Early-life exposure to a mixture of phthalates and phenols and child neurodevelopment

V. Mustieles, M. Rolland, I. Pin, C. Thomsen, A. K. Sakhi, A. Sabaredzovic, K. Guichardet, R. Slama, **C. Philippat**

INSERM U1209

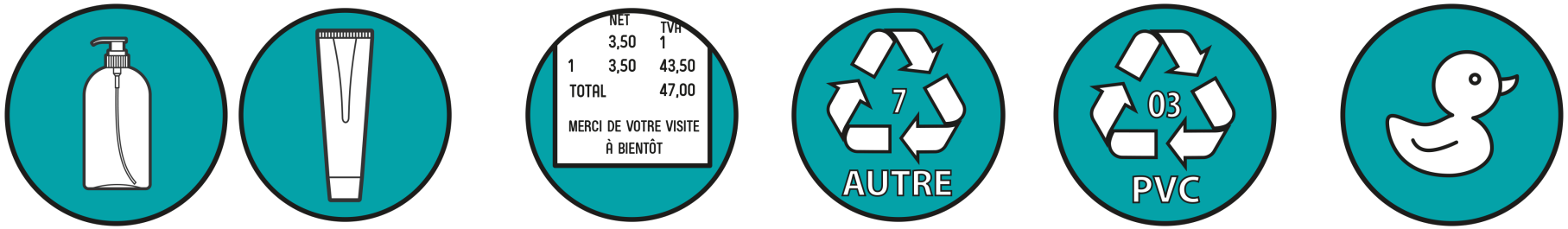
Aucun conflit d'intérêt

CHILD MENTAL HEALTH, A PUBLIC HEALTH PRIORITY

- **10-20% children** affected worldwide by neurodevelopmental disorders
- **Early onset,** often persist into adulthood
- Social and financial cost for the individual, their families and for society as a whole
- Multifactorial causes : genetic and environment (social, physical and chemical)

PHENOLS AND PHTHALATES

- Multiple uses in consumer products



- Widespread and modifiable exposure in general population
  - Detected in 70 to 100% of the urine samples tested[2]

[1] Olesen et al. 2012
[2] Casas et al. 2018

PHENOLS AND PHTHALATES = ENDOCRINE DISRUPTORS

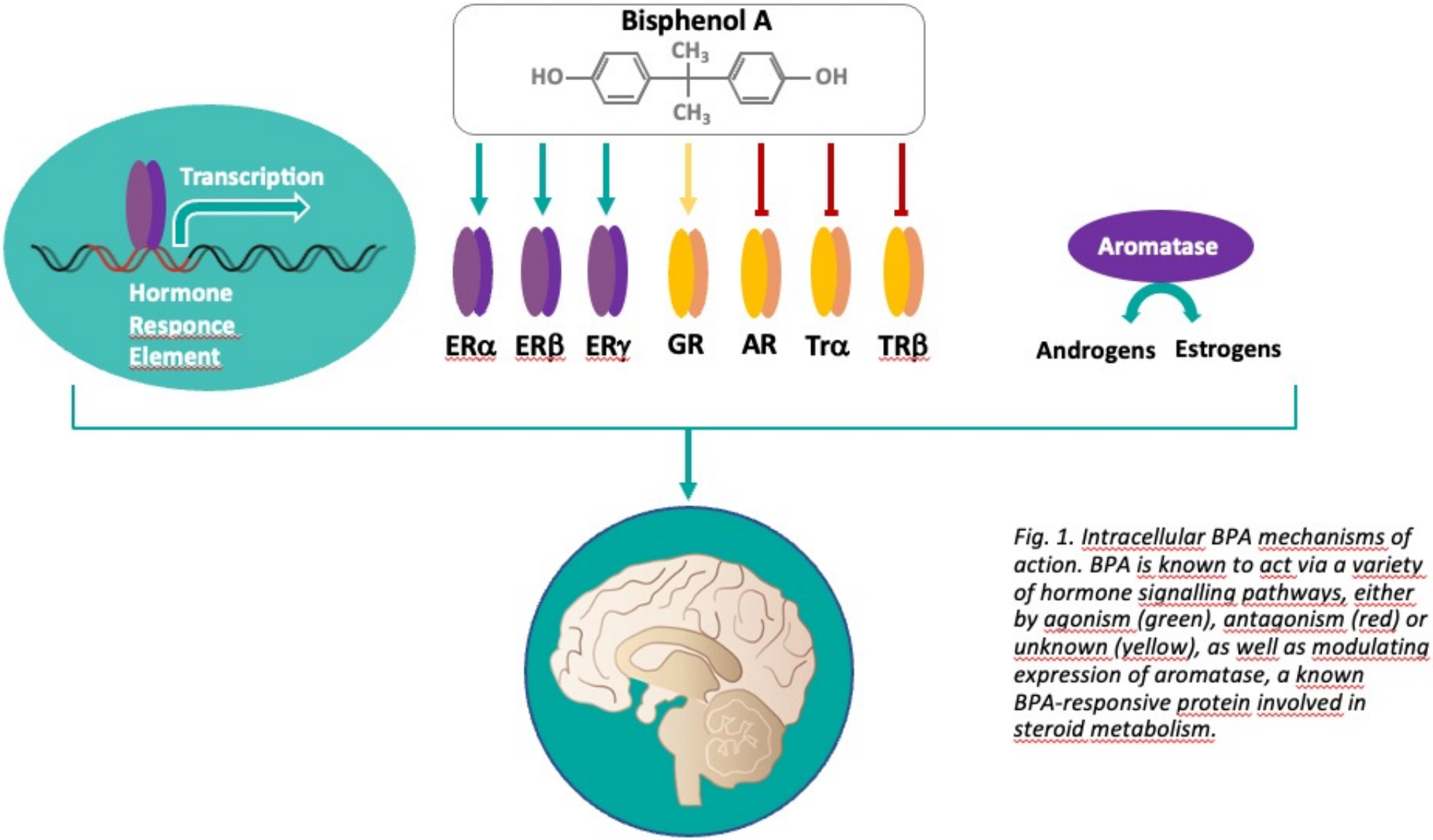


Fig. 1. Intracellular BPA mechanisms of action. BPA is known to act via a variety of hormone signalling pathways, either by agonism (green), antagonism (red) or unknown (yellow), as well as modulating expression of aromatase, a known BPA-responsive protein involved in steroid metabolism.

PHENOLS, PHTHALATES AND CHILD NEURODEVELOPMENT: EPIDEMIOLOGICAL STUDIES

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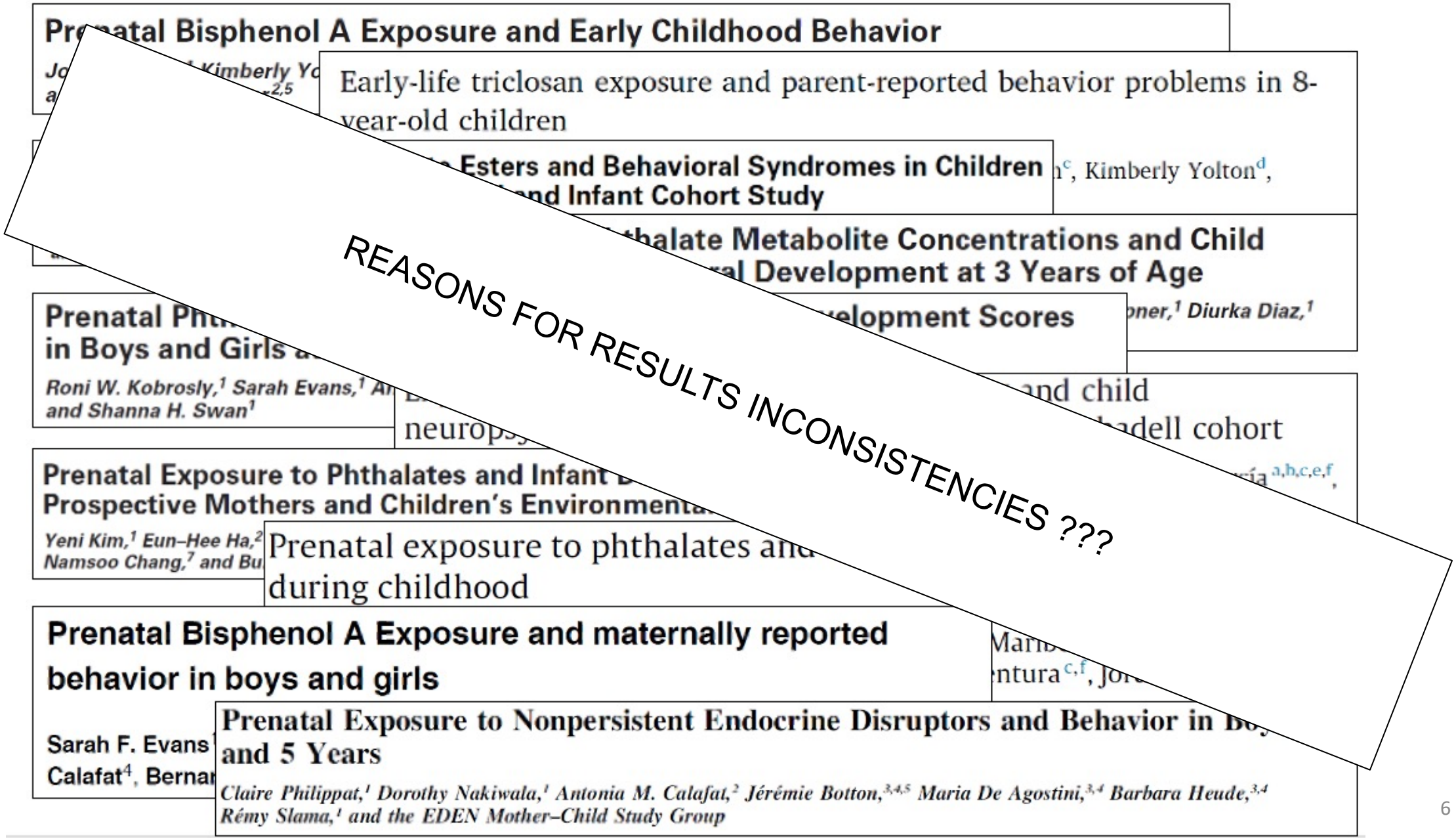
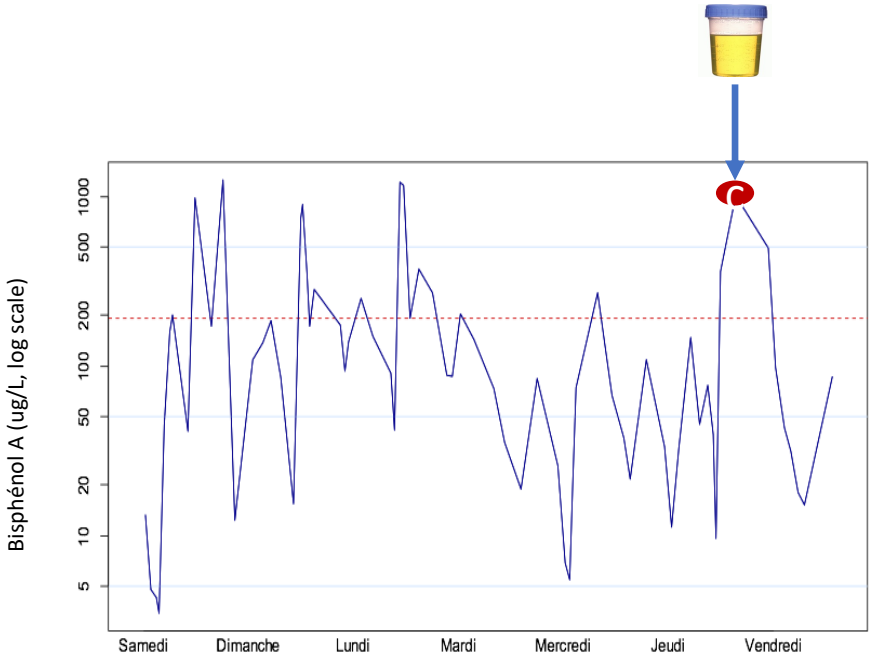


EXPOSURE MEASUREMENT ERROR



Urinary concentrations of bisphenol A measured i
all the urine produced over a week - Intraclass
correlation coefficient of 0.2 - *Vernet et al, EHP 2(*

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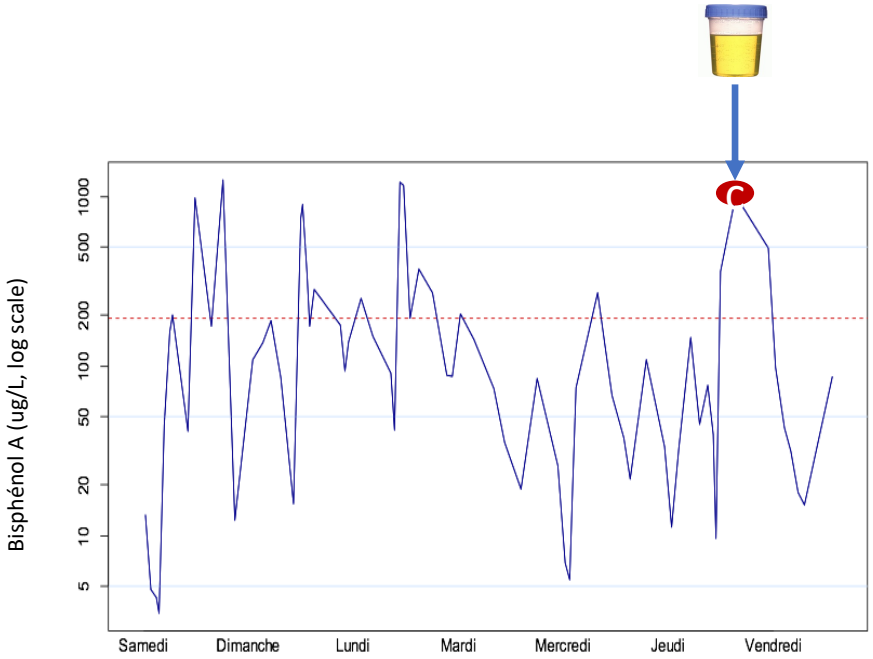
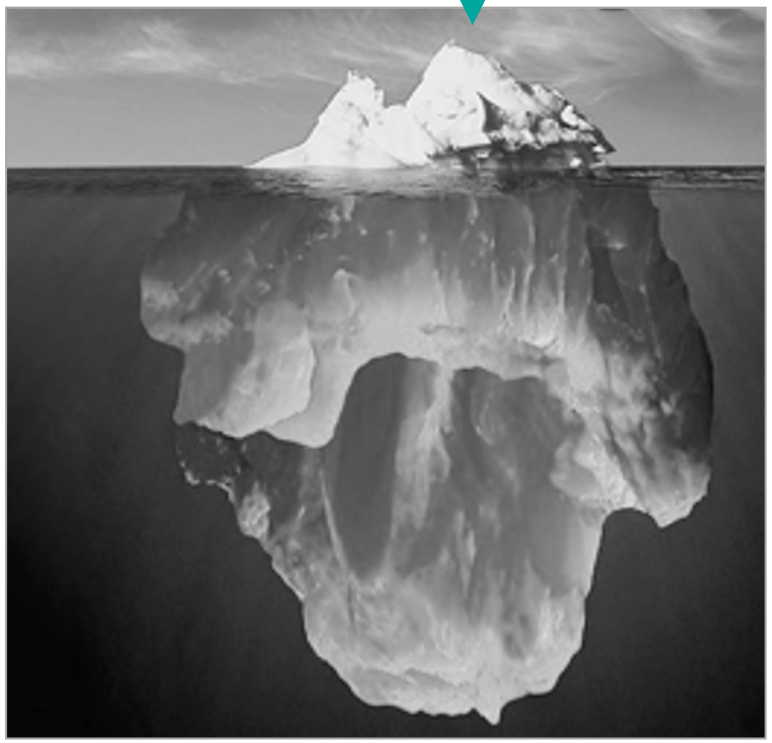


Biais toward the nul

What epidemiologists see (20%)

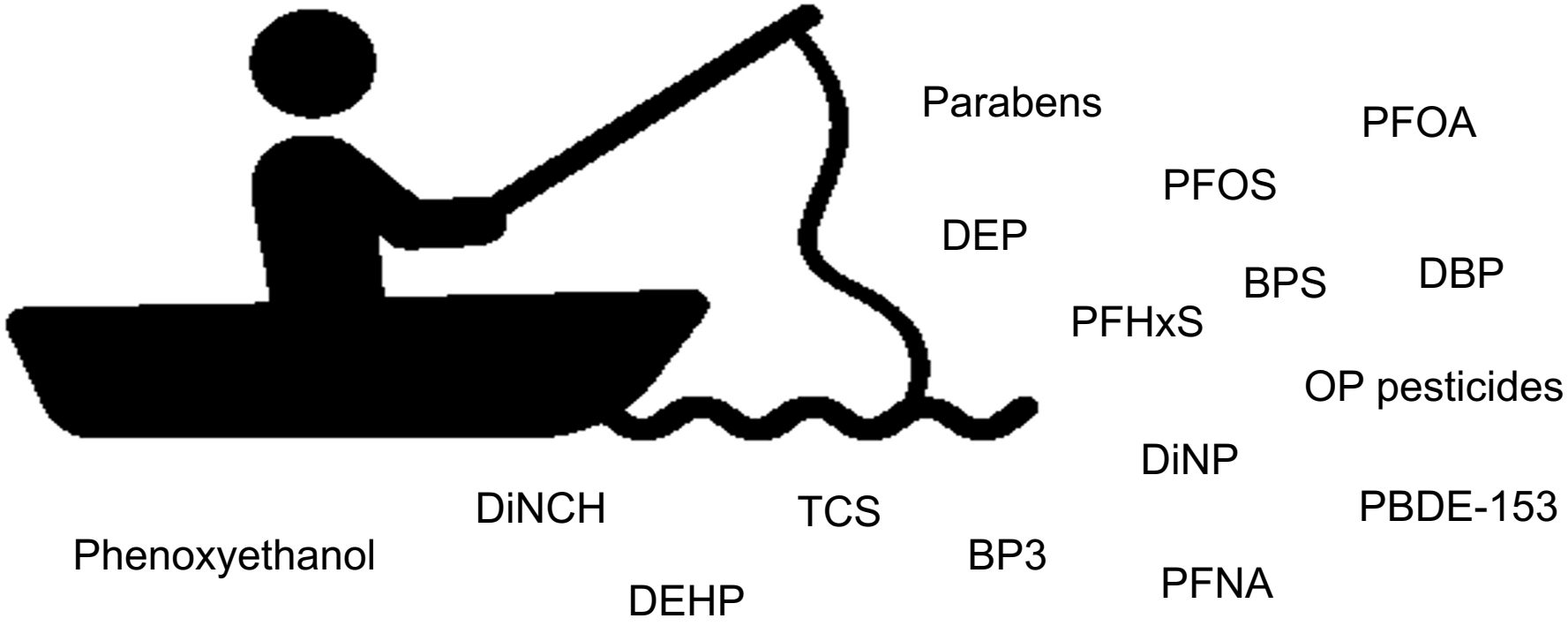


Real Effet

Urinary concentrations of bisphenol A measured in all the urine produced over a week - Intraclass correlation coefficient of 0.2 - *Vernet et al, EHP 2018*

Perrier et al. 2016

FISHING EXPEDITION



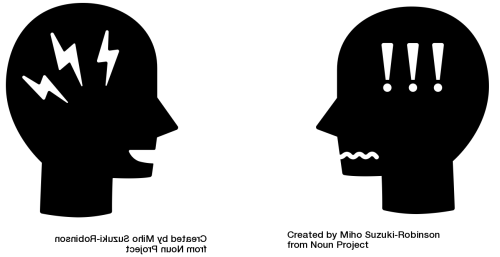
High rate of false positives even if a correction for mutliple comparisons is applied (Agier et al. 2016)

AIMS

To develop a new methodology based on compounds prioritization to look at the associations between early life exposure to phenols, phthalates and social behavior

Early life exposure to environmental chemicals

Social behavior



STUDY POPULATION

SEPAGES: 484 mother-child pairs from Grenoble area

SEPAGES Cohorte COUPLE ENFANT

Recruitment
2014-2017
2 Trim (T2)

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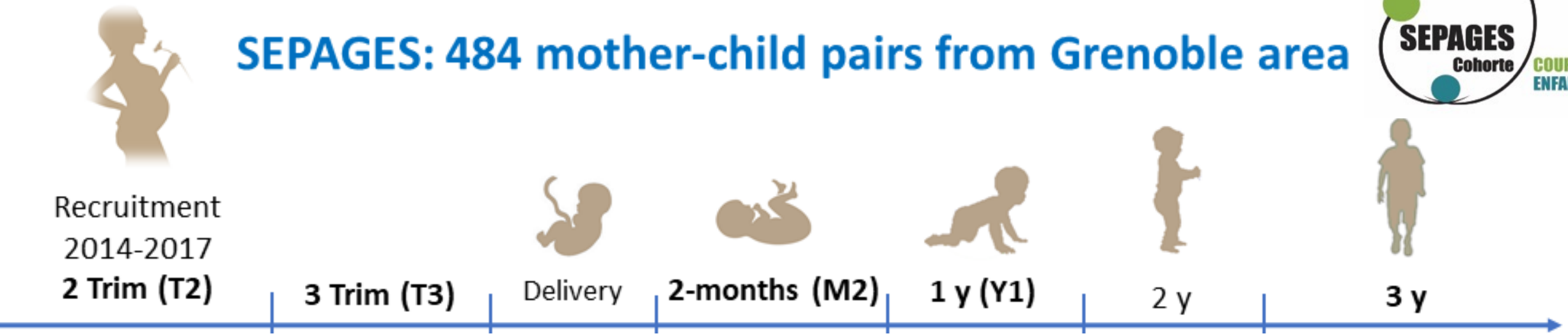

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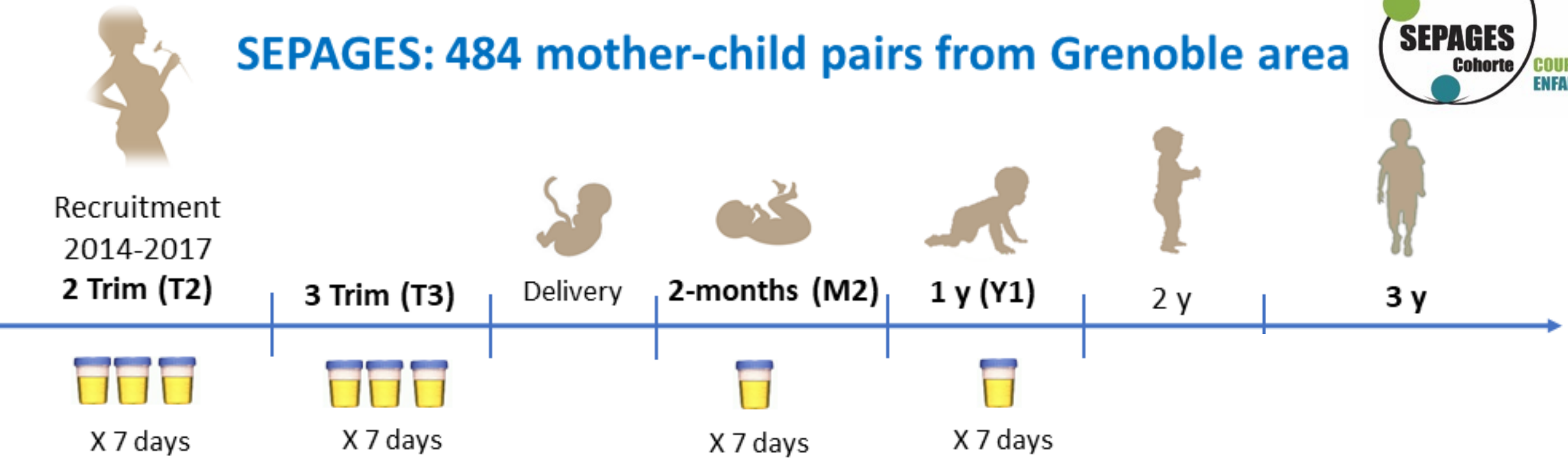

Collection of multiple urine samples, and subsequent within-subject pooling for assessments of phenols and phthalates at T2, T3, M2 and Y1

STUDY POPULATION

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Recruitment
2014-2017
2 Trim (T2)

3 Trim (T3)

Delivery

2-months (M2)

1 y (Y1)

2 y

3 y

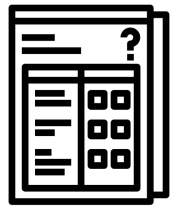
X 7 days

X 7 days

X 7 days

X 7 days

Parent-reported
Social Responsiveness Scale (SRS)



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Social responsiveness scale (SRS)

Evalue le comportement social de l'enfant et les traits liés aux troubles du spectre autistique

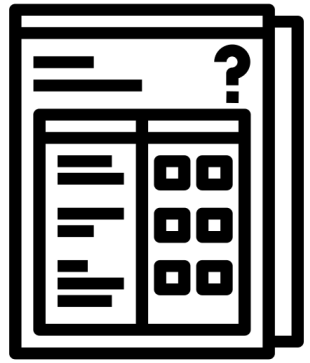
Ex: Est capable de communiquer ses sentiments / Ses expressions faciales ne concordent pas avec son discours

Corrélation forte (0,7) avec l'Entretien Diagnostique de l'Autisme Révisé (ADI-R)

Cinq sous-échelles

- Conscience Sociale,
- Cognition Sociale,
- Communication Sociale,
- Motivation Sociale
- Intérêts Restreints et Comportements Répétitifs

} Score total



METHODOLOGY

COMPOUND PRIORITIZATION

- ✓ Structured literature review
- ✓ In vivo toxicological and epidemiological studies
- ✓ Weight of evidence (WoE) for an effect on social behavior: Limited / Moderate / Sufficient

METHODOLOGY

STATISTICAL ANALYSIS: Associations with social behavior scores

Uni-pollutant models

- ✓ False discovery (FDR) correction -> only for compounds with limited weight of evidence

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- ✓ Bayesian Weighted Quantile Sum (BWQS) regression restricted or not to the prioritized compounds

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Mixture model

- ✓ Bayesian Weighted Quantile Sum (BWQS) regression restricted or not to the prioritized compounds

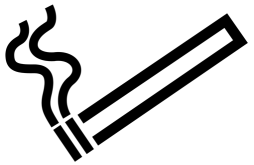
Adjustment factors

- ✓ Maternal age, pre-pregnancy BMI, education, anxiety/depression, active and passive smoking, parity, mode of child daycare, family environment, breastfeeding, child age at SRS evaluation and child sex.

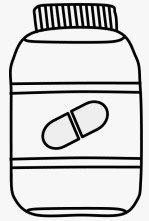
POPULATION CHARACTERISTICS

Maternal education
57.4%: Master degree or more

Maternal age at conception
Average: 32 years



Smoking status
6.0%: Smoked at least once during pregnancy



Vitamins
93.1%: Took vitamins at least once during pregnancy

Child sex
54.6%: Boys

Parity
46.6%: First child

Exposure

Detection frequencies

- Phthalates: > 95% except for a few at 2 months (freq ranged between 64 and 84%)
- Phenols : > 90% for all but bisphenol AF, B, F and triclocarban detected in less than 5%

RESULTS: Literature review for compound prioritization

Of 821 publications identified, 34 *in vivo* toxicological and 37 epidemiological were tabulated, allowing to prioritize chemicals.

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Chemical	Weight of evidence	Type of Analysis	Correction for multiple comparisons	Included in the mixture model
Bisphenol A	Supportive	Confirmatory	No	Yes
DEHP	Supportive	Confirmatory		
MEP	Moderate	Confirmatory		
MnBP	Moderate	Confirmatory		
MBzP	Moderate	Confirmatory		
Triclosan	Moderate	Confirmatory		
Bisphenol S [a]	Limited	Confirmatory		
MiBP	Limited	Exploratory	Yes	No
DiNP	Limited	Exploratory		
DINCH	Limited	Exploratory		
ohMPHP	Limited	Exploratory		
Benzophenone-3	Limited	Exploratory		
Parabens	Limited	Exploratory		

[a] BPS was upgraded based on its high structural and biological similarity to BPA

Adjusted associations between the mixture and SRS scores

Exposure window	N	Social Responsiveness (SRS) Scale	Overall mixture[a] B (95% CI)	Mixture restricted to prioritized chemicals[b] B (95% CI)
Second trimester (T2)	406	Total	0.87 (-1.27, 3.01)	0.71 (-1.14, 2.56)
Third trimester (T3)	399	Total	1.00 (-1.00, 3.00)	0.59 (-1.17, 2.35)
Neonates (M2)	380	Total	-0.47 (-2.29, 1.36)	-0.63 (-2.15, 0.89)
Infants (Y1)	358	Total	1.16 (-0.73, 3.05)	1.38 (-0.18, 2.94)

Beta1 represents the mean change in SRS scores per quartile increase of the mixture

[a] Included bisphenol A, triclosan, ∑DEHP, MEP, MnBP, MBzP, MiBP, ∑DINP, ∑DiNCH , oh-MPHP, benzophenone-3, ∑Parabens

[b] included bisphenol A, triclosan, ∑DEHP, MEP, MnBP and MBzP

Adjustment factors: Maternal age, pre-pregnancy BMI, education, anxiety/depression, active and passive smoking, parity, mode of child daycare, family environment, breastfeeding, child age at SRS evaluation and child sex.

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		Social Awareness	0.36 (-0.02, 0.75)	0.37 (0.04, 0.69)
		Social Cognition	-0.19 (-0.67, 0.30)	-0.07 (-0.48, 0.34)
		Social Communication	0.84 (0.14, 1.53)	0.91 (0.31, 1.50)
		Social Motivation	0.04 (-0.52, 0.59)	0.03 (-0.46, 0.52)
		Restricted Interests and Repetitive Behaviors (RRB)	0.07 (-0.35, 0.48)	0.19 (-0.17, 0.55)

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Discussion

Decreased bias compared to previous studies relying on spot samples

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- Described potential modes of action
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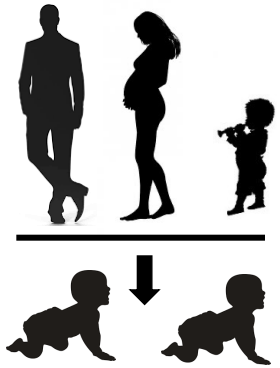
Sensitivity windows: first study with infancy exposure

- inclusion in further biomonitoring studies?

Increased exposure to the prioritized mixture = worse social behavior at 3 years

Perspectives

Familles à « haut risque »
au moins 1 enfant diagnostiqué avec TSA
(n=1200)

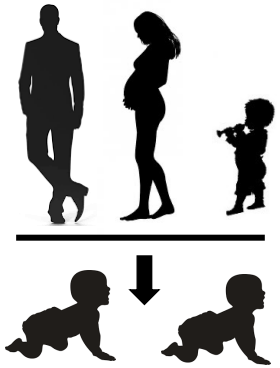


Nombre attendu d'enfants avec trouble à 6 ans

- TSA (n=200)
- TND (n=340)
- Dév. Typique. (n=660)

6 ans de suivi

Familles à « faible risque »
au moins 1 enfant mais aucun TSA ni autre TND
(n=500)



Nombre attendu d'enfants avec trouble à 6 ans

- TSA (n=5)
- TND (n=50)
- Dév. Typique. (n=445)

Prévalence globale TSA: 1%; TND: 10%

COHORTE MARIANNE
AUX ORIGINES DU DÉVELOPPEMENT DE L'ENFANT

PI:
A. Baghdadli

Acknowledgement

Co-authors

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