Pre- and postnatal exposure to pyrethroids in French children from the ELFE cohort

Ophélia Gestin, Elisa Thépaut, Michèle Bisson, Brice M.R. Appenzeller, Linda R. Macheka, Paul Palazzi, Alba Iglesias-González, Cécile Zaros, Cleo Tebby and Florence Zeman
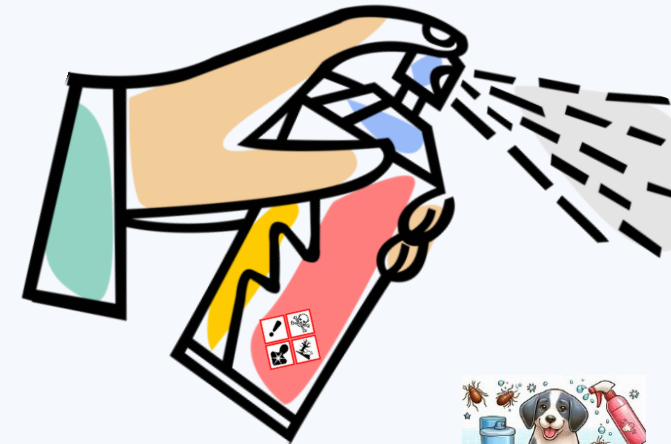
Pyrethroids (PYR) – Overview

- Synthetic insecticides molecules derived from pyrethrins, use since the 60's

- Non-persistent molecules

- Family comprising many molecules, widely used in various fields

Pyrethroids (PYR) – Potential effects

Many widely described effects, including neurotoxicity

Interaction with voltage-gated sodium channels in neurons of insects, but also of mammals organisms

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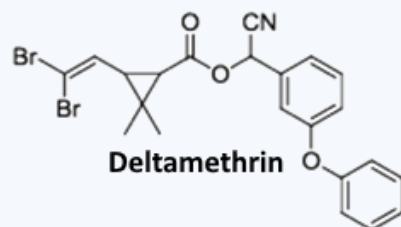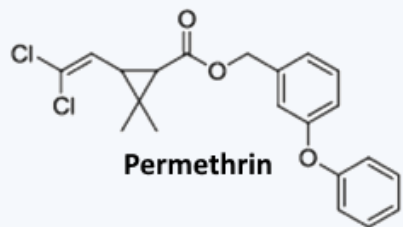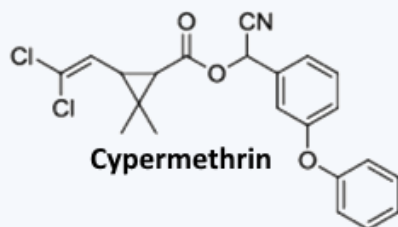
Pre- and postnatal exposure can be associated with **neurodevelopmental disorders** (Furlong *et al.*, 2017, Xue *et al.*, 2013, Qi *et al.*, 2022)

Childhood is a sensitive period for PYR exposure

Pyrethroids (PYR) – ADME processes

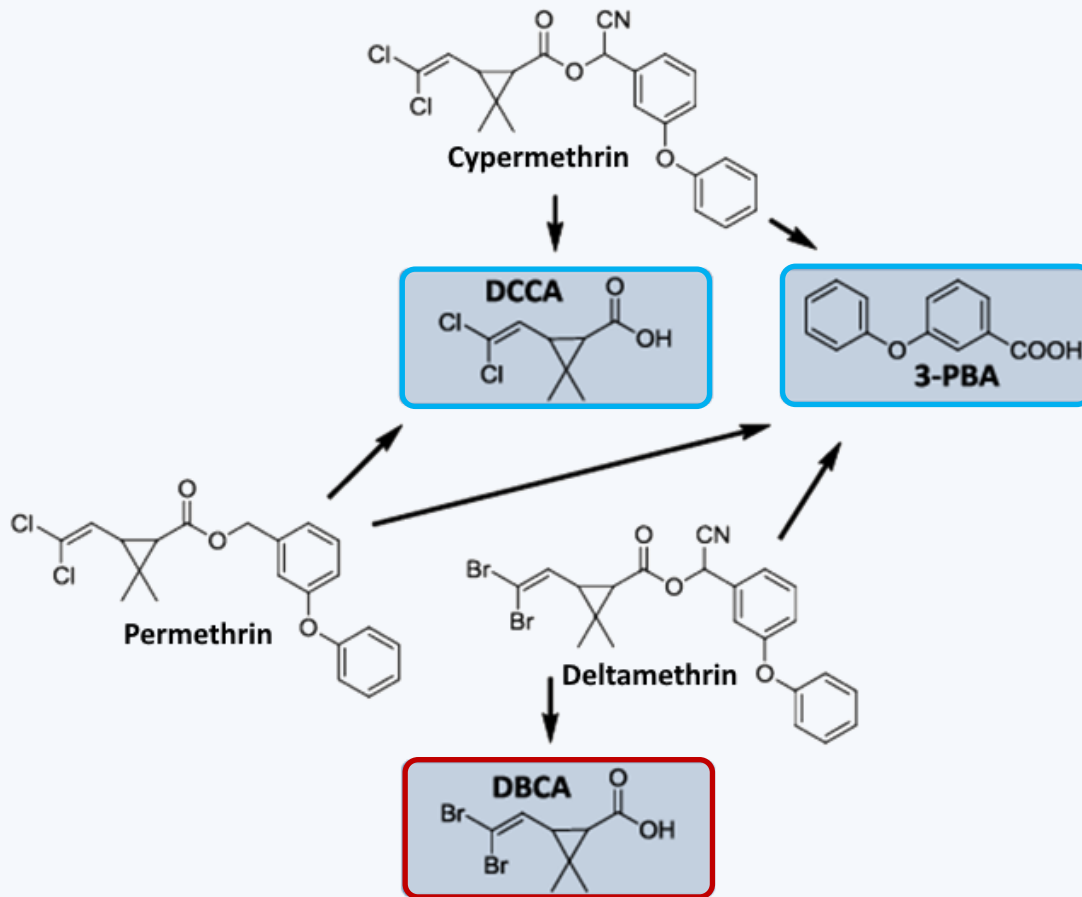Parent molecules are supposed to be mainly absorbed by ingestion

Cypermethrin

Permethrin

Deltamethrin

Pyrethroids (PYR) – ADME processes

Parent molecules are supposed to be mainly absorbed by ingestion

Parent molecules are metabolized into specific or non-specific metabolites, by P450 cytochromes, carboxylesterases
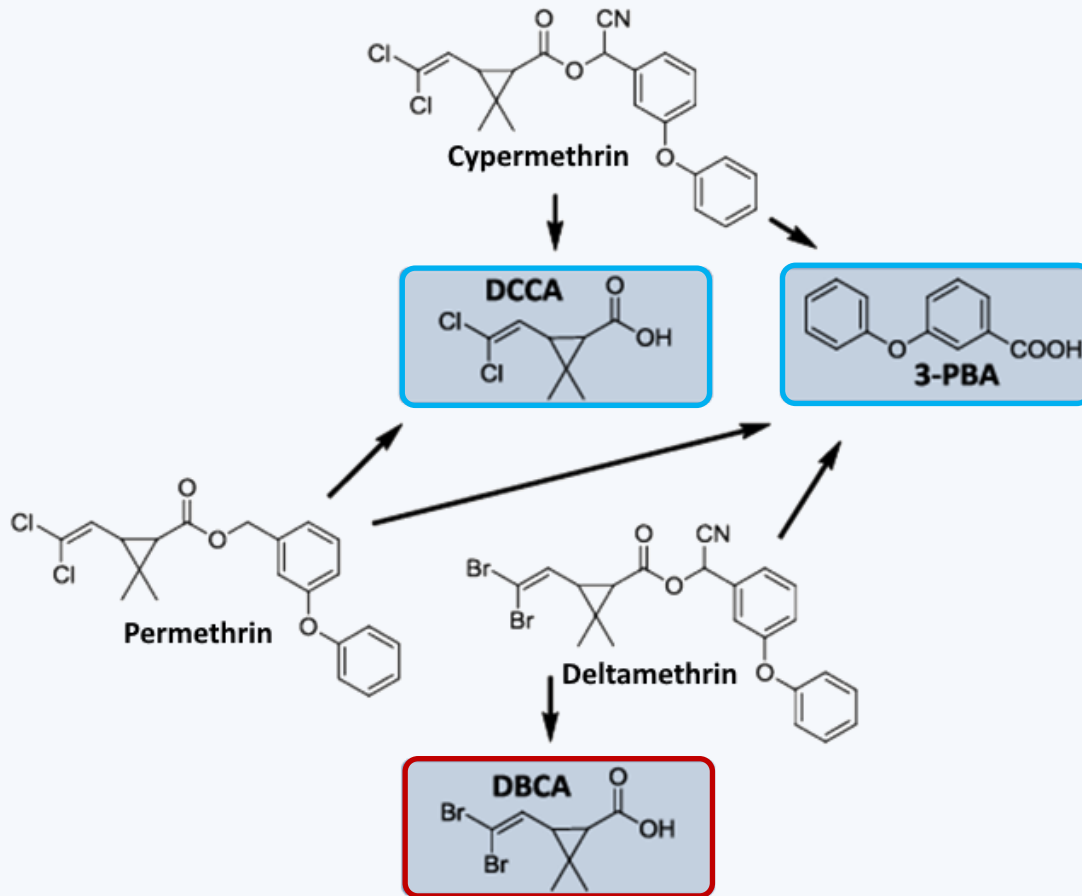
Pyrethroids (PYR) – ADME processes

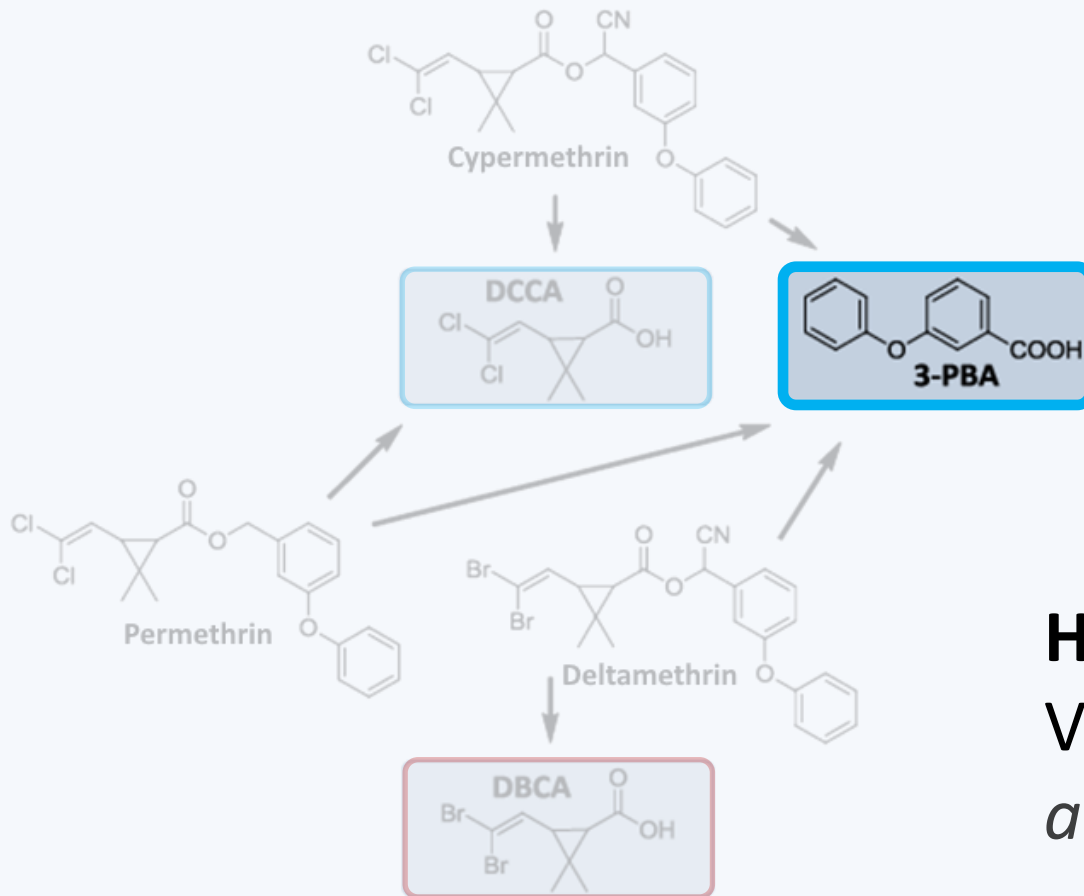Parent molecules are supposed to be mainly absorbed by ingestion

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Elimination of parent molecules and especially metabolites, mainly by urine

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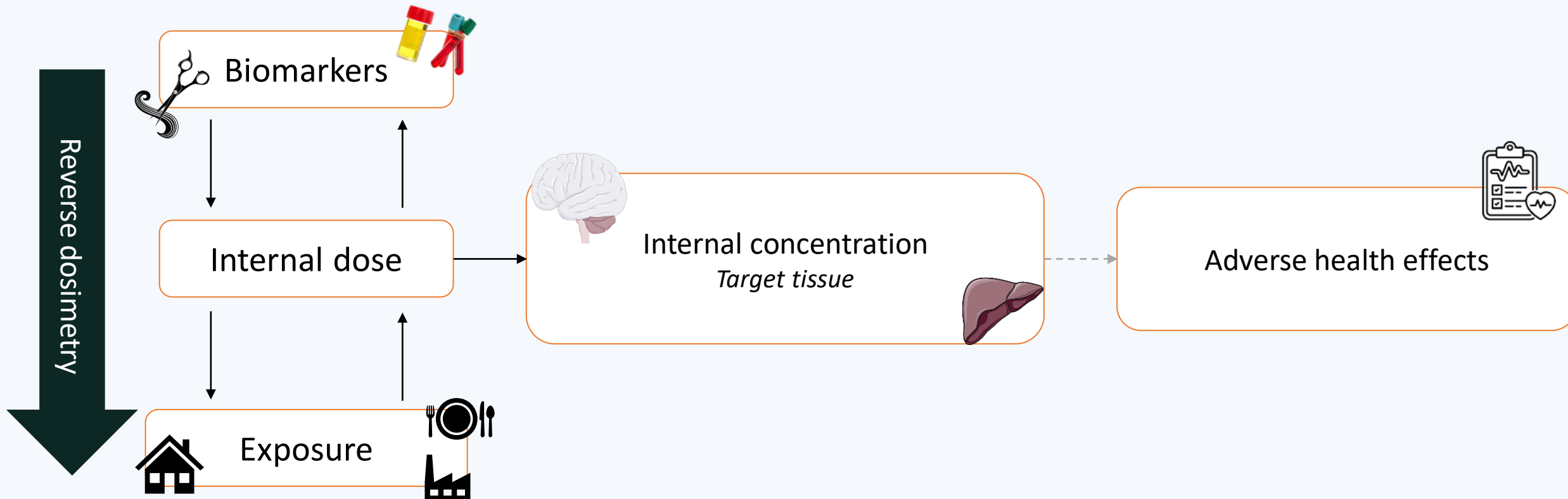Elimination of parent molecules and especially metabolites, mainly by urine

HBM-GV (Human BioMonitoring – Guidance Value) = 3.25 µg 3-PBA.L^{-1} urine (Tarazona *et al.*, 2022)

Human biomonitoring data

Reverse dosimetry

Physiologically Based PharmacoKinetic (PBPK) models

They describe the fate of a substance in an organism

They are composed by differential equations

The compartments represent tissues/matrices and arrows correspond to blood flows, as shown on the right
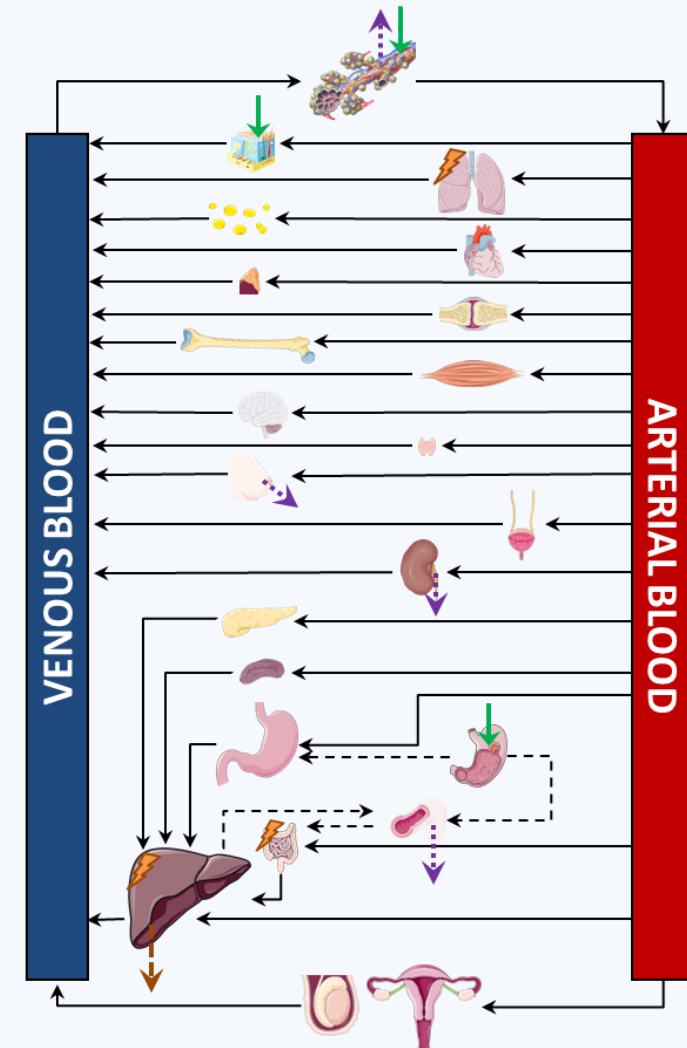
# Physiologically Based PharmacoKinetic (PBPK) models

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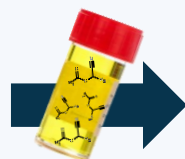
PBPK models include all the biological processes involved in ADME processes of a chemical substance

To use PBPK models we need data, as physiological parameters and substance-specific parameters
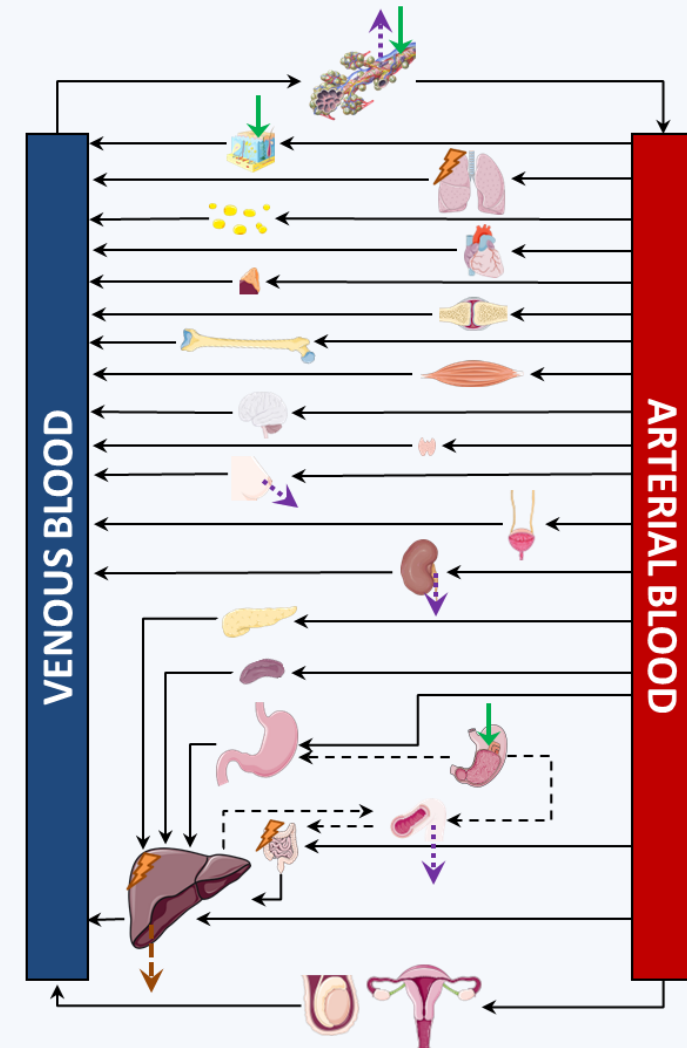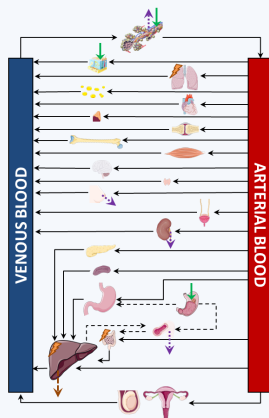
Objectives of this work

To use data from the ELFE cohort to determine exposure of children (pre-natal and post-natal)
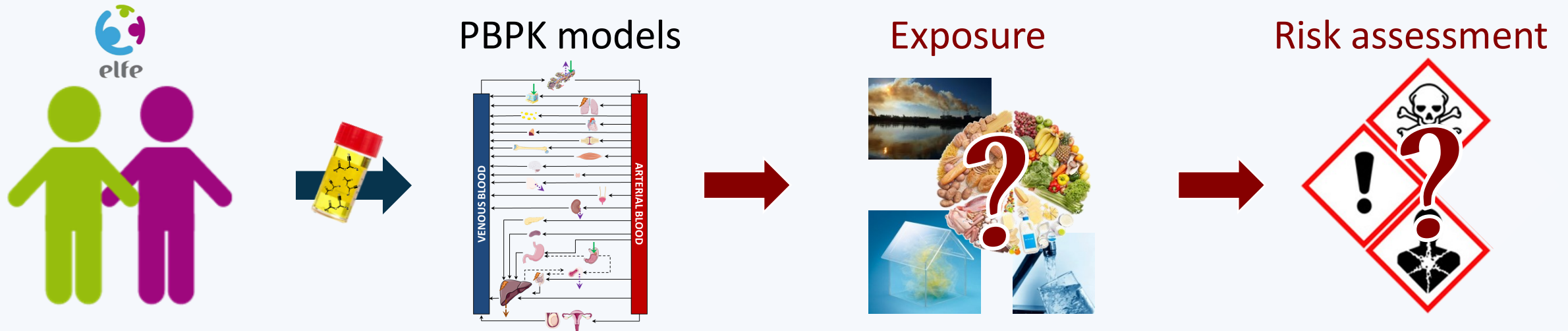

PBPK models Exposure Risk assessment

Objectives of this work

To use data from the ELFE cohort to determine exposure of children (pre-natal and post-natal)

PBPK models   Exposure   Risk assessment

Objectives of today: focus on fetuses only

ELFE cohort

- French Longitudinal Study of Childhood

- Objective: how children development, health and socialization are influenced by their environment, from the womb to adolescence
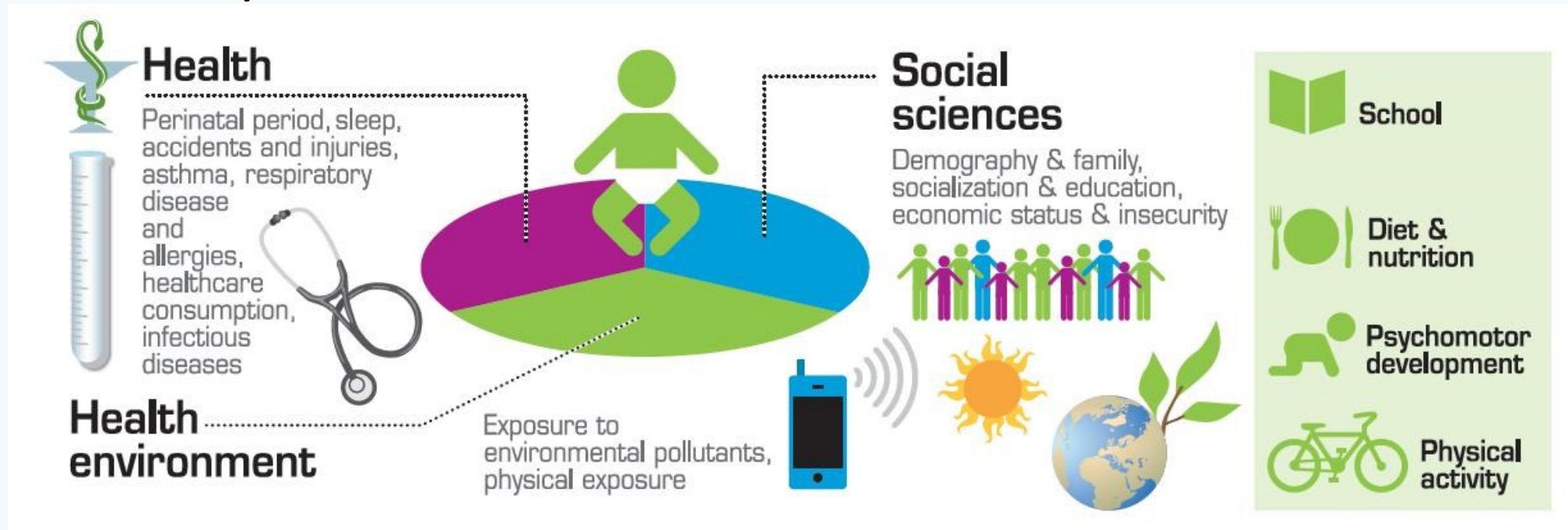
ELFE cohort

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ELFE cohort

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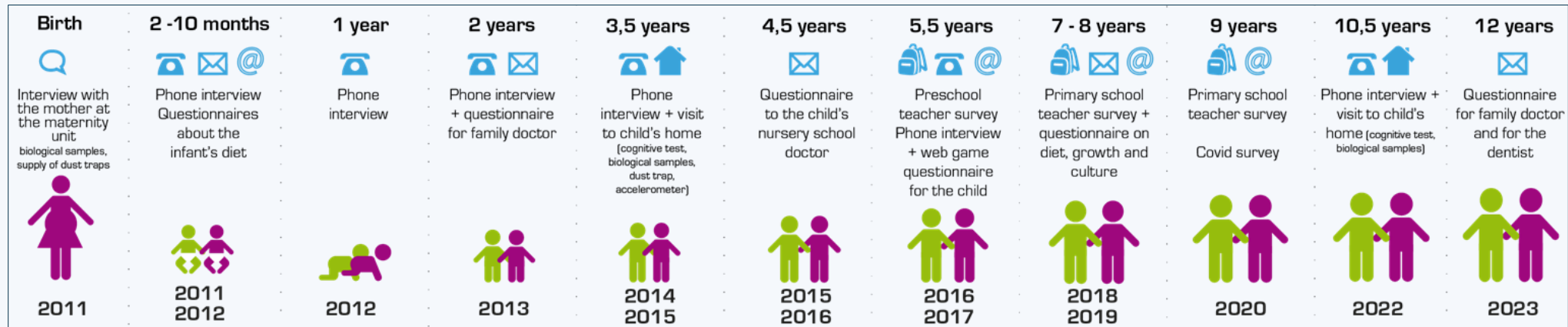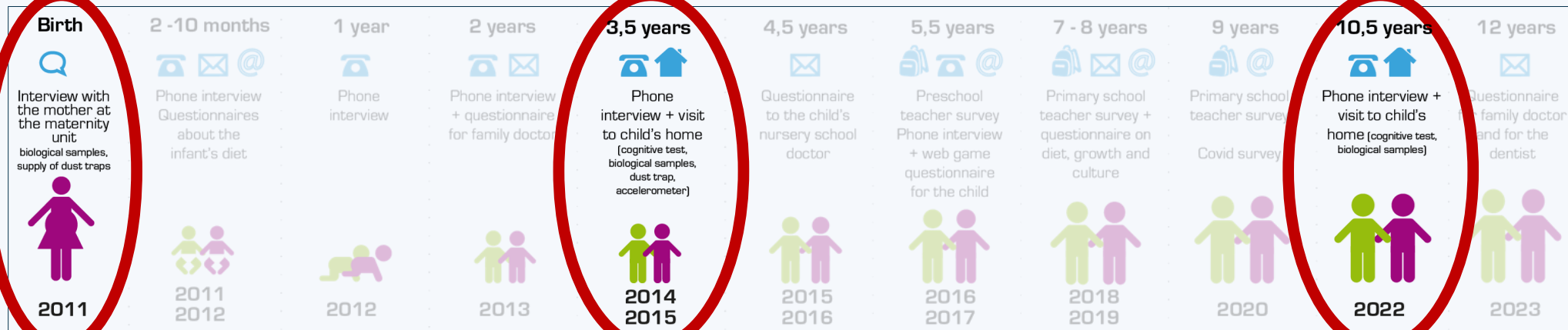- Follow-up of children, from pregnant mother to age 20

- Sampling of different matrices (*e.g.* hair, urines or blood)

ELFE cohort

Biomarkers were analyzed in the perinatal component of the French HBM program (Dereumeaux *et al.,* 2016) and by the Luxembourg Institute of Health (LIH) in the POPEYE project (Beranger *et al.,* 2018)

Birth

Interview with the mother at the maternity unit
biological samples, supply of dust traps

2011

Environment International 97 (2016) 56–67

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Biomarkers of exposure to environmental contaminants in French pregnant women from the Elfe cohort in 2011

Clémentine Dereumeaux [a,*], Abdesattar Saoudi [a], Marie Pecheux [a], Bénédicte Berat [a], Perrine de Crouy-Chanel [a], Cécile Zaros [b], Serge Brunel [a], Corinne Delamaire [a], Alain le Tertre [a], Agnès Lefranc [a], Stéphanie Vandentorren [a], Laurence Guldner [a]

[a] Direction of Environmental Health, Santé publique France, 12 rue du Val d'Osne, 94415 Saint Maurice Cedex, France
[b] French National Institute for Health and Medical Research (Inserm), The "Elfe" INED-INSERM-EFS team, 133, boulevard Davout, 75020 Paris, France

Environment International 120 (2018) 43–53

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Multiple pesticide analysis in hair samples of pregnant French women: Results from the ELFE national birth cohort

Rémi Béranger [a,*], Emilie M. Hardy [b], Célia Dexet [b], Laurence Guldner [c], Cécile Zaros [d], Alexandre Nougadère [e,1], Marie-Astrid Metten [a], Cécile Chevrier [c,2], Brice M.R. Appenzeller [b,2]

ELFE cohort

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An analysis of pyrethroid exposure in pregnant women and their fetuses using PBPK models **has just been published** by Thépaut *et al.,* 2024

Environmental Research 251 (2024) 118606

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

ELSEVIER

PBPK modeling to support risk assessment of pyrethroid exposure in French pregnant women

Elisa Thépaut [a], Michèle Bisson [b], Céline Brochot [a,f], Stéphane Personne [c],
Brice M.R. Appenzeller [d], Cécile Zaros [e], Karen Chardon [c], Florence Zeman [a,*]

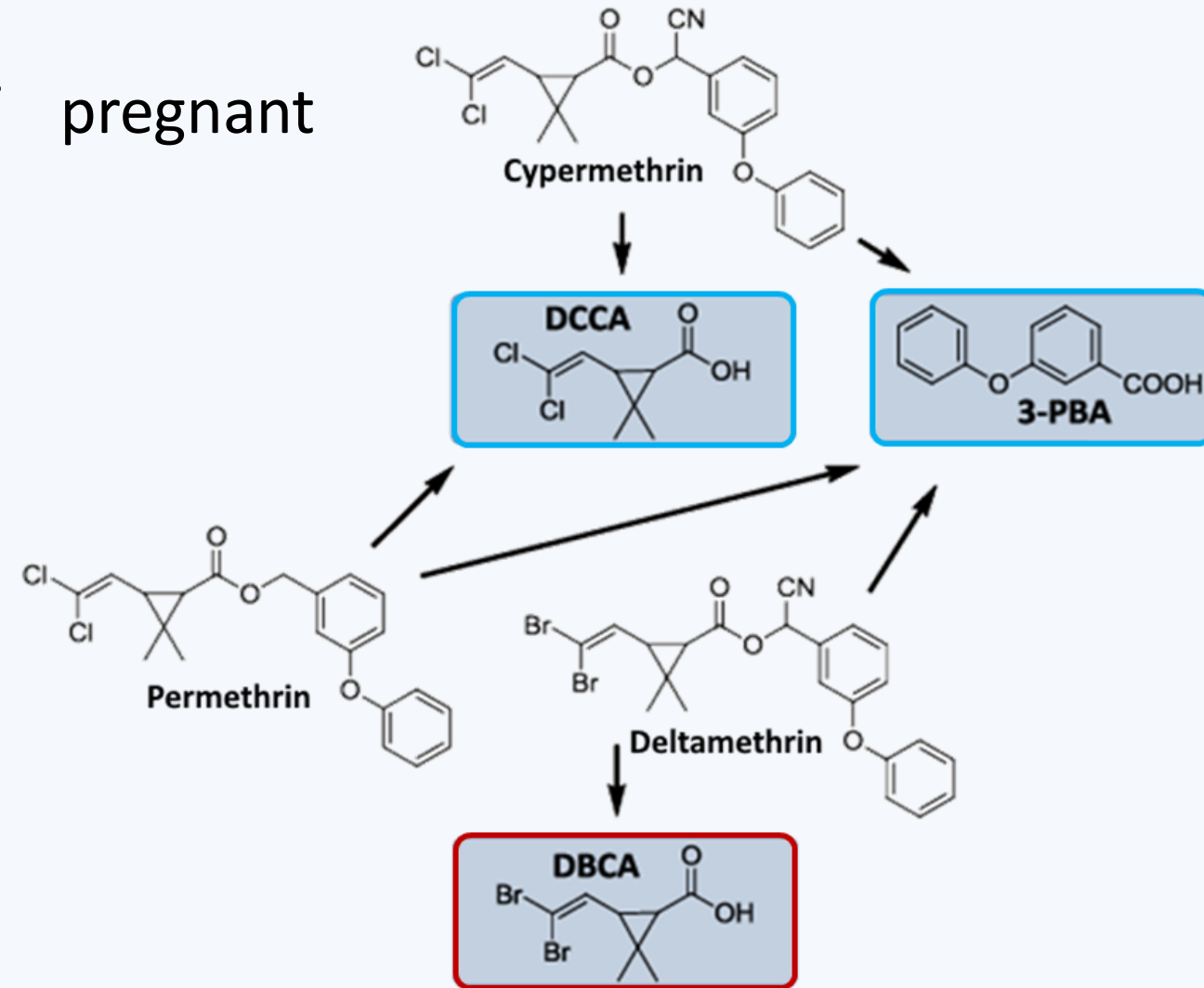=> The results presented today are those of Thépaut *et al.,* 2024

Human biomonitoring data

Biomarkers measure in urine of pregnant women:

- cis- and trans- DCCA
- 3-PBA
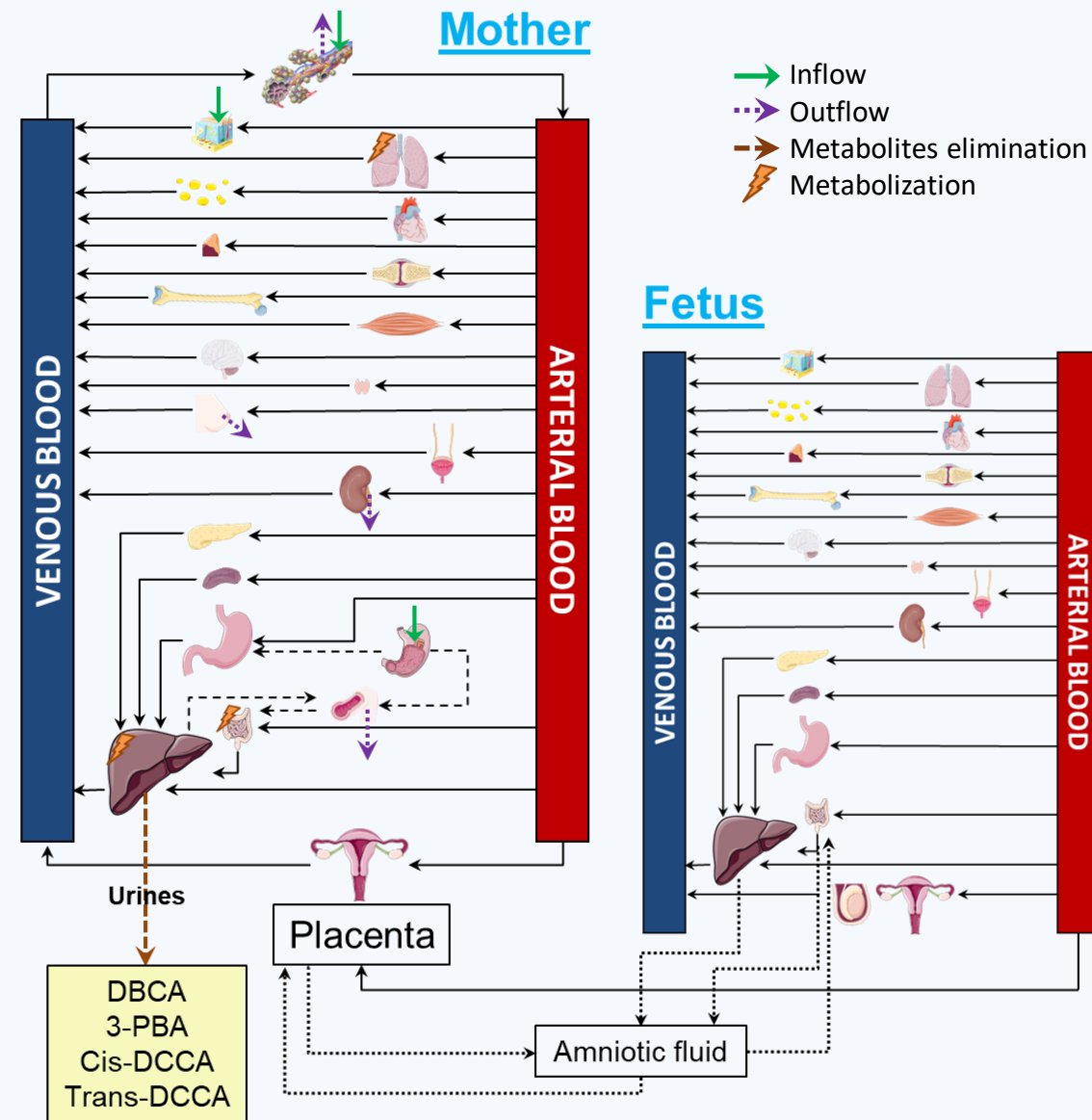- DBCA

Number of urine samples = 924

p-PBPK model

Adapted to pregnancy from Quindroit *et al.,* (2019)

3 parent molecules and their isomers:
- Deltamethrin
- ∑Cypermethrin = 42% cis + 58% trans
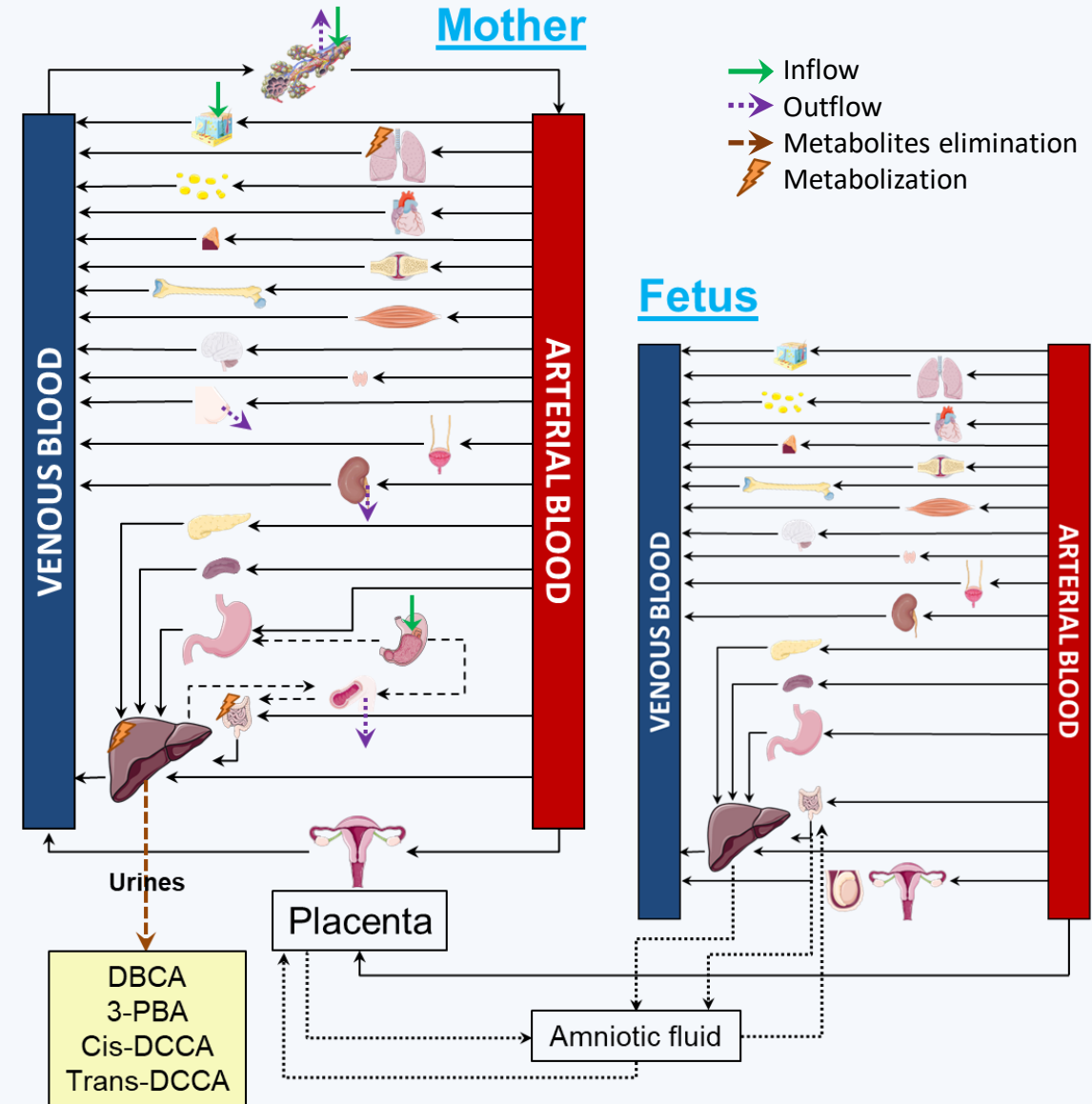- ∑Permethrin = 40% cis + 60% trans

p-PBPK model

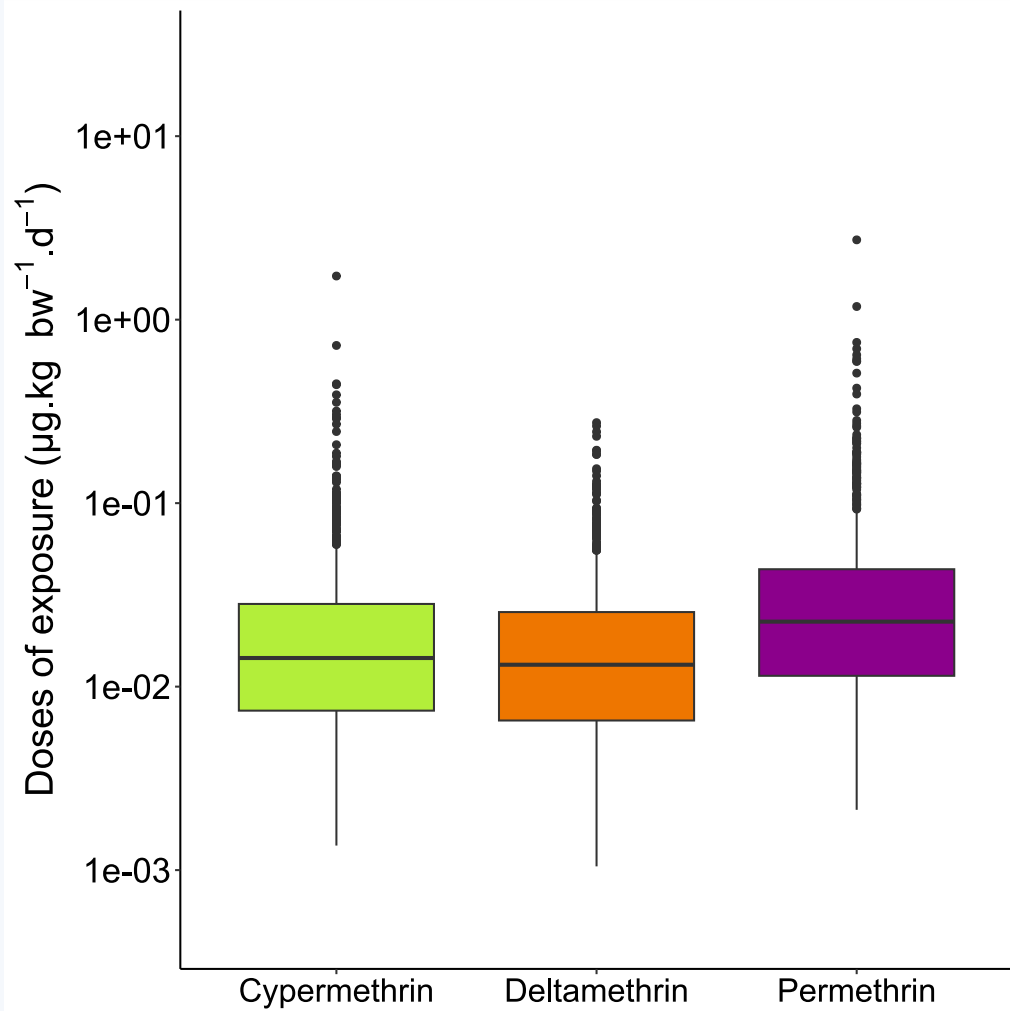Adapted to pregnancy from Quindroit *et al.*, (2019)

3 parent molecules and their isomers

Describe the excretion of 4 different urinary metabolites, at steady-state

With PBPK models, exposure and internal concentrations can be estimated from urinary data

Ingestion doses of pyrethroids by pregnant women

Exposure predictions are:

- in the **same range** as thus determined in the French adult population by Quindroit *et al.,* (2019)

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- **below** the Toxicity Reference Values (TRV, red lines) determined by different public health institutions (ANSES 2021, WHO JMPR 2001, Health Canada 2017)
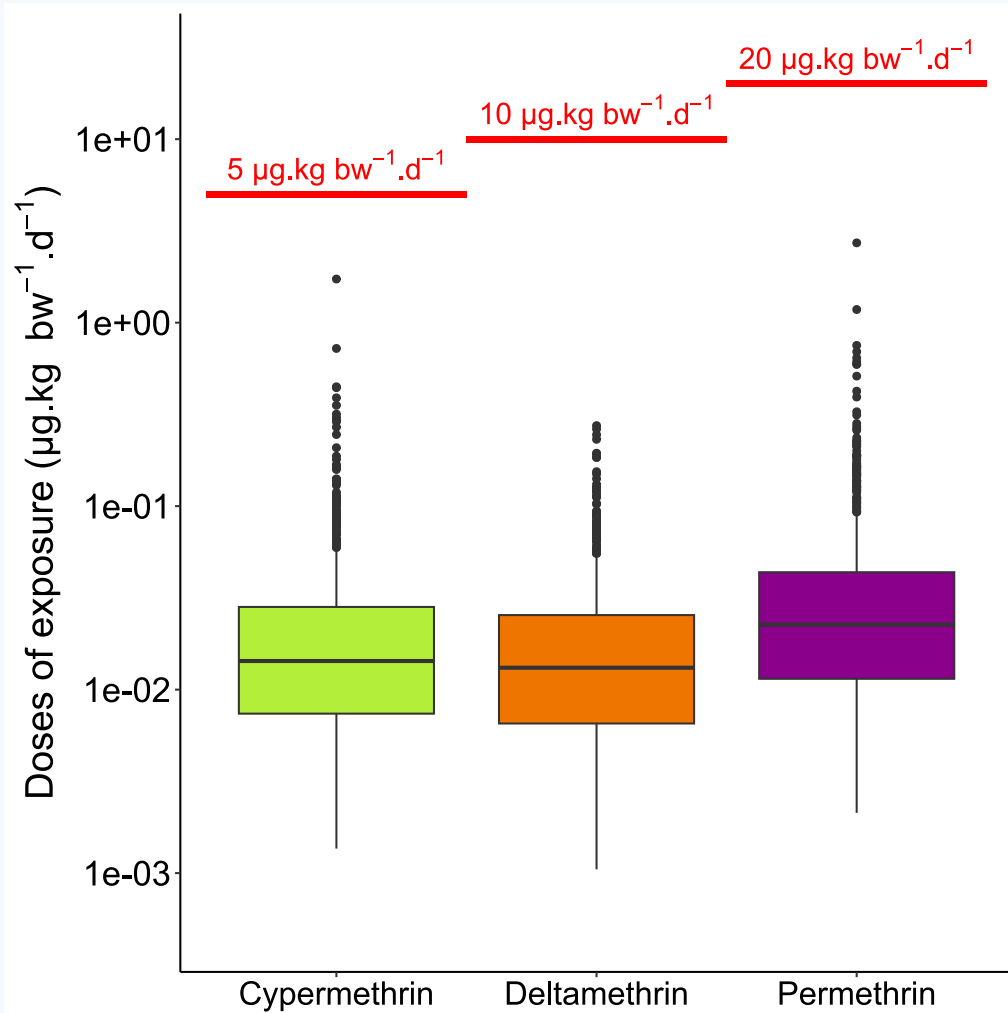
Ingestion doses of pyrethroids by pregnant women
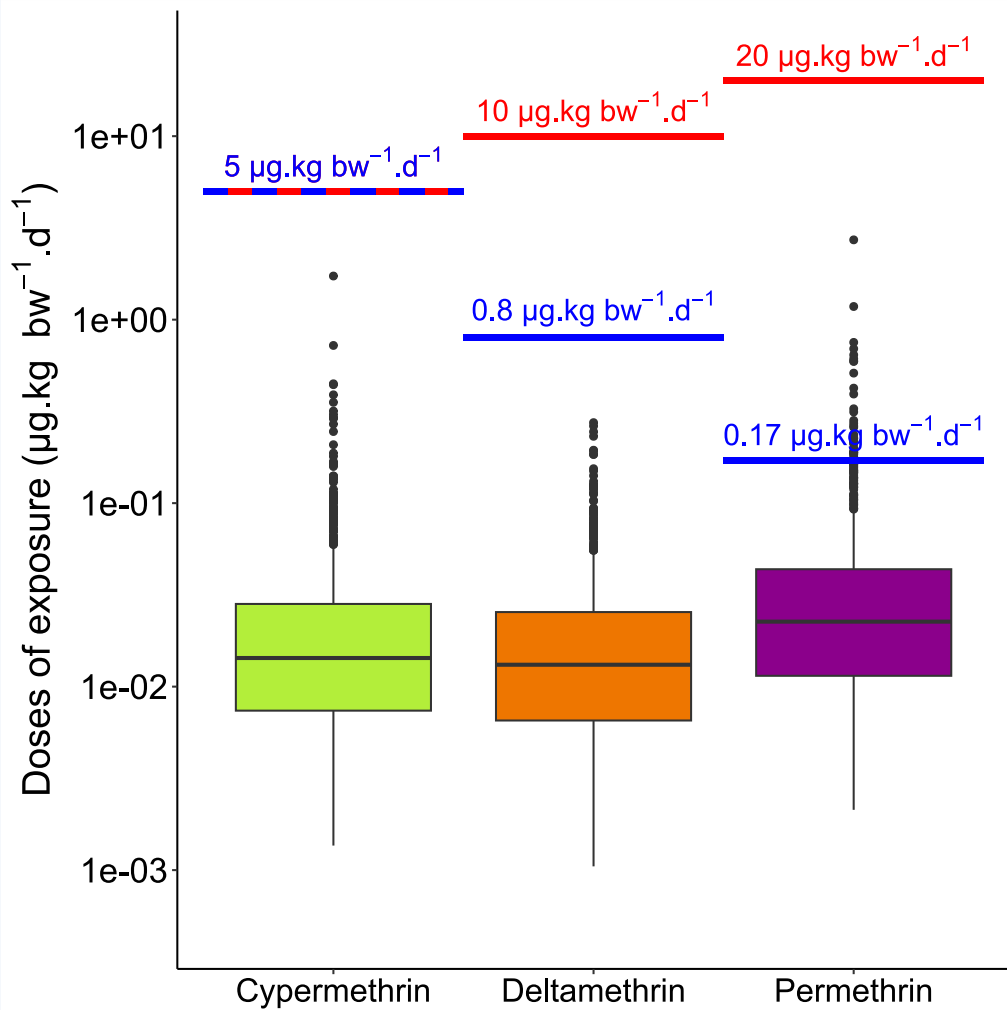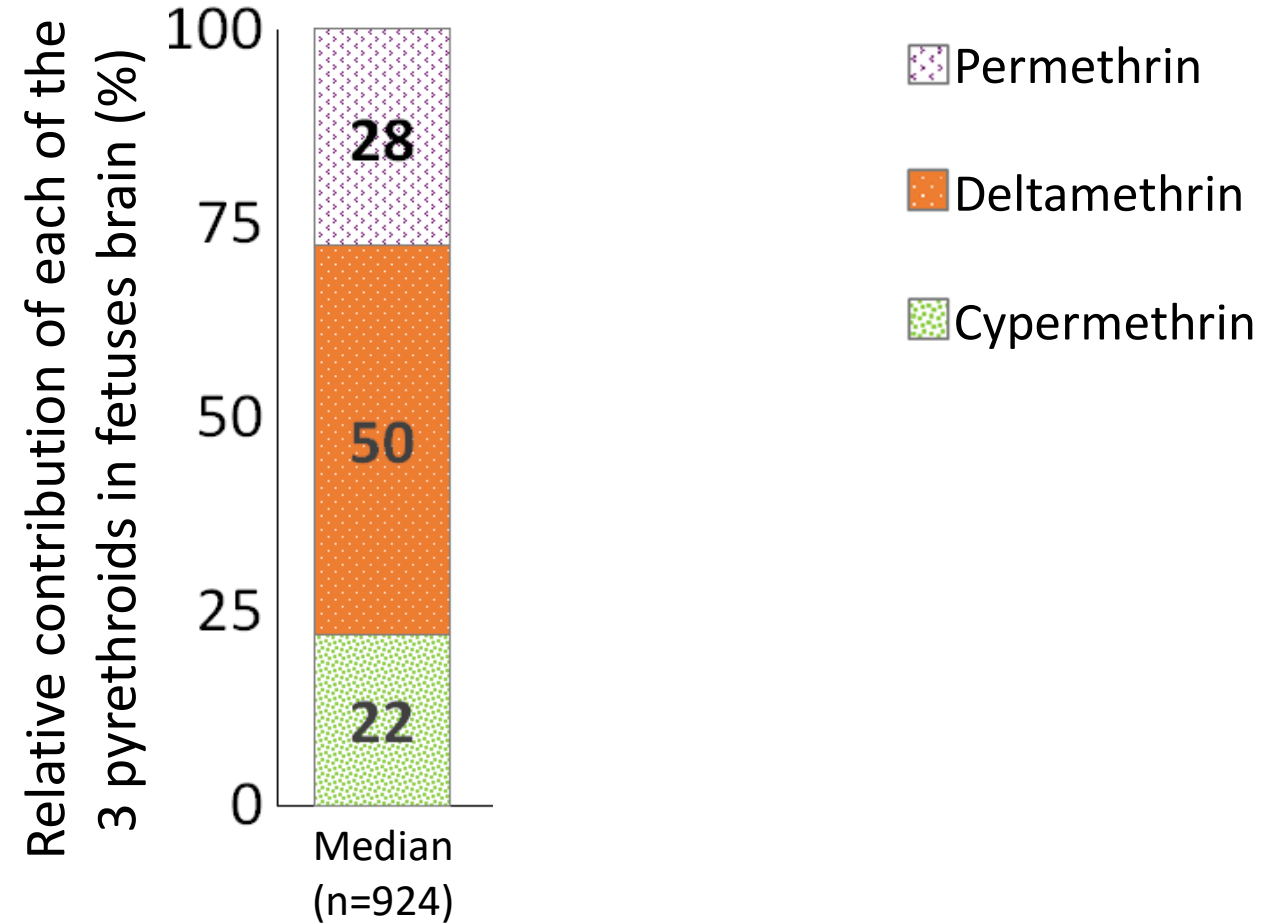

Exposure predictions are:

- in the **same range** as thus determined in the French adult population by Quindroit *et al.,* (2019)

- **below** the Toxicity Reference Values (TRV, red lines) determined by different public health institutions

- **exceed** the new-child/fetuses specific TRV (blue lines), for permethrin, for 2.5% of pregnant women (Gomez-Gimenez *et al.* 2017, Pitzer *et al.* 2019, Saito *et al.* 2019)

Pyrethroids concentrations in fetuses' brain

PBPK models are used to estimate the internal concentrations of molecules

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PBPK models are used to estimate the internal concentrations of molecules

They also provide an individual contamination profile, such as:

🤰 **Fetus A**, from the woman which have the highest $[DBCA]_{urine}$

Figure: Relative contribution of each of the 3 pyrethroids in fetuses brain (%). Median (n=924) — Cypermethrin 22, Deltamethrin 50, Permethrin 28. Highest $[DBCA]_{urine}$ (**Fetus A**) — Cypermethrin 3, Deltamethrin 93, Permethrin 4.

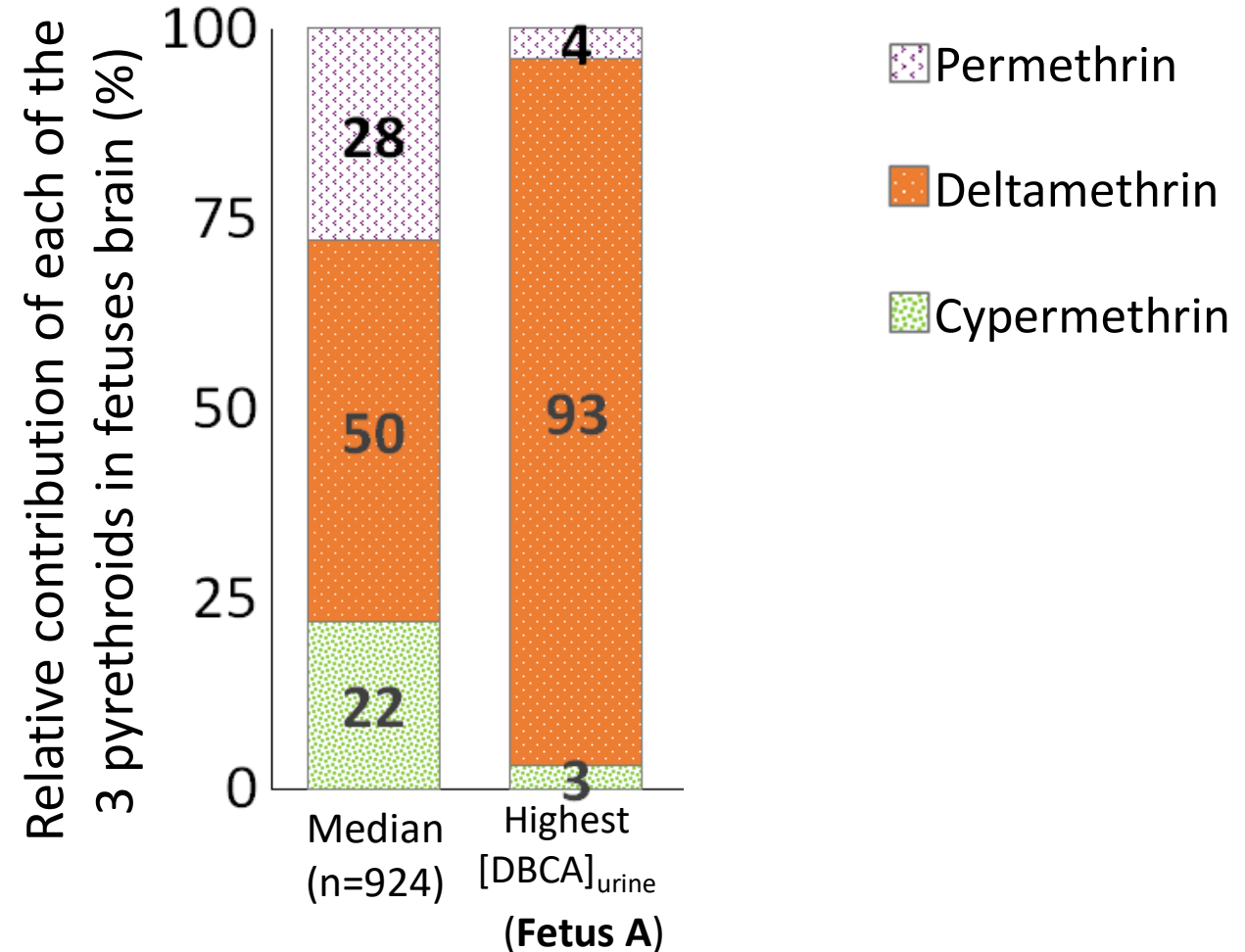Legend: Permethrin, Deltamethrin, Cypermethrin

Pyrethroids concentrations in fetuses' brain

PBPK models are used to estimate the internal concentrations of molecules

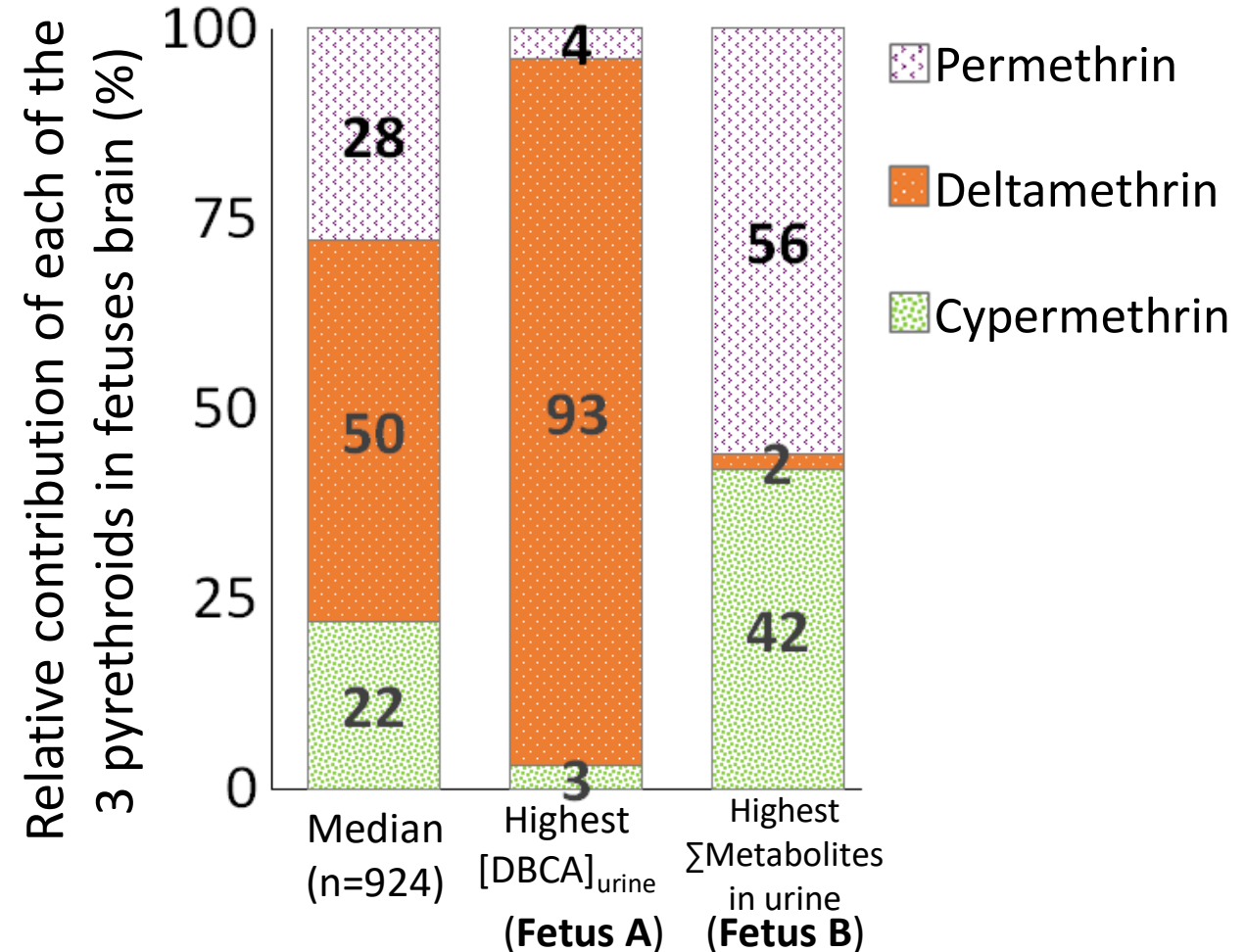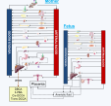They also provide an individual contamination profile, such as:

- **Fetus A**, from the woman which have the highest [DBCA]$_{urine}$

- **Fetus B**, from the woman which have the highest sum of metabolites in urine

Chart legend: Permethrin, Deltamethrin, Cypermethrin

Y-axis: Relative contribution of each of the 3 pyrethroids in fetuses brain (%)

X-axis categories:
- Median (n=924): Cypermethrin 22, Deltamethrin 50, Permethrin 28
- Highest [DBCA]$_{urine}$ (**Fetus A**): Cypermethrin 3, Deltamethrin 93, Permethrin 4
- Highest ΣMetabolites in urine (**Fetus B**): Cypermethrin 42, Deltamethrin 2, Permethrin 56

Key facts to remember

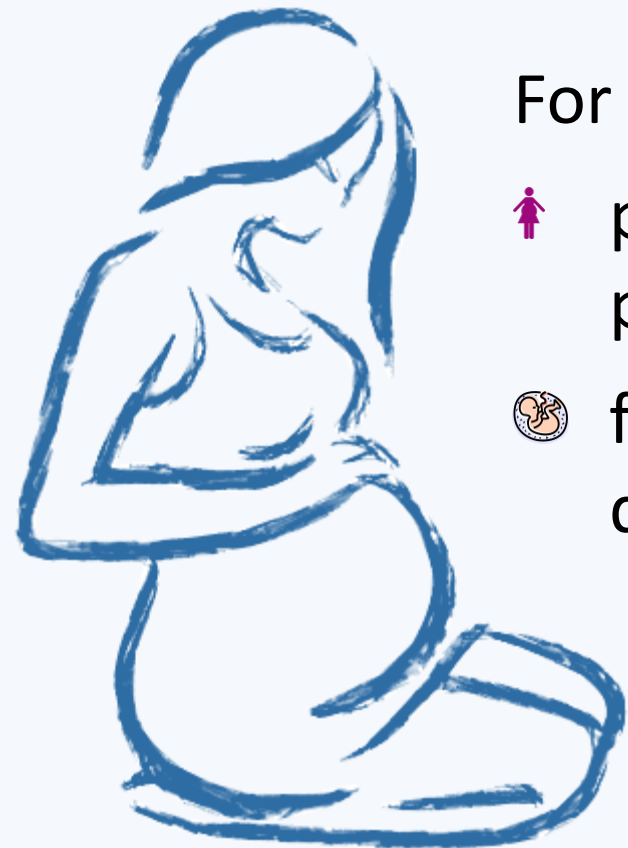A PBPK model specific to pyrethroids was adapted to pregnancy (p-PBPK model)

Key facts to remember

A PBPK model specific to pyrethroids was adapted to pregnancy (p-PBPK model)

For the first time:

- pyrethroids exposure of French pregnant women was predicted

- fetal exposure to pyrethroids and their internal doses was determined

Key facts to remember

A PBPK model specific to pyrethroids was adapted to pregnancy (p-PBPK model)

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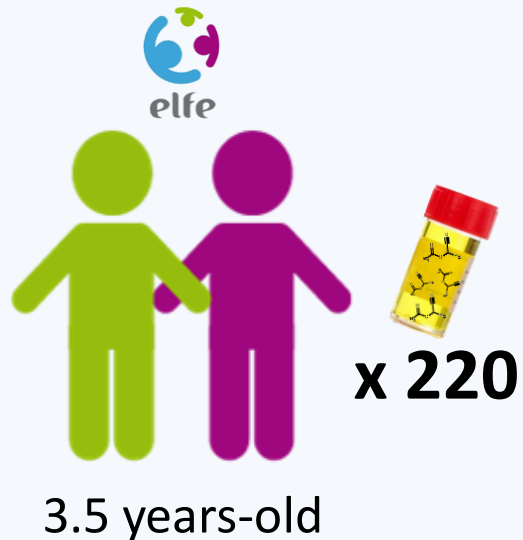- fetal exposure to pyrethroids and their internal doses was determined

➢ 2.5% of the pregnant women from the ELFE cohort exceeded child specific TRV (toxicological reference value) for the permethrin

Future outlook – next steps?

For 3.5 years-old children: 220 urine samples were available

Biomarkers were analyzed in the NEUROPHYTO project by the LIH

x 220

3.5 years-old

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They quantified other pyrethroids, such as λ-cyhalothrin and its metabolite CFMP, which we will also consider

At 3.5-year-old, 11% of children of the ELFE cohort exceed the HBM-GV of 3.25 µg 3-PBA.L urine^{-1}

Future outlook – next steps?

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At 3.5-year-old, 11% of children of the ELFE cohort exceed the HBM-GV of 3.25 µg 3-PBA.L urine^{-1}

➢ Characterize the exposure of the ELFE children, at 3.5 yo, using PBPK models, to better assess the risks
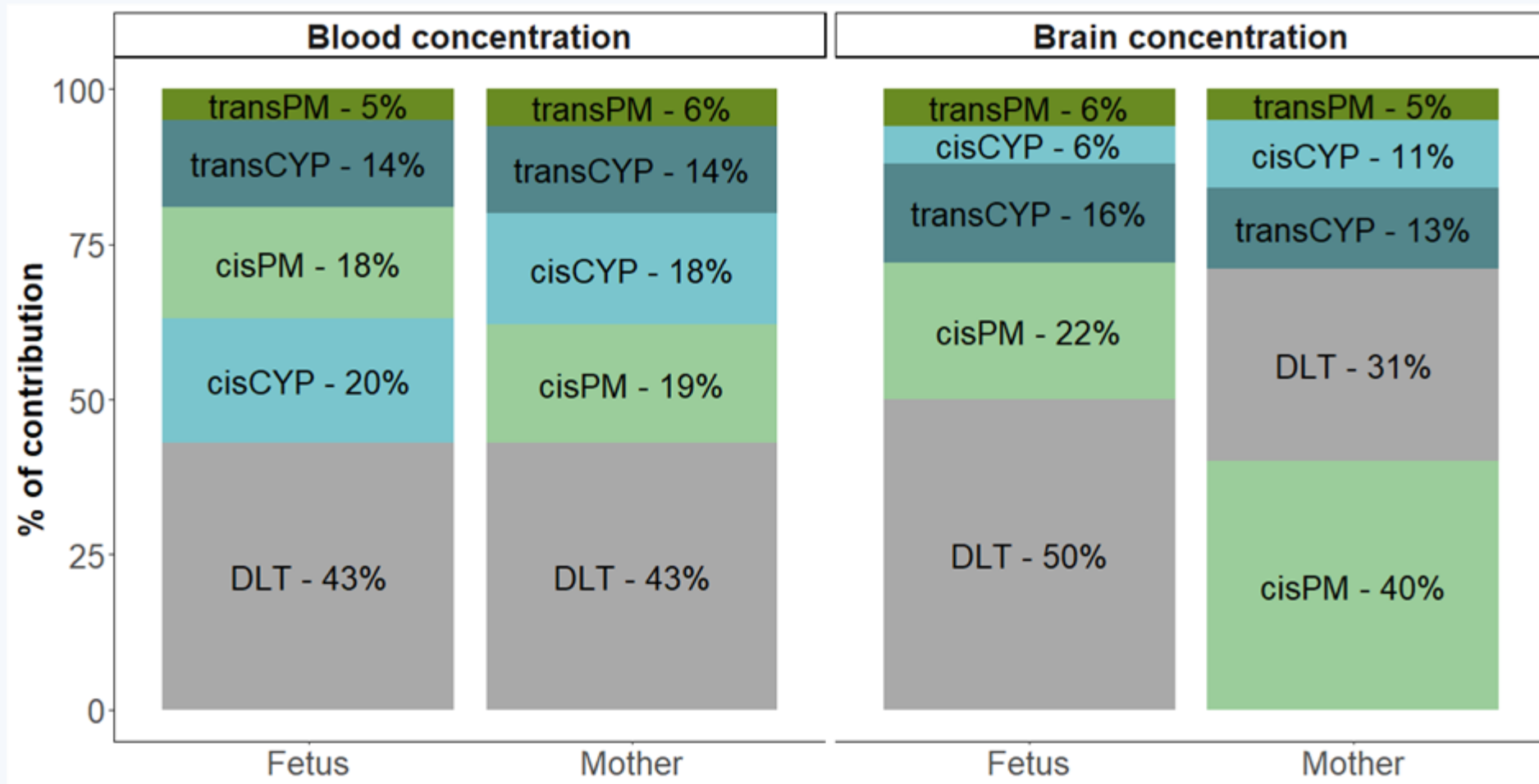
Thank you for your attention

Any questions?

To contact us: ophelia.gestin@ineris.fr

or florence.zeman@ineris.fr

Prenatal and postnatal exposure to pyrethroids in French children from the ELFE cohort

Ophélia Gestin, Elisa Thépaut, Michèle Bisson, Brice M.R. Appenzeller, Linda R. Macheka, Paul Palazzi, Alba Iglesias-González, Cécile Zaros, Cleo Tebby and Florence Zeman

Mean contributions to internal concentrations in pyrethroids for both blood and brain for mothers and fetuses from the Elfe cohort. DLT: deltamethrin, cisPM: cis-permethrin, transPM: trans-permethrin, cisCYP: cis-cypermethrin, transCYP : trans-cypermethrin.
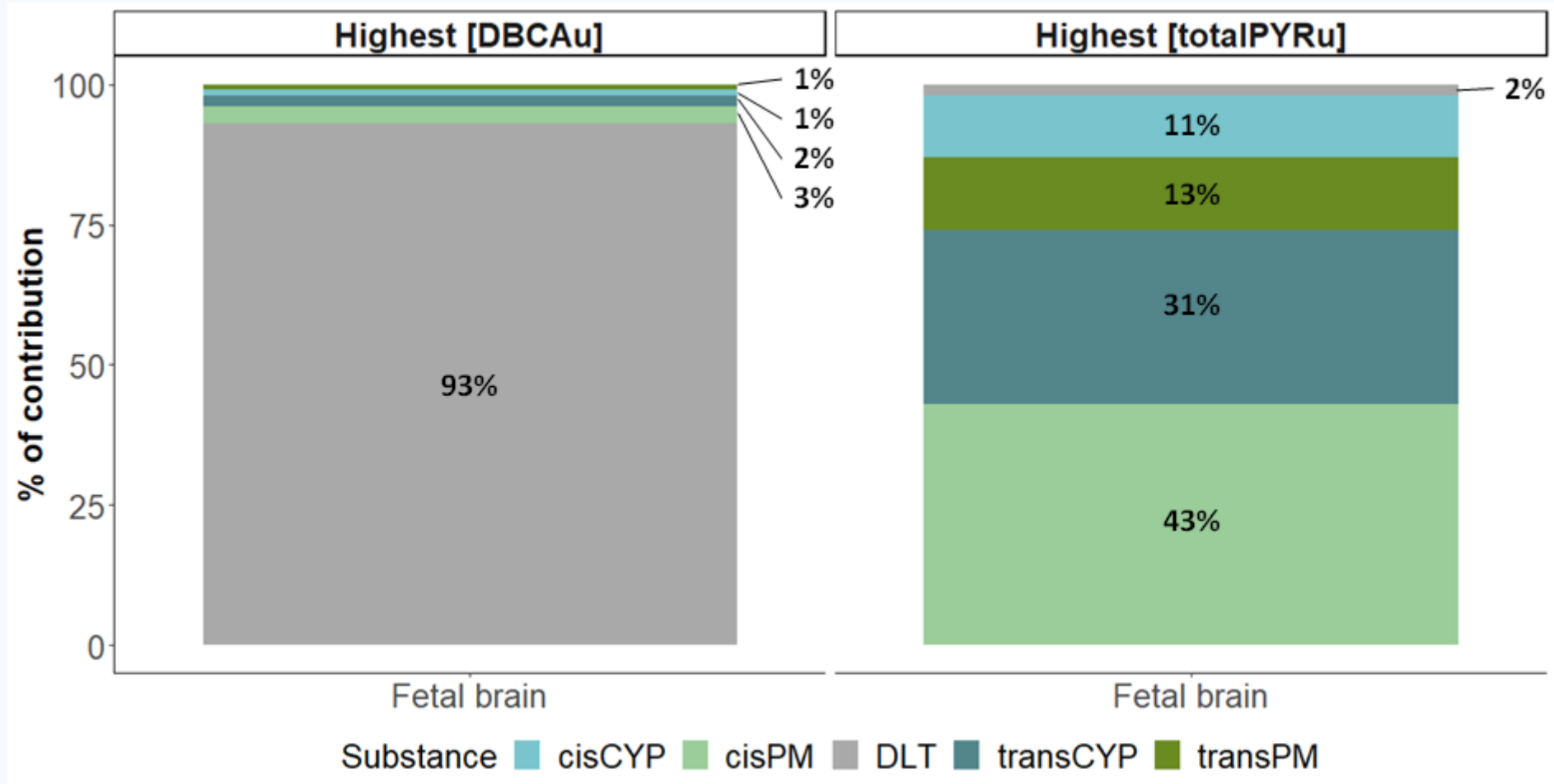
Contributions of each pyrethroids to the total pyrethroid fetal brain concentrations for two women from the Elfe cohort. On the left, the woman with the highest urinary DBCA concentration measured in urine (5.4 µg/L) and on the right the woman with the highest overall (3-PBA: 36µg/L and trans-DCCA: 38µg/L) urinary metabolite concentrations. DLT: deltamethrin, cisPM: cis-permethrin, transPM: trans-permethrin, cisCYP: cis-cypermethrin, transCYP : trans-cypermethrin.