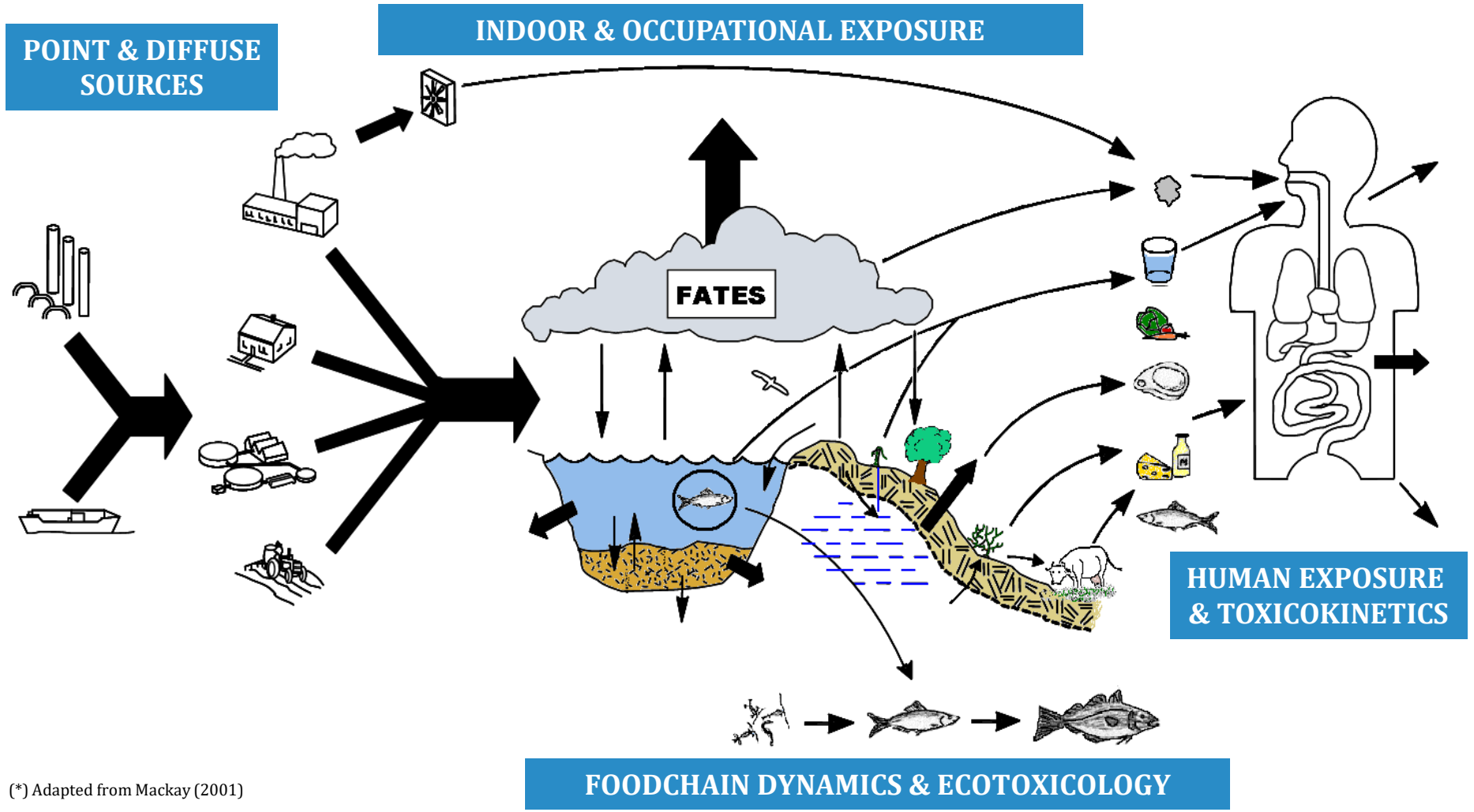
Chemical exposome in brain cancer: An exploratory study

Dr. Pablo Gago-Ferrero
@PGagoFerrero

Introduction

- **Chemicals of emerging concern in the environment**

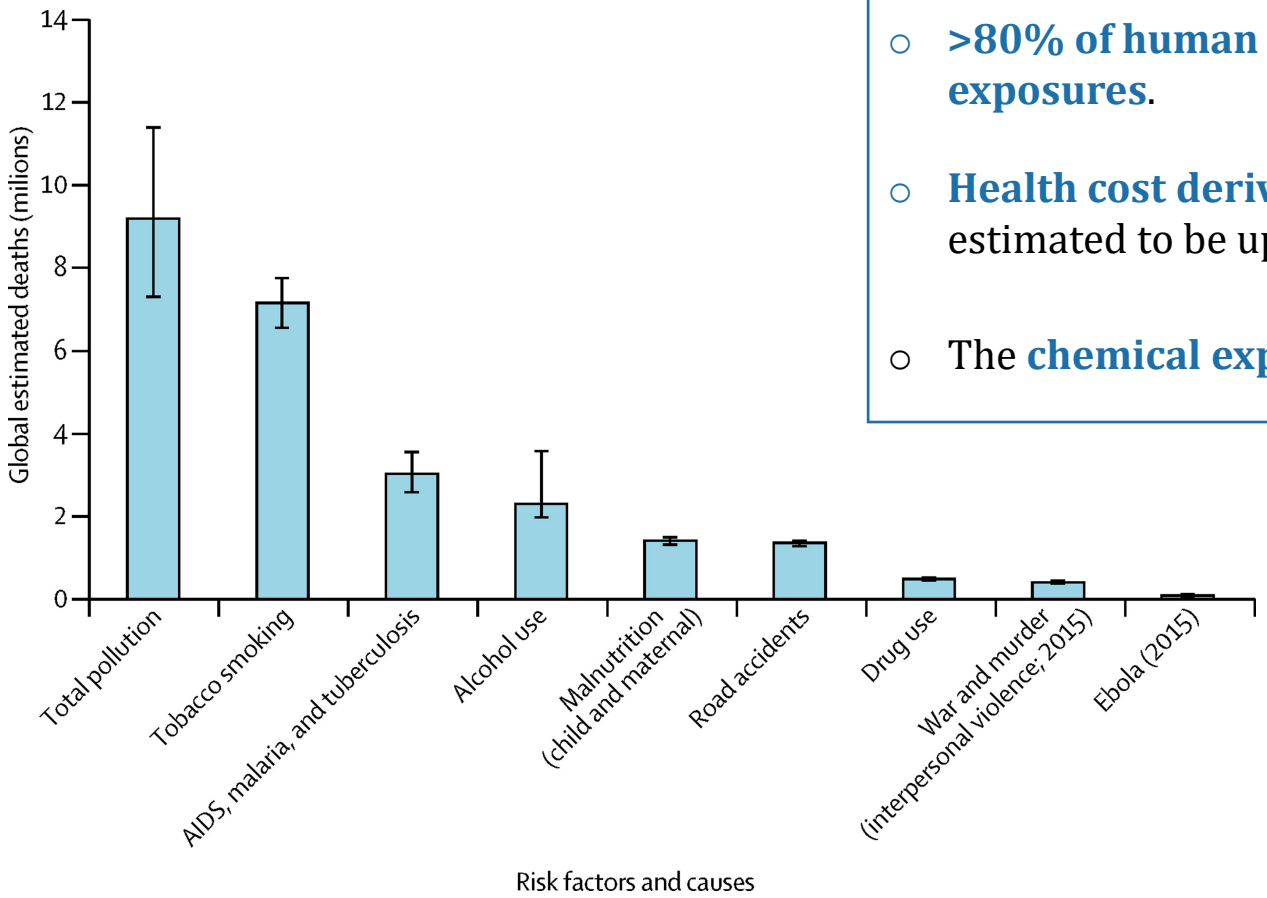


(*) Adapted from Mackay (2001)

Introduction

- **Chemical exposure - Health**

Pollution is the largest environmental cause of disease and premature death in the world today.
Diseases caused by pollution were responsible for an estimated 9 million premature deaths in **2015—16% of all deaths worldwide**.



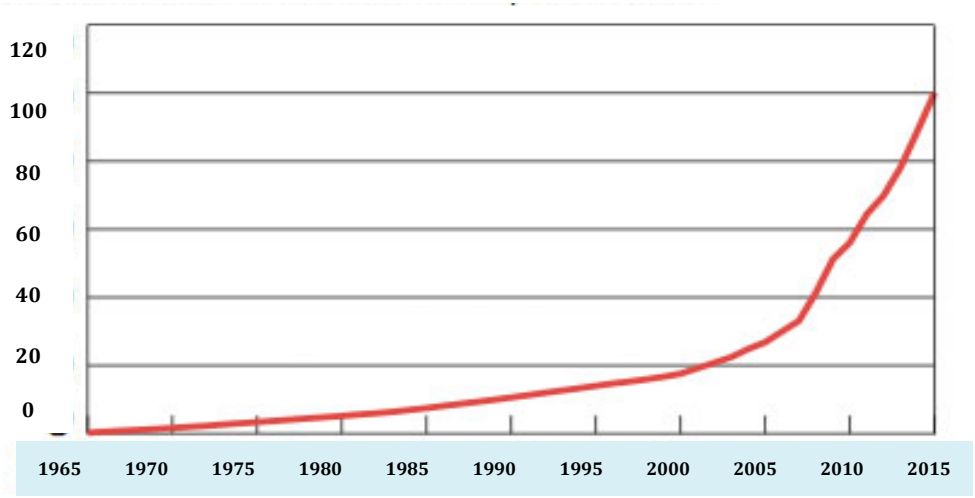
- **>80% of human chronic diseases** are linked to **environmental exposures**.
- **Health cost derived from the chemicals** present in the environament is estimated to be up to **10% of the global GDP**
- The **chemical exposome** is **far from being** completely **understood**.

The Lancet 2018 391, 462-512DOI: (10.1016/S0140-6736(17)32345-0)

Introduction

- **Pollutants & Human exposure**

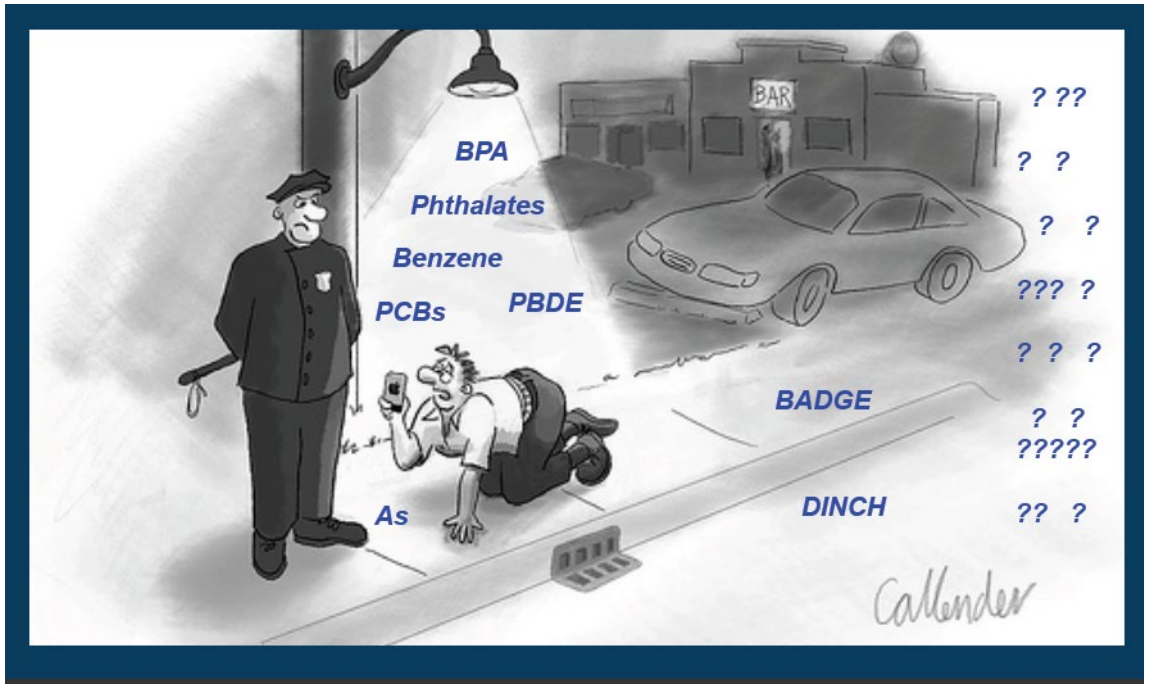
144 MILLION REGISTERED COMPOUNDS



Source: CAS

>150,000 used heavily
since 1950s

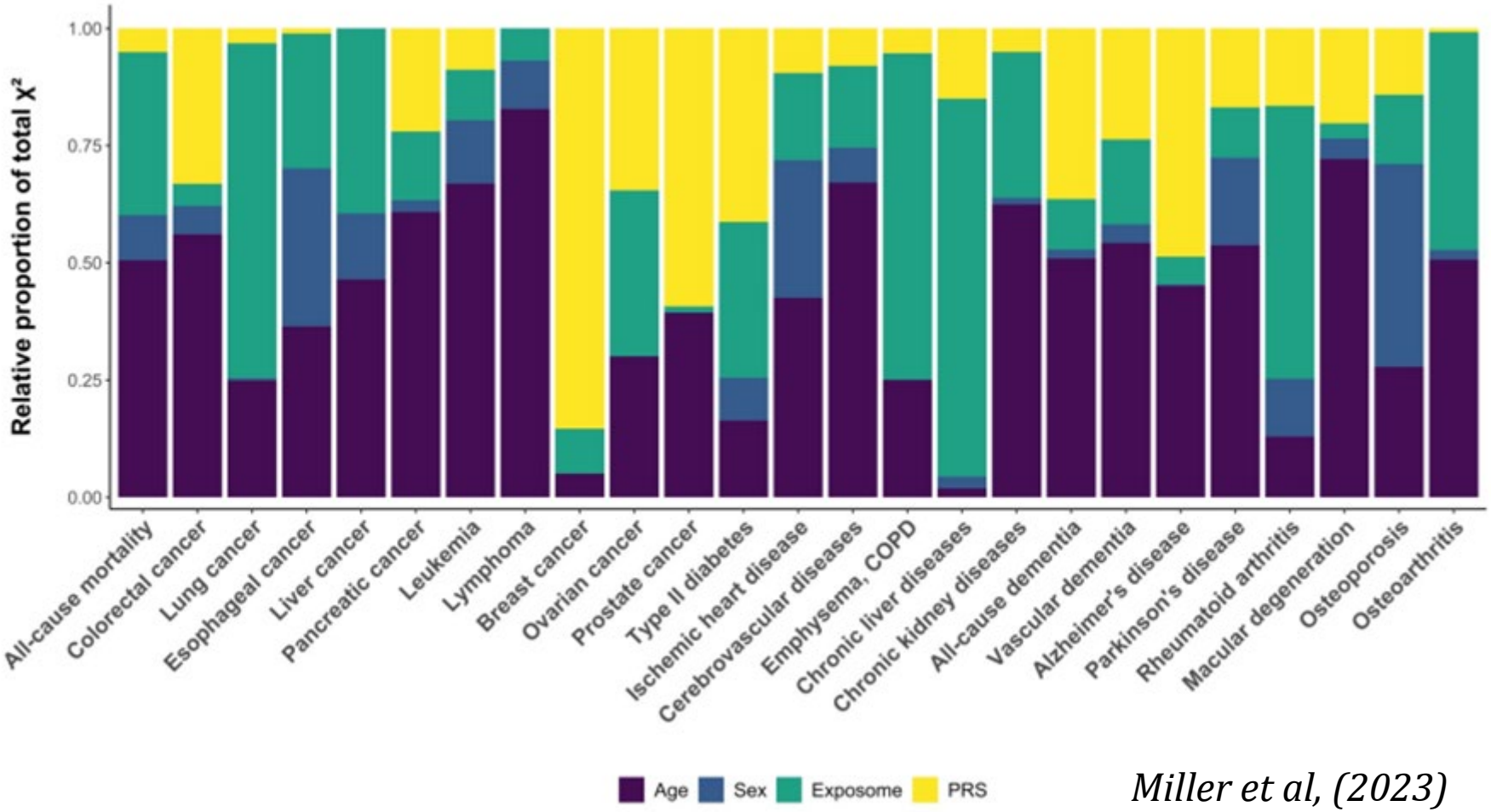
~ 5,000 globally dispersed



"Not everything that can be measured is worth measuring, and not everything worth measuring is measurable" (Daughton, 2004)

Introduction

- **Why the (chemical) exposome?**



Miller et al, (2023)

Introduction

- **Diffuse gliomas**

  - Diffuse gliomas are the most common brain tumours in adults

Diffuse gliomas in data

- 308,102 / 251,329 people were diagnosed / died in 2020
- 5-year survival rate: ~30%
- >400 people are treated annually in Barcelona metropolitan area
- Second highest cause of cancer mortality in people under 19 years of age

Risk factors

- **Age**
- **Gender**
- **Ionizing radiation**

Hypothesis

- **Environment exposure might play an important role**
  (<5% of patients have a family history).

Introduction

- **Chemical exposures**

Heavy metals **Organic chemicals**

Inhalation

Ingestion

Dermal contact

Introduction

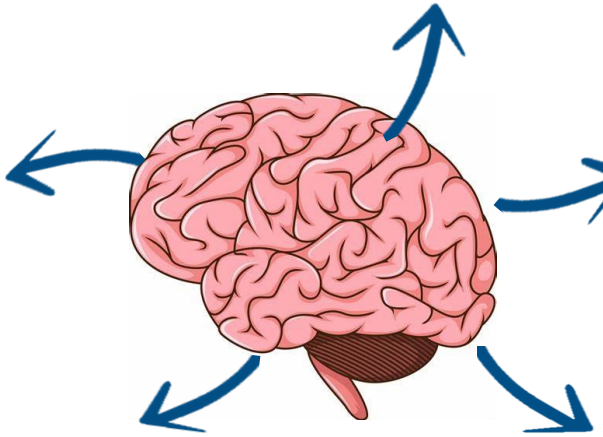
- **Organic chemicals in human brain and brain tumor**

❑ **Detected in both brain and brain tumor**

PFAS
- Gliomas (n=26): 17 PFAS, nd –51 ng g^{-1} [2]
- Autopsy brain (n=30): 21 PFAS, nd – 486 ng/g w.w. [3,4]

❑ **Detected in brain**

Polycyclic aromatic hydrocarbons (PAHs)
- 13 PAHs : nd – 4,166 ng/g. [5]



Benzophenones
- Benzophenone-3, n=24: nd - 0.32 ng/g [6]

Bisphenols
- BPA, BPF, 4-n-nonylphenol: nd – 30.8 ng/g [6-8]

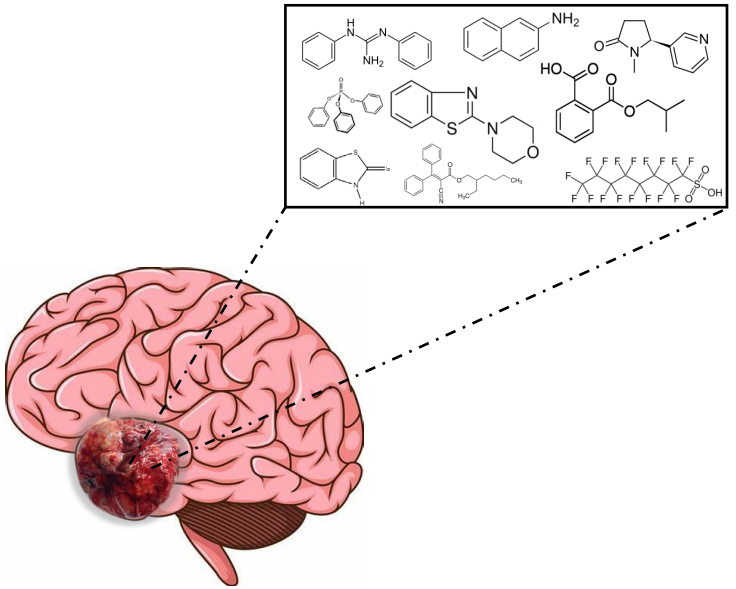
Parabens & triclosan & triclorocarban
- 4 parabens, triclosan and triclorocarban: nd – 5.95 ng/g [6,7]

Polychlorinated biphenyls (PCBs)
- ∑ 24 PCBs: nd - >15 ng/g [9,10,11]

[1] Review: (Denuzière et al., 2022); [2] (Xie et al., 2022); [3] (Di Nisio et al., 2022); [4] (Perez et al., 2013); [5] (Pastor-Belda et al., 2019); [6] (van der Meer et al., 2017); [7] (Geens et al., 2012); [8] (Charisiadis et al., 2018; [9] (Chu et al., 2003); [10] (Mitchell et al., 2012); [11] (Bachour et al., 1998);

Introduction

- **Objective**



1 Determine the chemical exposome that accumulates in brain tumors

- Explore possible exposure pathways

Cohort

- **Bellvitge Glioma Cohort**

Historical unique cohort; >500 brain tumour patients

Bellvitge Glioma Cohort

Hospital de Bellvitge, Barcelona, 2005-present

Previous sample information

- Histopathology tumour samples
- Sociodemographic characteristics
- Clinical outcomes
- Molecular biology
- Presurgical MRI (including 1H-MRS)
- Postsurgical and follow-up MRI data.

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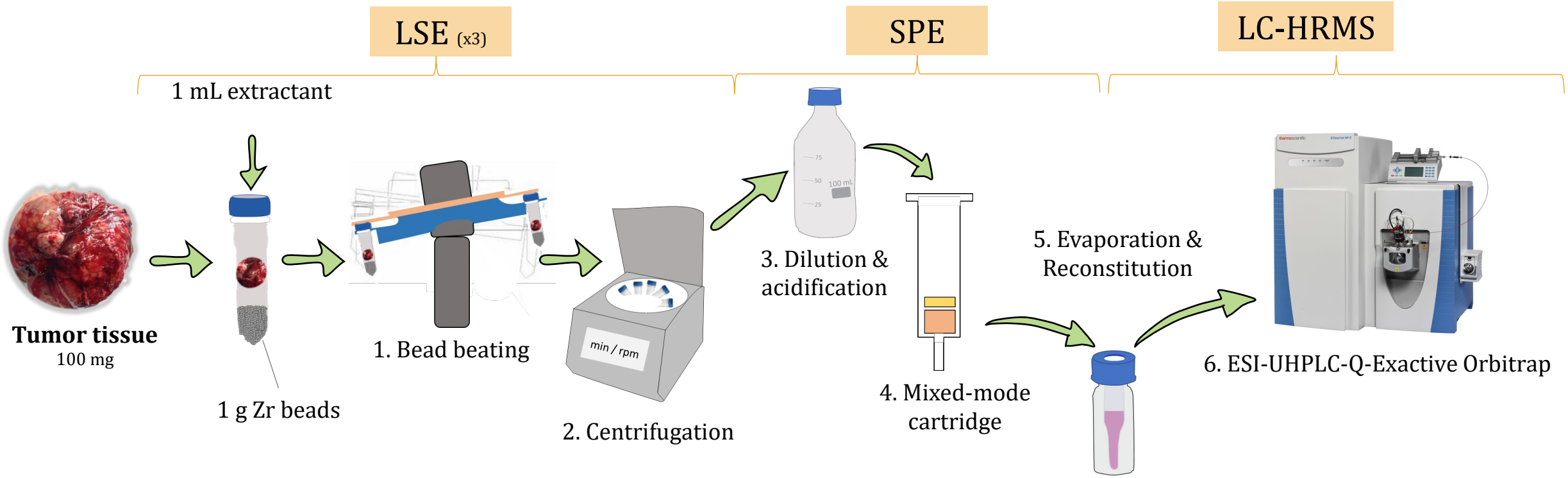
Bellvitge Hospital Universitari

IDI BELL
Institut d'Investigació Biomèdica de Bellvitge

Methodology

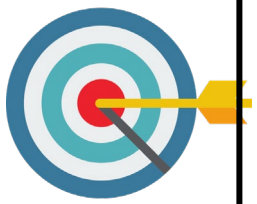
- **Sample treatment and instrumental analysis**



Gutiérrez-Martín, Daniel et al., 2023. Tumoral and normal brain tissue extraction protocol for wide-scope screening of organic pollutants. MethodsX, volume 10, 102069.

Methodology

Target analysis



~1,000 chemicals

in-house database

- Known Retention Time ✓
- Known fragmentation ✓
- Accurate mass ✓
- Standard available ✓

Alygizakis et al., 2019. TrAC Trends in Analytical Chemistry, vol. 115, 129-137

>10,000 chemicals

- ~~Known~~ Retention Time ✓

Predicted

- Known fragmentation ✓
- Accurate mass ✓
- Standard available ❓

Target chemicals

- confidence level 1 (*quantified)*

Suspect chemicals

- confidence level 1 (quantified)

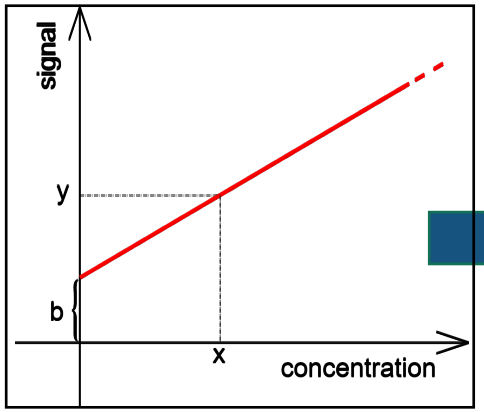
(when confirmed with standard)

- confidence level 2 (semiquantified)

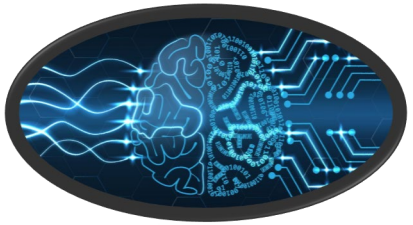
(when not confirmed)

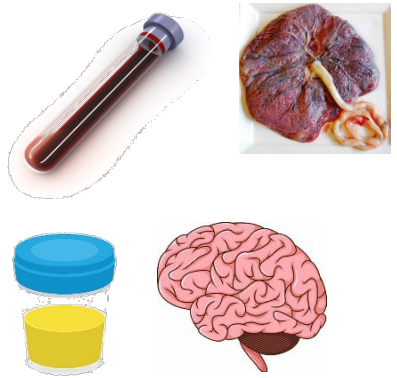
Methodology

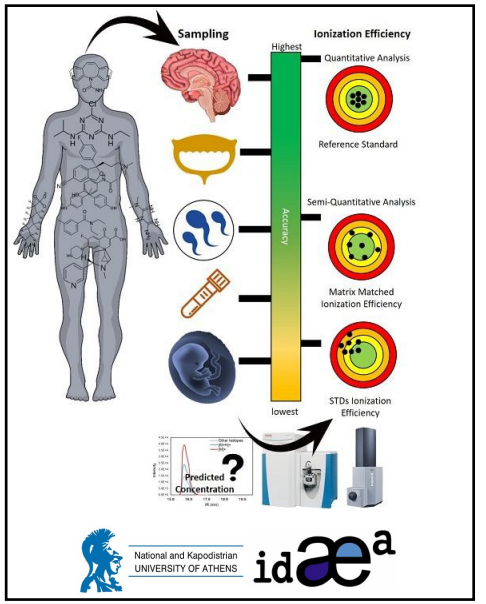
- **Quantification & Semi-quantification**



Semi Quantification based on IE: Training a machine learning predictor of IE with real standards and in-silico molecular descriptors







Matrix IE predictor

Ionization Efficiency (IE)

PREDICTOR:

Input: Calibration curve: (SMILES, slope of the curve) - Harmonize IE from predictor to each system
SMILES and Area for compound to predict

Output: Estimated concentration

Analyte	No IE	Solvent	Matrix
4,4'-Dihydroxybenzophenone	2%	7%	87%
6:2 FTSA	0.2%	8%	38%
Atenolol	315%	842%	73%
Mono-2-ethylhexyl phthalate	1129%	20%	117%
Octocrylene	730%	259%	27%
Caffeine	10%	11%	75%

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Results

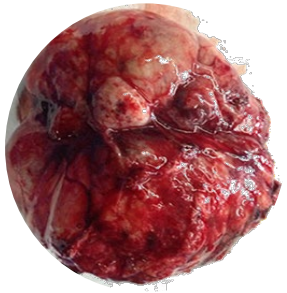
- **Proof of concept**

Subsample of n=33

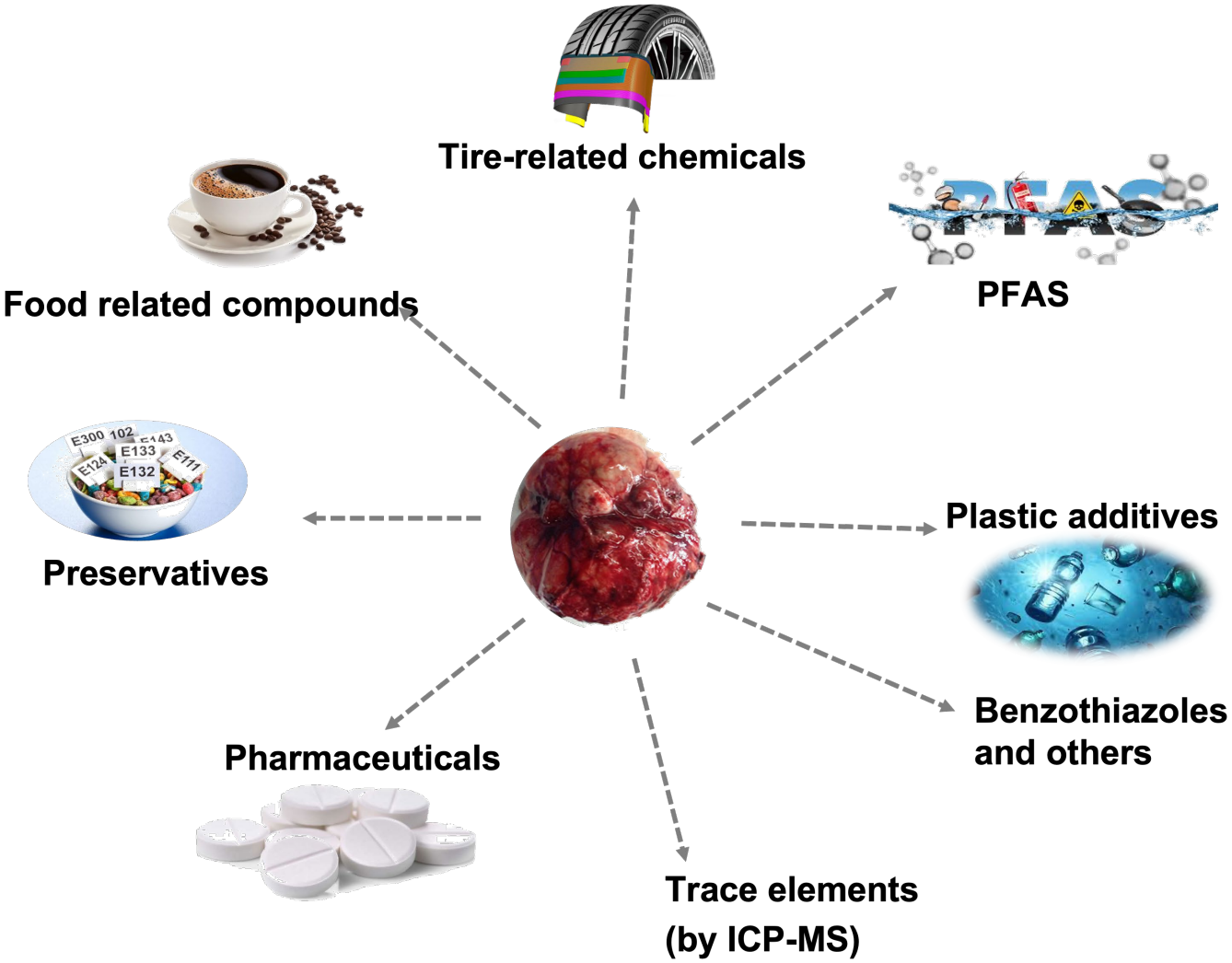
18 Controls

48 contaminants

Concentration range: pg/g → 100 ng/g

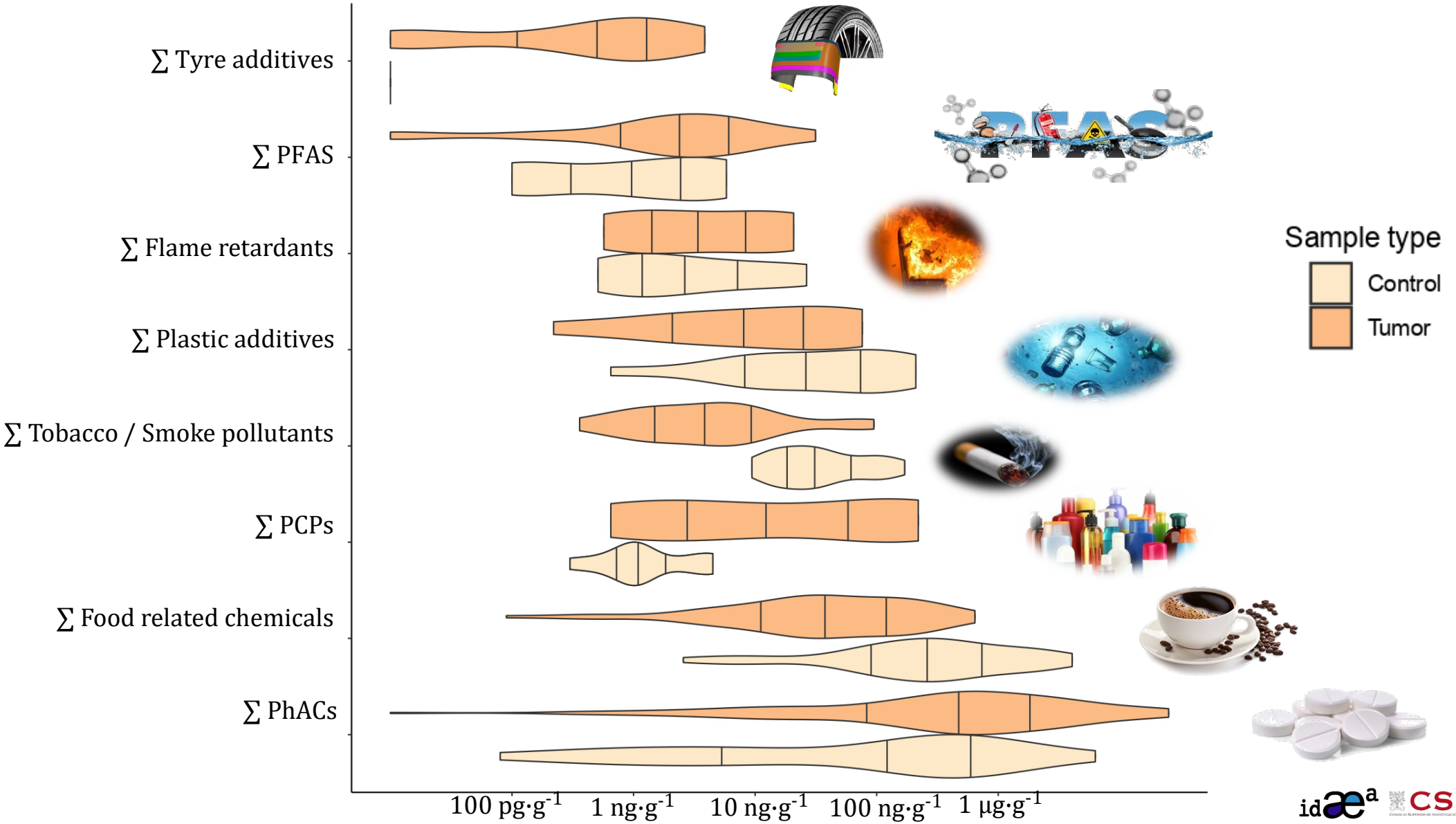


In the Freezer
>500 samples



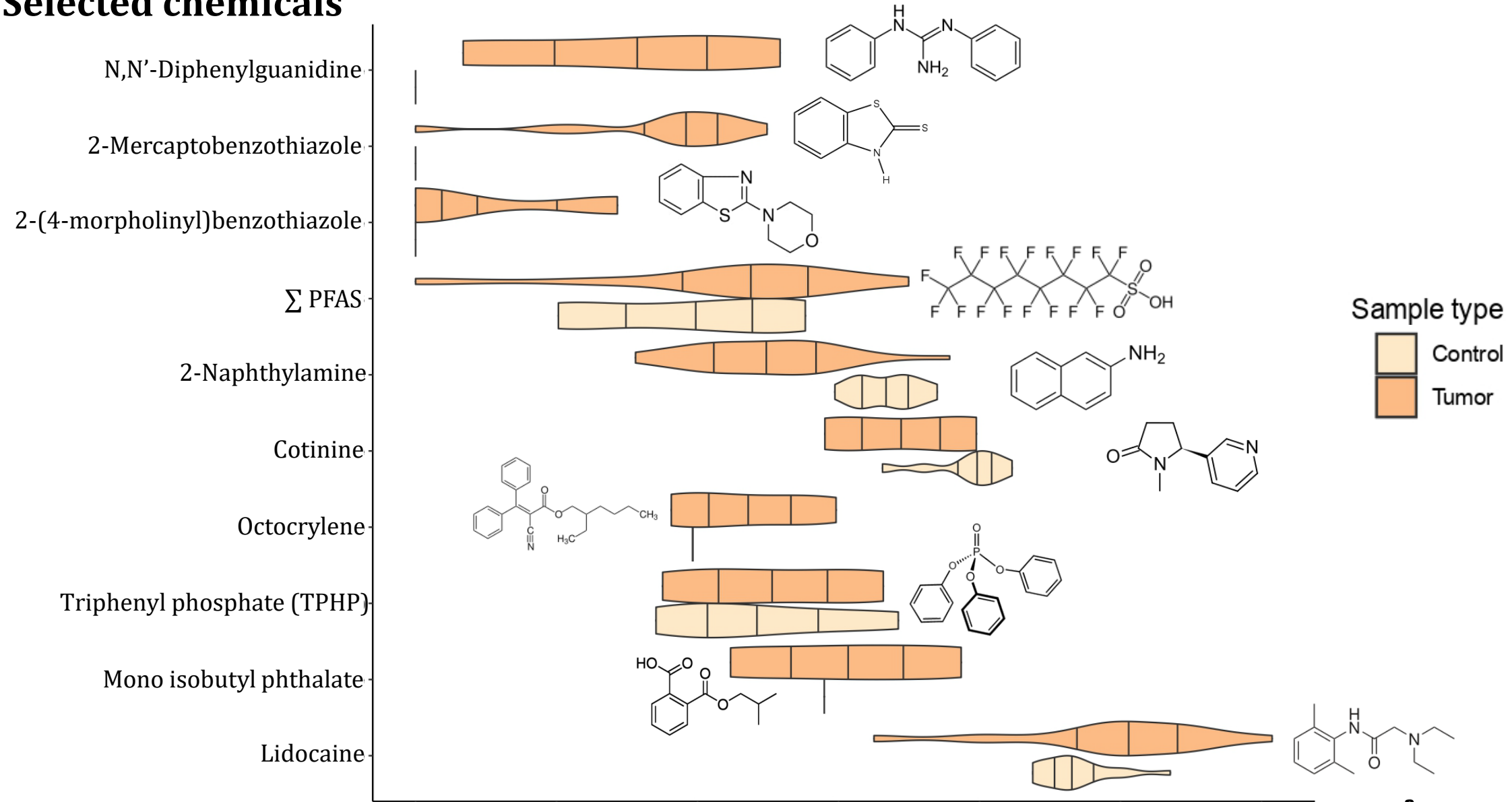
Results

- **Differences between chemicals in control and tumoral tissue**



Results

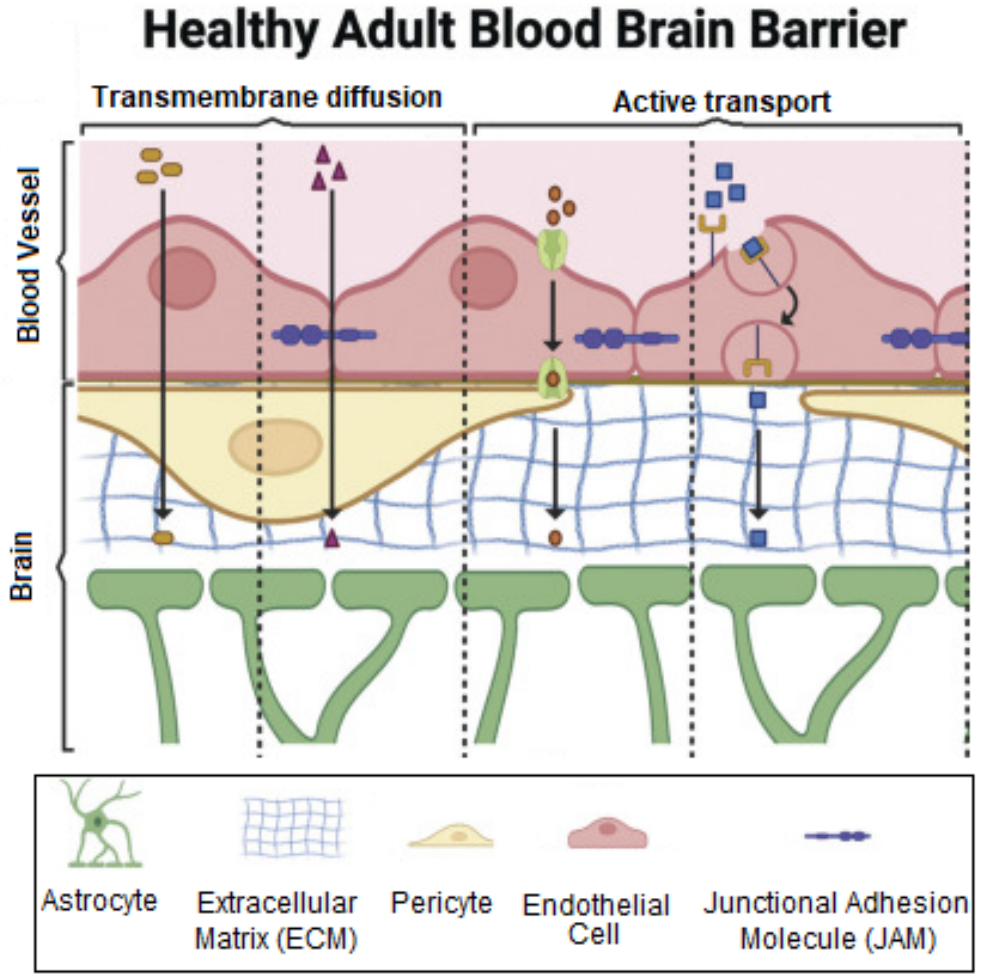
- **Selected chemicals**



Discussion

Blood brain barrier

- Highly vascularized nature of the brain→ **Enhanced risk of brain exposure to toxicants found in the blood**.
- The brain is **protected from direct exposure** to many compounds in the blood by the **blood brain barrier (BBB).**
- Two main mechanisms
  - **Transmembrane diffusion** (<500 Da): Unbound or free fractions of lipophilic chemicals can generally diffuse feely across the BBB
  - **Saturable active transport**
- Higher levels in tumoral tissue
  - BBB damaged → higher penetration of contaminants
  - Tumours are more vascularized

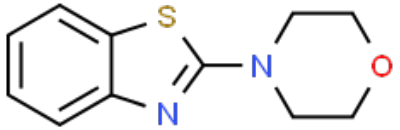


Source: Starnes et al., 2019. Front Toxicol, 11;4:881584

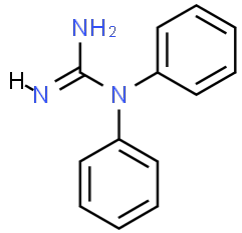
Results

- **Tyre additives**

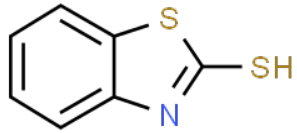
2-(4-morpholinyl)benzothiazole



N,N'-Diphenylguanidine



2-mercaptobenzothiazole



			Concentration range (ng/g)	
	DF Control	DF Tumour	Control	Tumour
2-(4-morpholinyl)benzothiazole	nd	10%	nd	nd – 0.27
N,N'-Diphenylguanidine	6%	19%	nd – 0.0015	nd – 3.1
2-Mercaptobenzothiazole	nd	42%	nd	nd – 3.9

DF: Detection frequency. nd: non-detected

Discussion

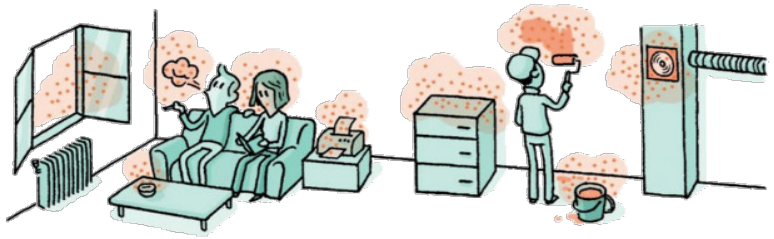
- **Exposure pathways to xenobiotics**

Inhalation

Ingestion

Dermal contact

Indoor Environment



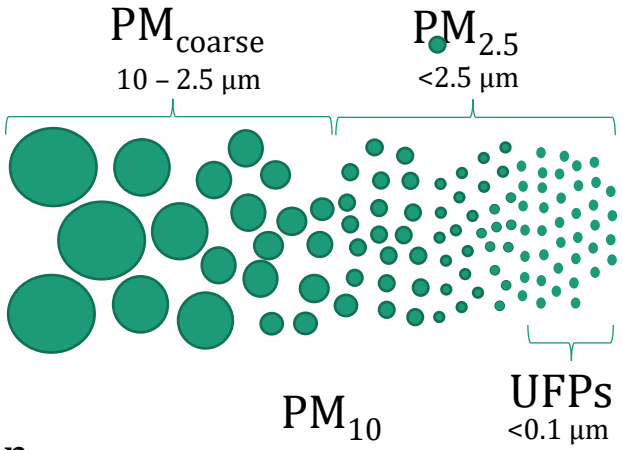
Outdoor environment

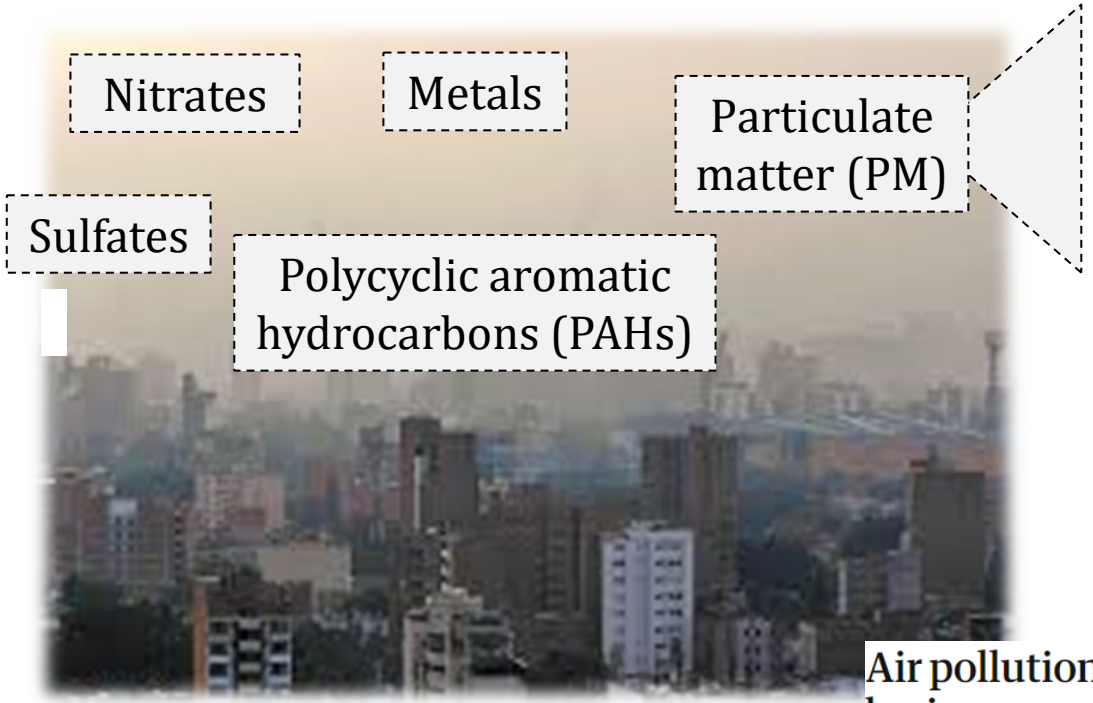
Discussion

- **Brain cancer & Air pollution**

→ Epidemiological evidence, but still weak

- IARC classified outdoor air pollution as carcinogenic
- Air pollution varies among locations





Small inhaled particles reach the brain

Association between PM and Brain cancer?

→ (McKean-Cowdin et al., 2009); (Valberg et al., 2010)

→ (Jørgensen et al., 2016); (Andersen et al., 2018); (Weichenthal et al., 2020); (Ah et al., 2020); (Manangama et al., 2020); (Yu et al., 2022)

Air pollution nanoparticles linked to brain cancer for first time

Exclusive: tiny particles produced by motor traffic can invade the brain and carry carcinogens

The Guardian

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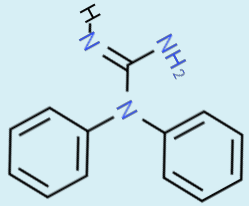
Discussion

- **Chemicals in air particulate matter**

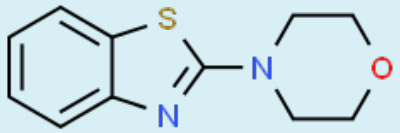
Tyre additives

N,N'-Diphenylguanidine

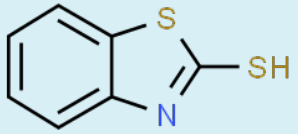


➢ Air mean: 93.9 pg/m3 [1]

2-(4-morpholinyl)benzothiazole



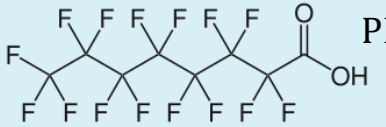
2-mercaptobenzothiazole



➢ PM: 591 pg/m3 [2]

Other chemicals

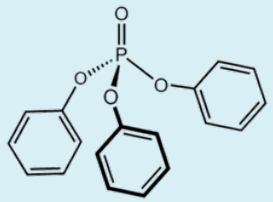
PFAS [3]



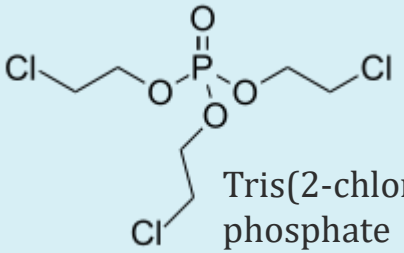
PFOA

PFNA

Flame retardants [4]

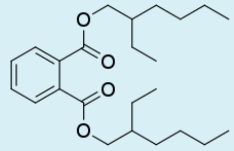


Triphenyl phosphate

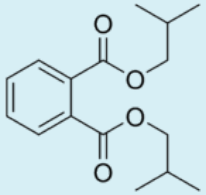


Tris(2-chloroethyl) phosphate

Plastic additives [5,6]



DEHP



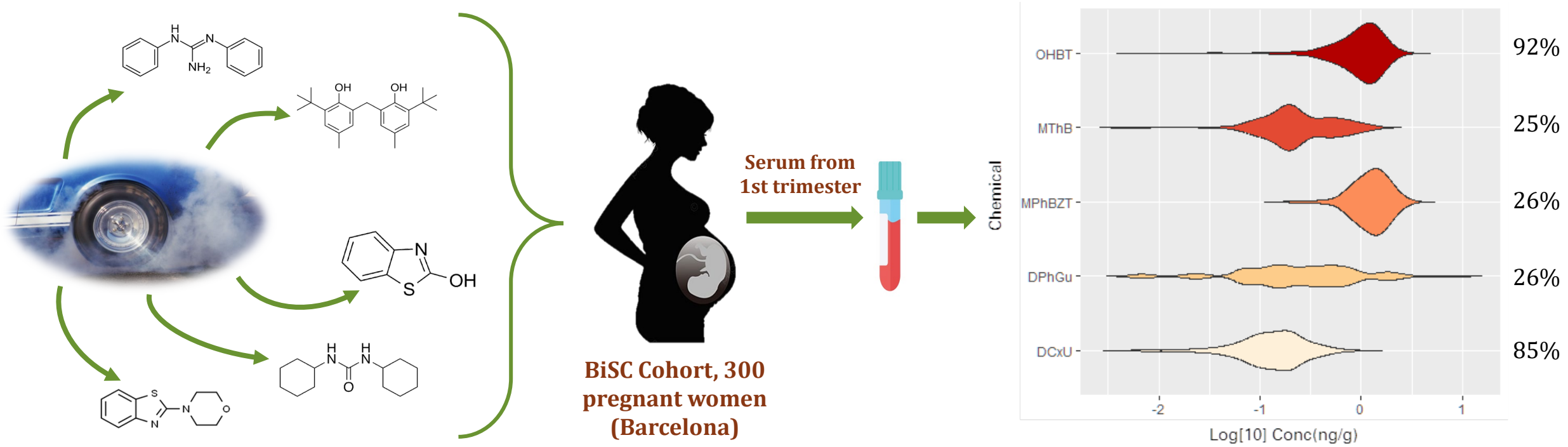
Diisobutyl-phthalate

[1] Johannessen et al., 2022. Environmental pollution 314, 120206 [2] Avagyan et al., 2014. Environ Sci Pollut Res 21, 11580–11586 (2014). [3] Kourtchev et al., 2022. STOTEN vol. 835, 155496 [4] Azizi et al., 2023. Env. Pollution, vol. 318, 120895. [5] Gao et al., 2018. STOTEN, vol 645, 1400-1409 [6] Huo et al., 2023. STOTEN, vol. 863, 160852

Discussion

- **Exposure to tyre additives during pregnancy**

- 5 tyre additives detected: N,N'-Diphenylguanidine (DPhGu), N,N'-Dicyclohexylurea (DCxU), 2-(4-morpholinyl)benzothiazole (MphBZT), 2,2-Methylenebis(6-tert-butyl-4-methyl-phenol) (MThB) and 2-Hydroxybenzothiazole (OHBT).



Discussion

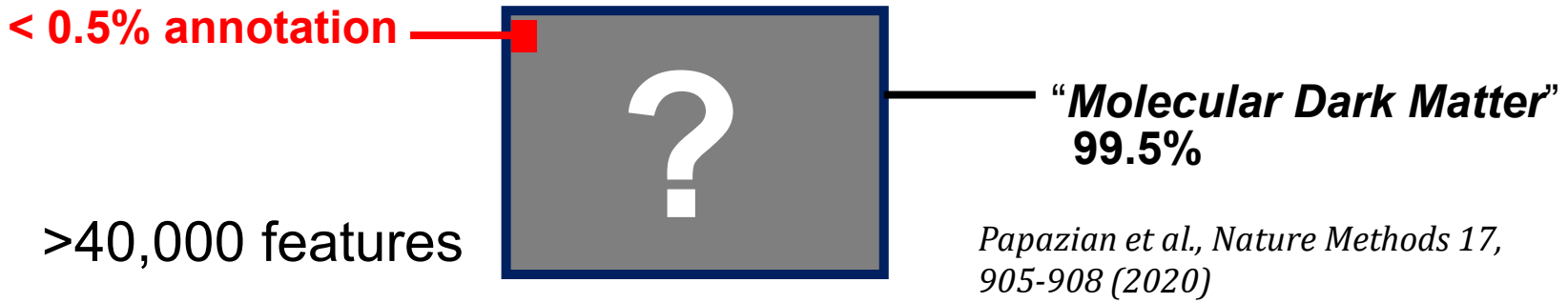
- **Organic fraction of PM**

- Organic molecules can be a **major mass fraction of total PM.**

  Jimenez, J. L. et al. Science. 326, 1525–1529 (2009).

- HRMS can reveal the molecular complexity → **Most substances remain uncharacterized** beyong assignment of molecular formula

  Lin, P.; Laskin, A. et al. Anal. Chem. 90, 12493–12502 (2018)



Papazian et al., Nature Methods 17, 905-908 (2020)

Conclusions

- **Conclusions**

- A wide range of organic contaminants can reach the brain (detected in tumoral and non-tumoral tissue).

- Air particulate matter can be a major exposure pathyway for some types of chemicals with potential to reach the brain.

Acknowledgements

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Dr. Marta Simó

Expo-HUM unit (2021-present)

Special Issue ES&T

- **Call for Papers: The exposome and Human Health**

Guest Editors

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NYU Langone Health, United States

Marja Lamoree
Vrije Universiteit Amsterdam, The Netherlands

Leisa-Maree Toms
Queensland University of Technology (QUT), Australia

Topics

- Novel and innovative approaches for human biomonitoring and human exposome for a broad range of chemicals.
- Exposure assessment and epidemiology of indoor and outdoor air quality, diet, drinking water.
- Environmental exposures and multi-omics.
- Novel and innovative study design to establish causality of the relationship between environmental exposures and human health across the life course.
- Modelling and impact of chemicals of emerging concern on human exposure and human exposome in general.
- Innovative studies focused on the link between ecosystem health and human health and their input on chemicals policy and regulation.
- Application of interdisciplinary research to better understand adverse health outcomes and their environmental origins.

Submission Deadline: June 20, 2023

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