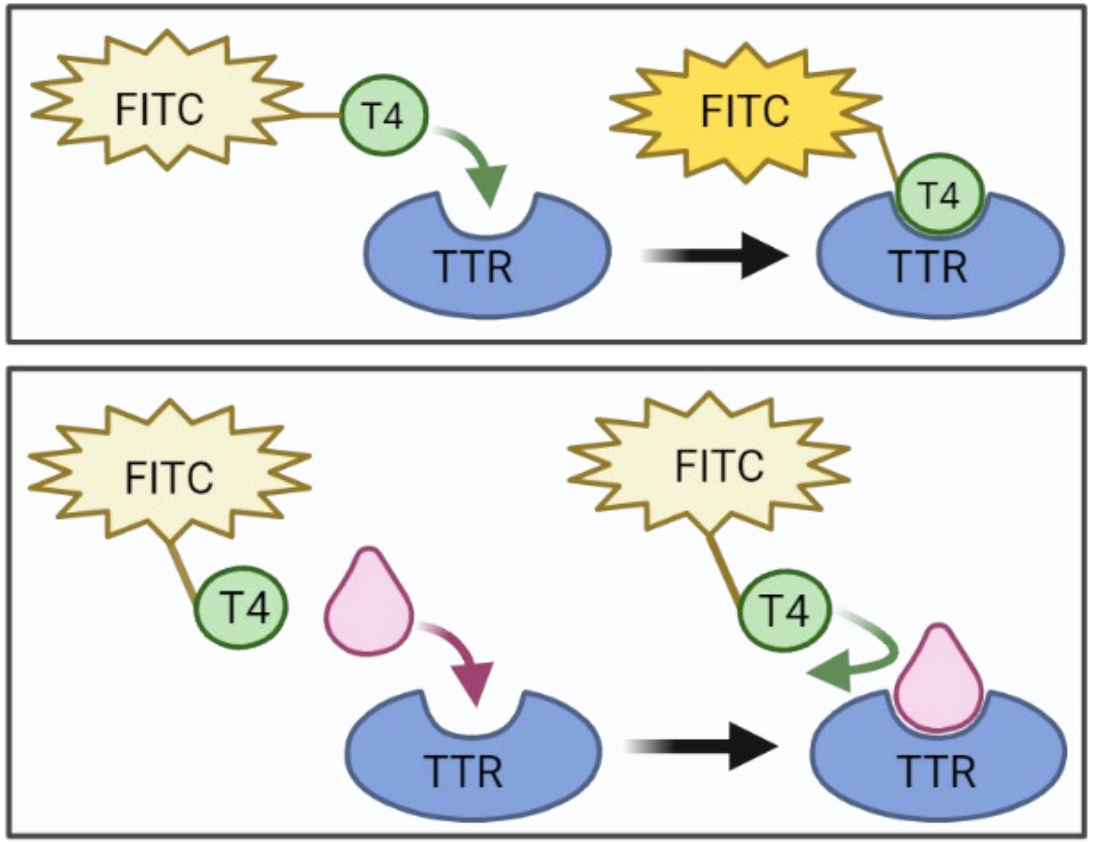
TR antagonism

- Only ametryn, difenoconazole, triadimenol and propiconazole showed TR antagonism



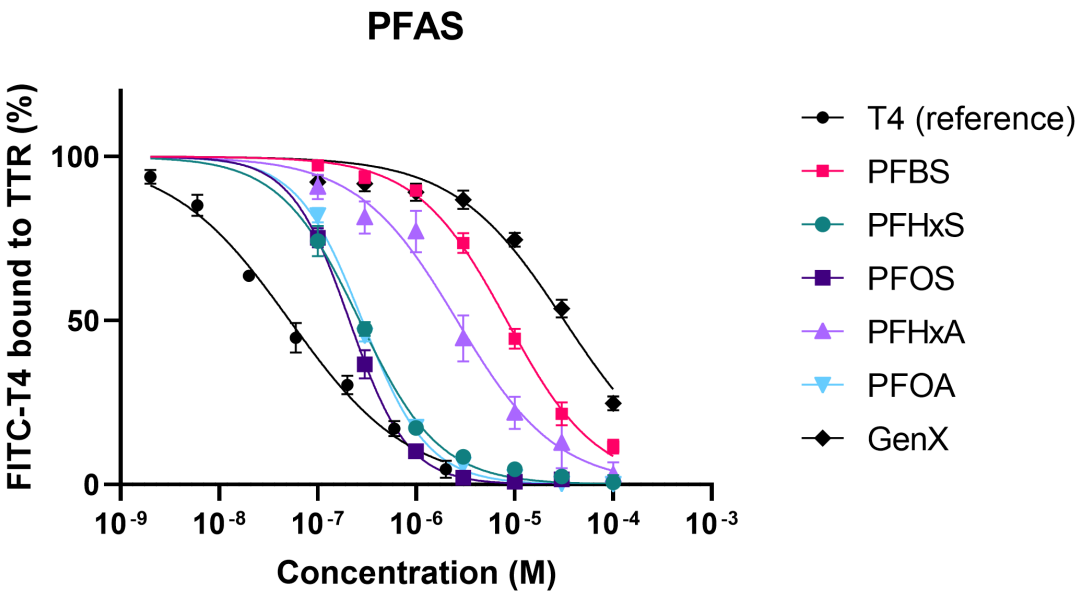
Binding to transthyretin (TTR)

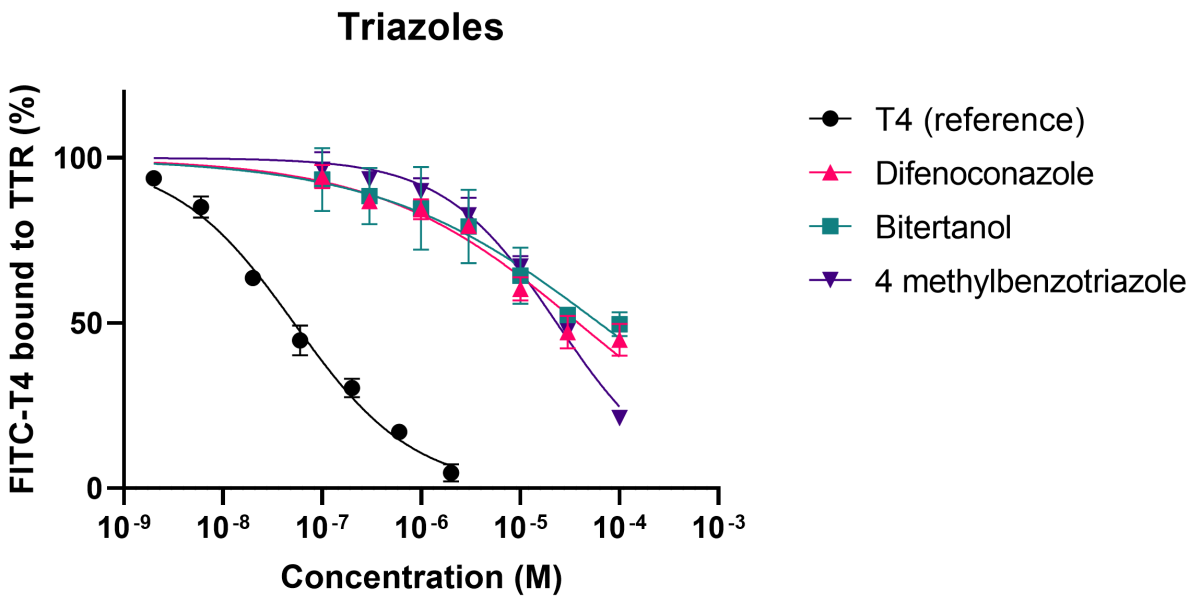
- TTR distributes T4 to target tissues, especially in the cerebrospinal fluid
- When compounds bind to TTR they prevent the transport of T4
- This may lead to decreased thyroid hormone activity in the brain



Binding to TTR

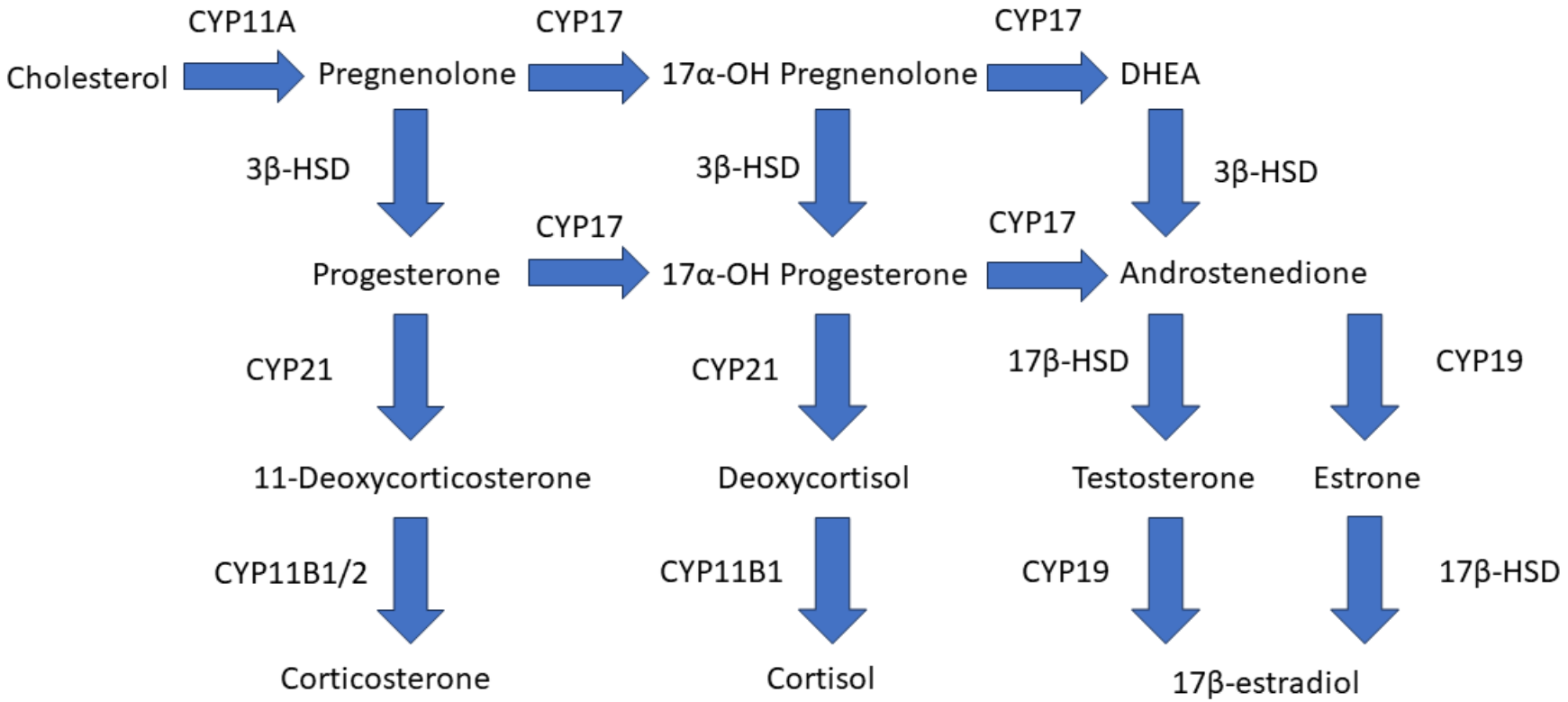
- PFAS are known to bind to TTR, triazoles were not previously tested





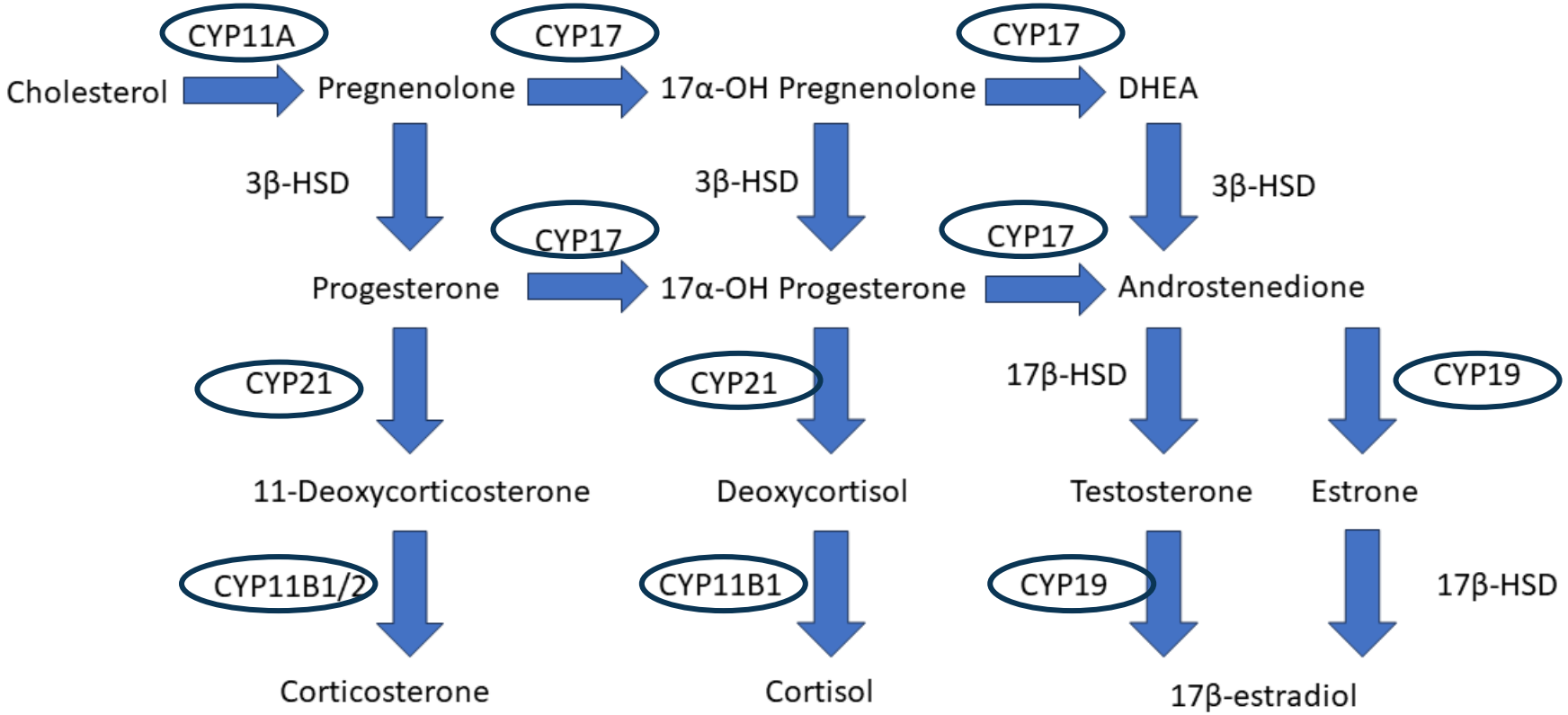
Steroidogenesis

- Production of steroid hormones, including testosterone, estradiol, progesterone and cortisol



Steroidogenesis

- Triazole fungicides are known to inhibit Cytochrome P450 enzymes



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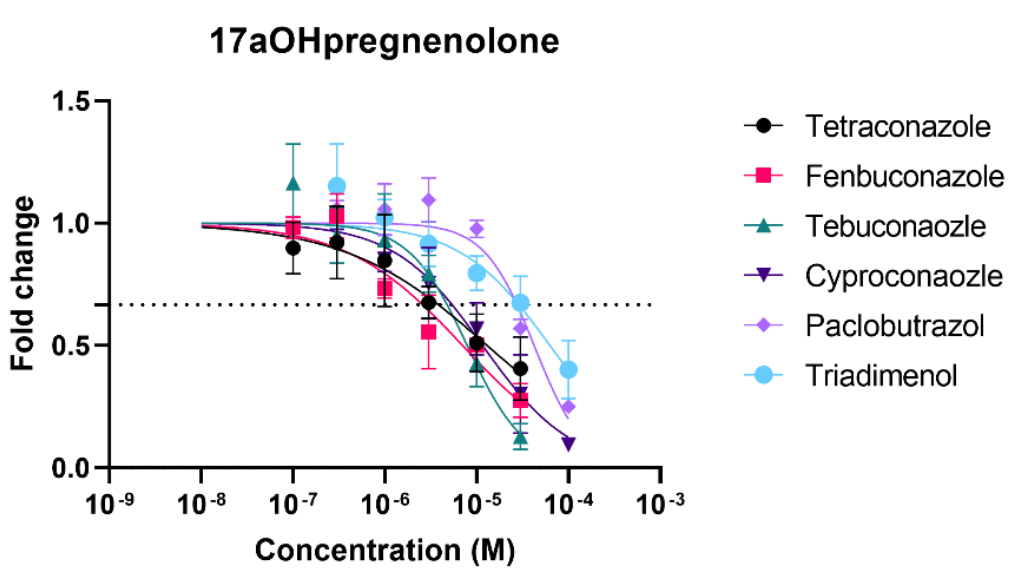

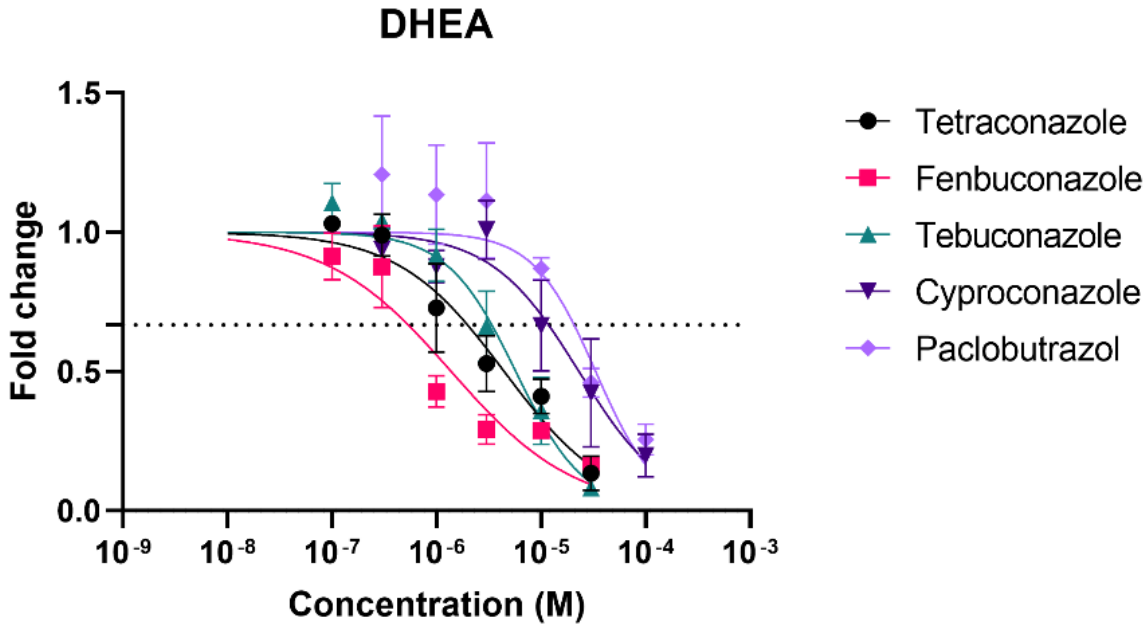

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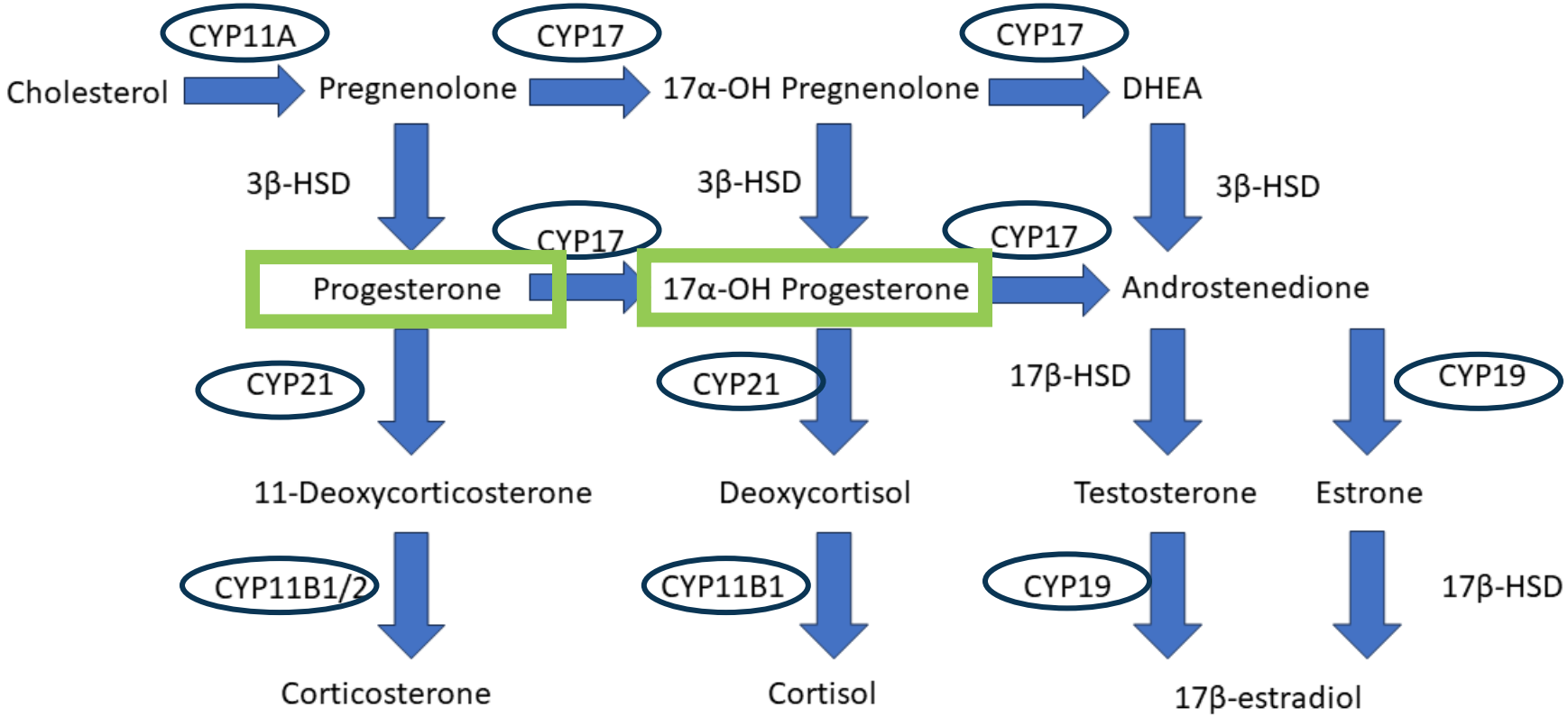
- Triazole fungicides are known to inhibit Cytochrome P450 enzymes
- As 3β-HSD still works, progesterone and 17 α-OH progesterone accumulate



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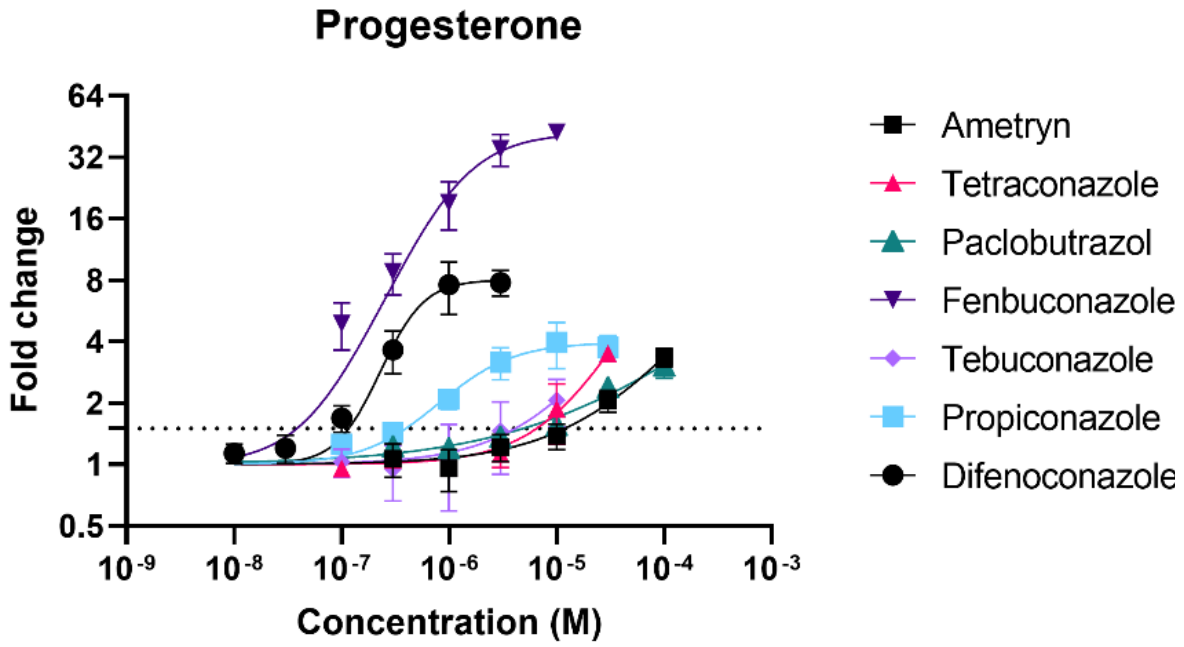
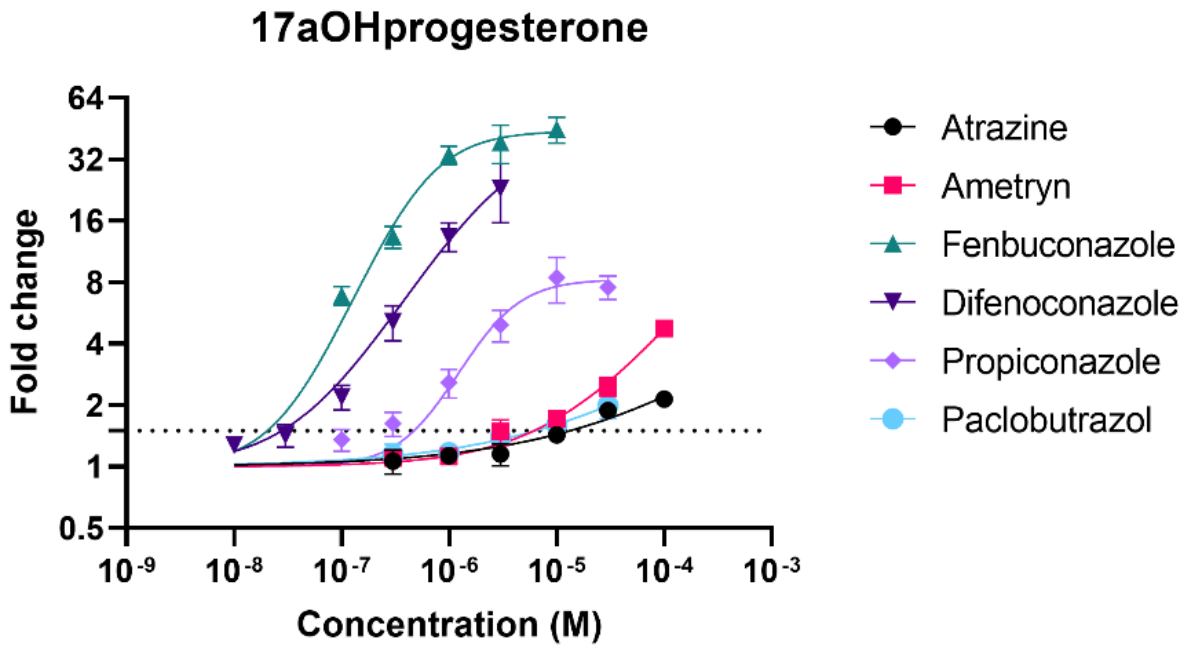
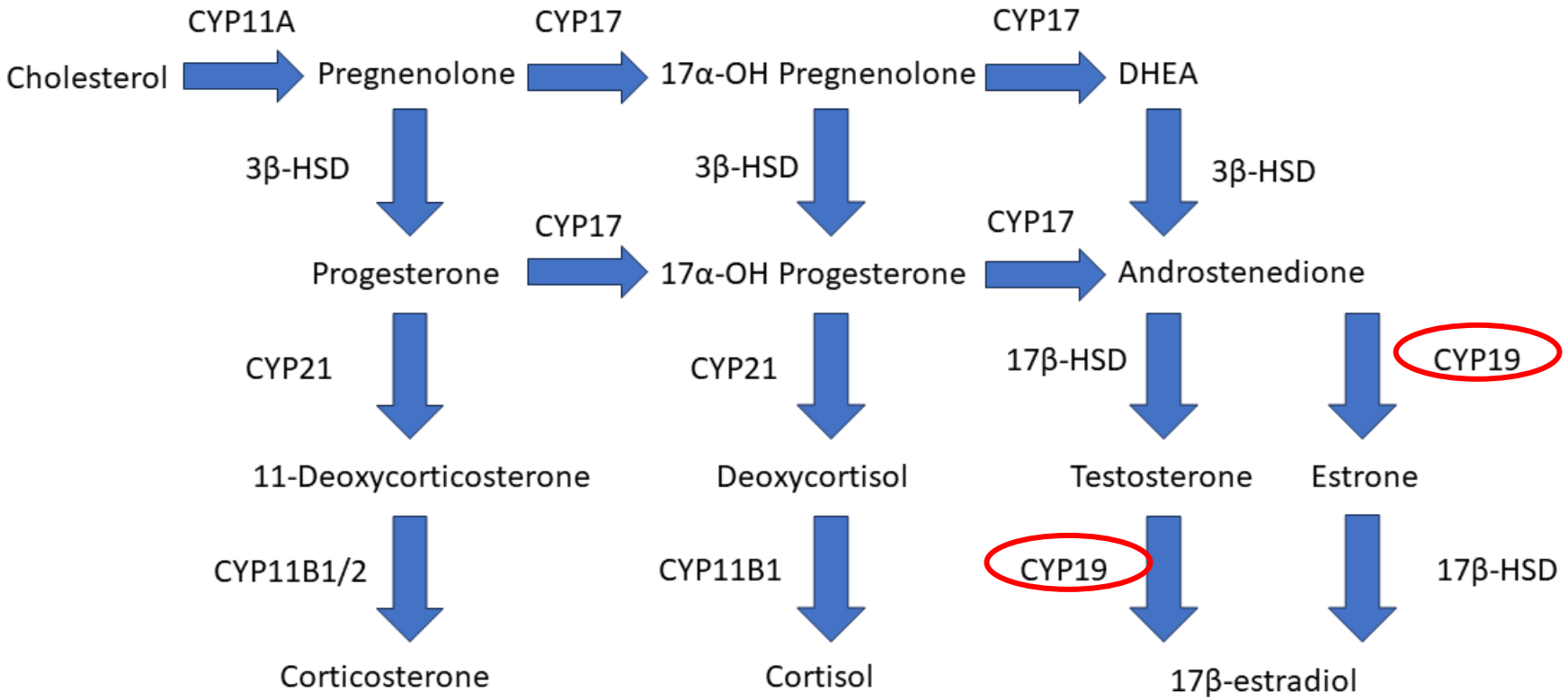




Steroidogenesis

- Atrazine is a cyclic AMP inducer, and induces all enzymes, but especially CYP19



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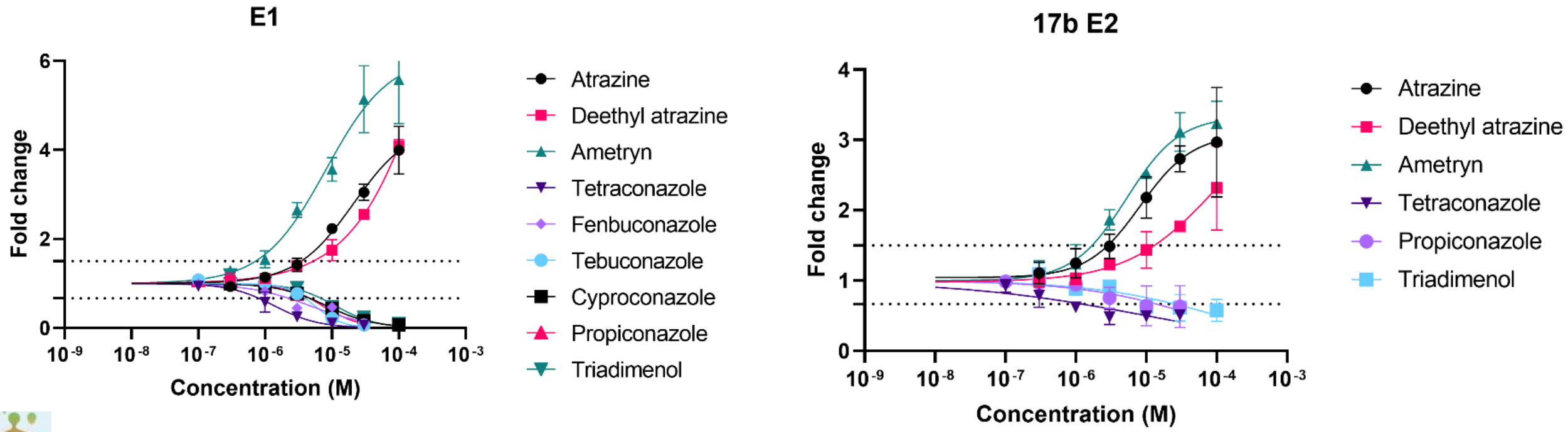

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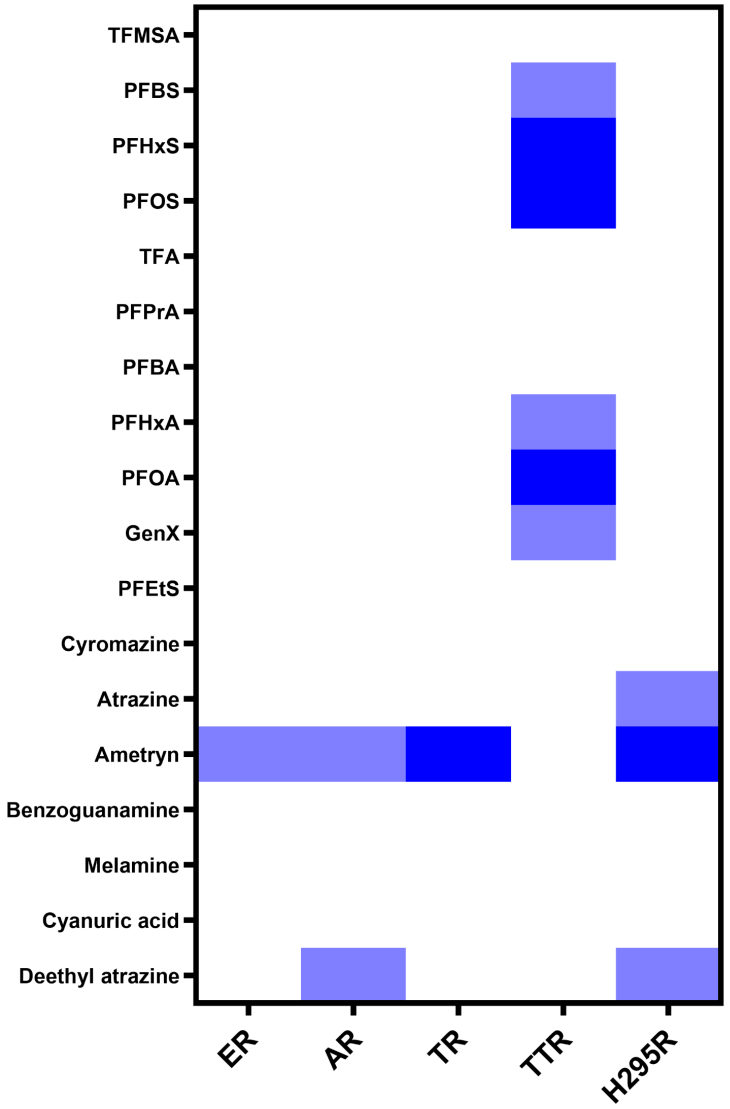
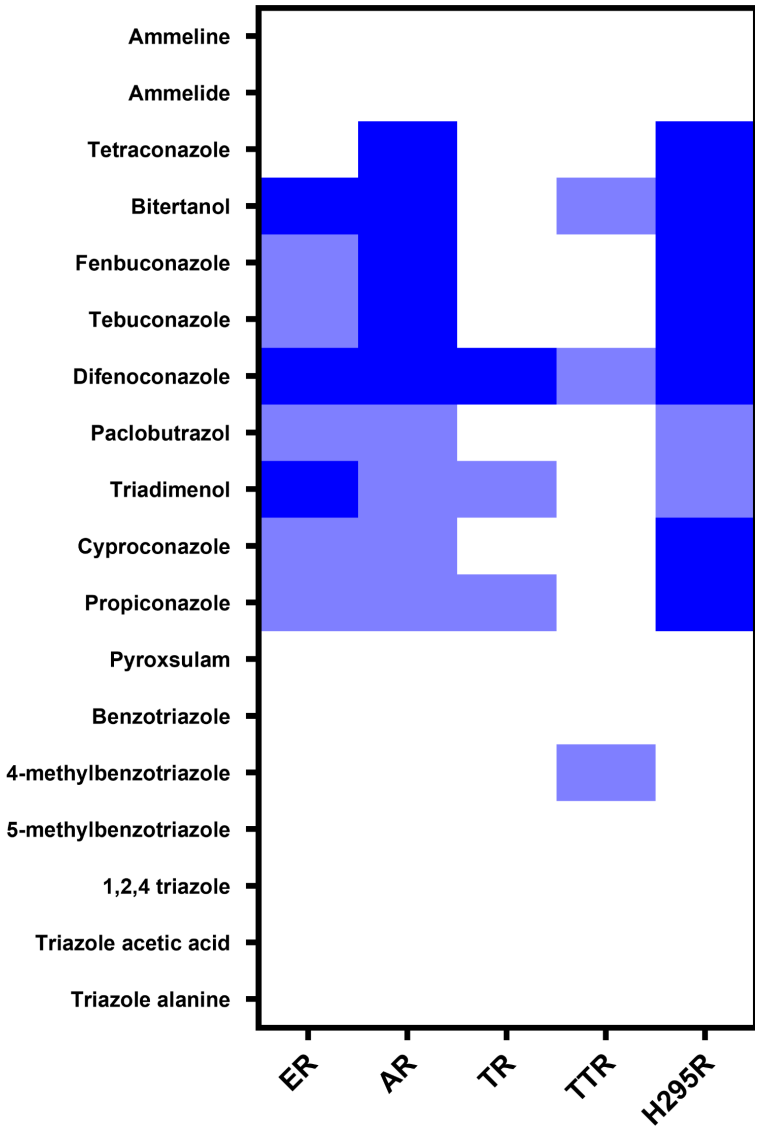
Conclusion

- Mostly triazole fungicides, atrazine and ametryn have effects on steroidogenesis and hormone receptors
- Mostly PFAS bind to TTR
- If you are interested in more details, please take a look at my poster





Acknowledgements

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ZerOPM

Thank you for your attention!

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CHALMERS UNIVERSITY OF TECHNOLOGY

Empa Materials Science and Technology

chemsec INTERNATIONAL CHEMICAL SECRETARIAT

NGI

DVGW | TZW Technologiezentrum Wasser

UNIVERSITY OF THE AEGEAN

Fraunhofer ITEM

NIVA Norwegian Institute for Water Research

UNIVERSITÉ DU LUXEMBOURG

TG ENVIRONMENTAL RESEARCH

Stockholm University

universität wien

Umwelt Bundesamt

VU VRIJE UNIVERSITEIT AMSTERDAM

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