

Pollutions : face au nombre de molécules émises, nous n'en saurons jamais assez sur leur nocivité

Journées Scientifiques de l'Environnement
Limites planétaires dépassées, et maintenant ?
Maison Départementale des Syndicats de Créteil

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Concepts

One Health (WHO)

- Ecosystems and human health related
- infections and all stressors

Global Health (UN)

- Worldwide health matters to all countries
- reducing disparities is critical

Planetary Health (Lancet)

- Human health and its dependency on Earth's ecosystems
- Implies planetary boundaries (or earth system boundaries)

Exposome

- all environmental stressors all life-long
- complements the genomes

Limites planétaires

Climate change

Atmospheric aerosol

Stratospheric ozone

Ocean acidification

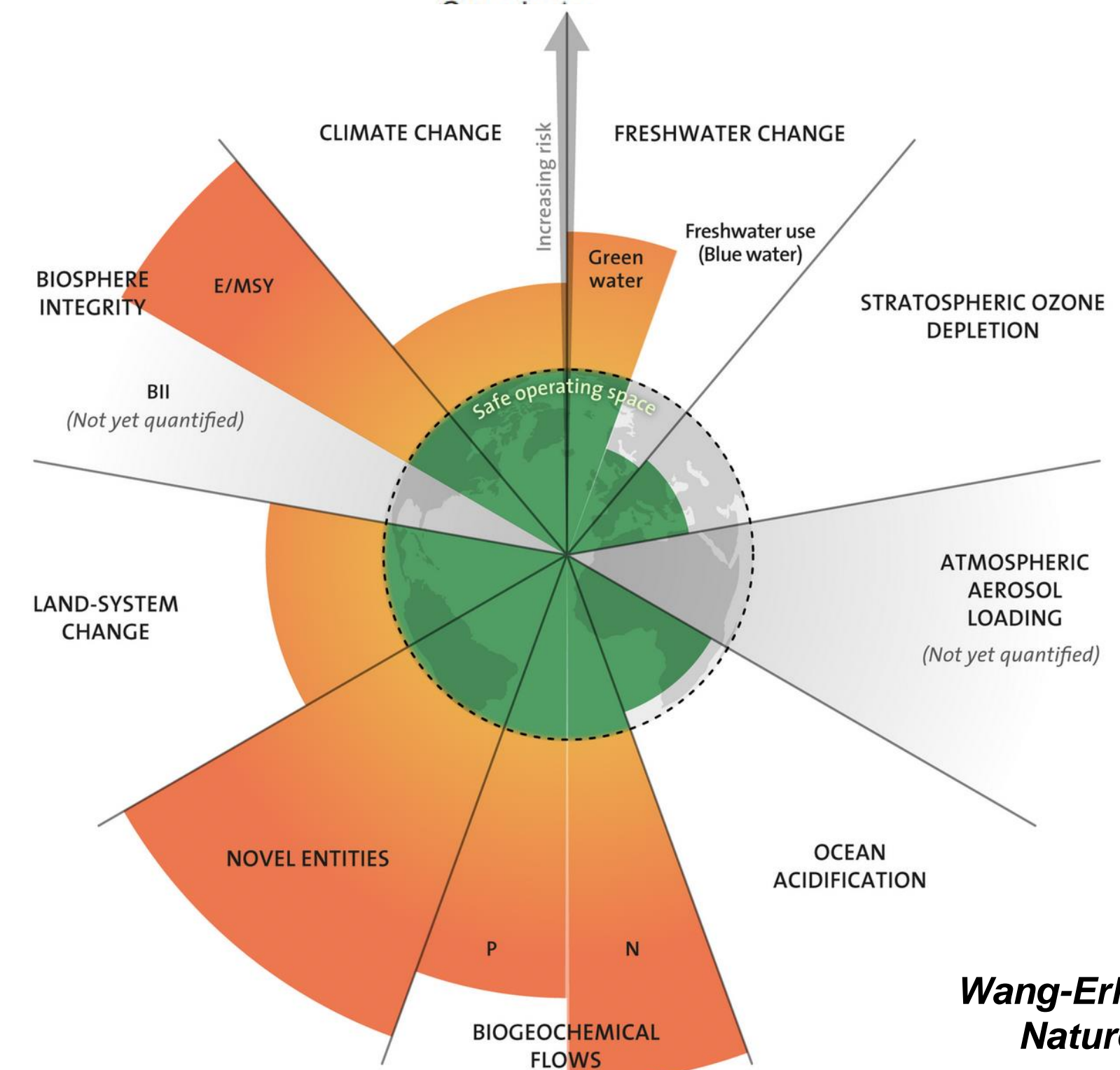
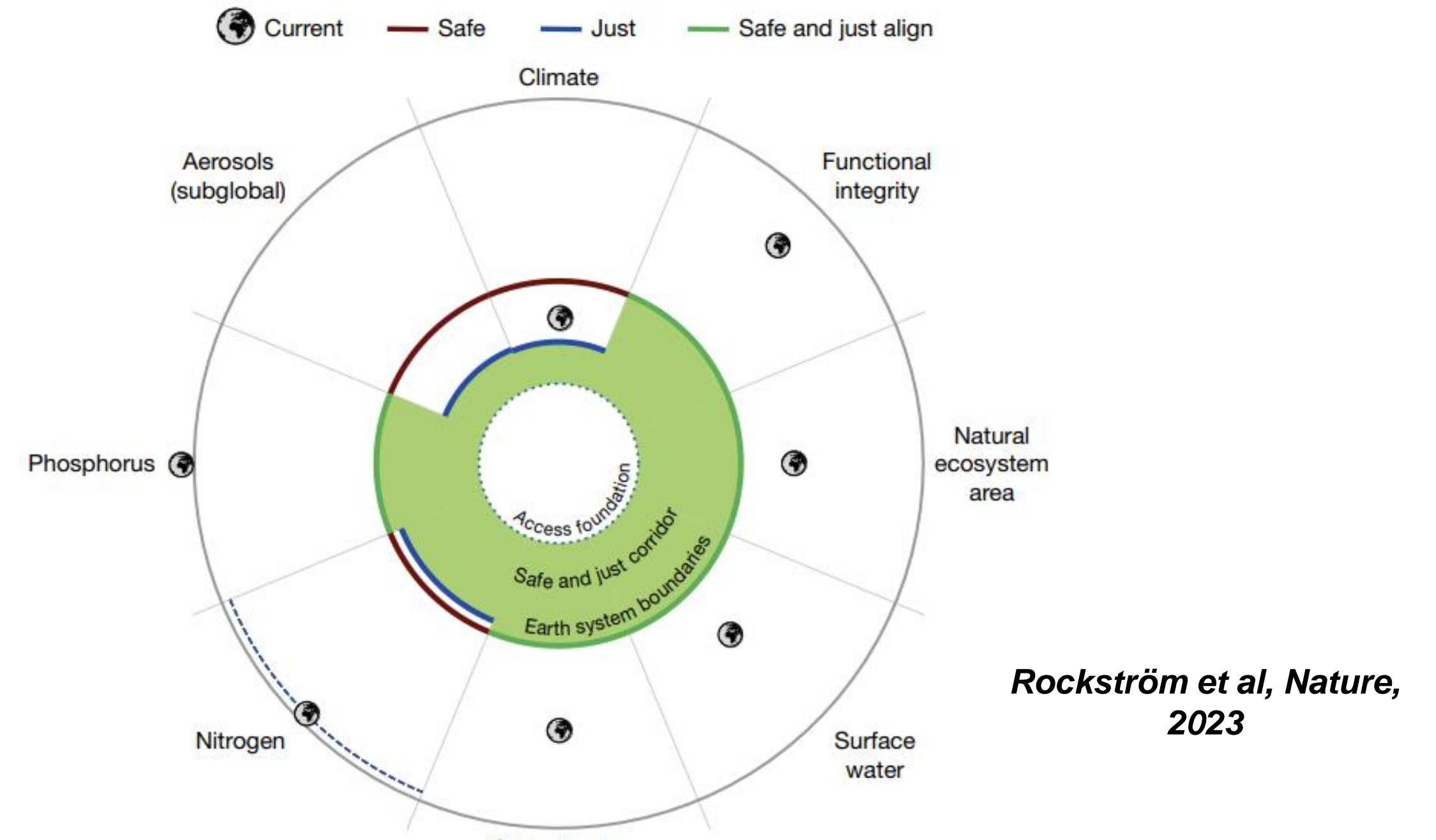
Freshwater change

Land use change

Biosphere integrity and diversity

Biogeochemical flows

Novel entities incl. chemical



La pollution tue!

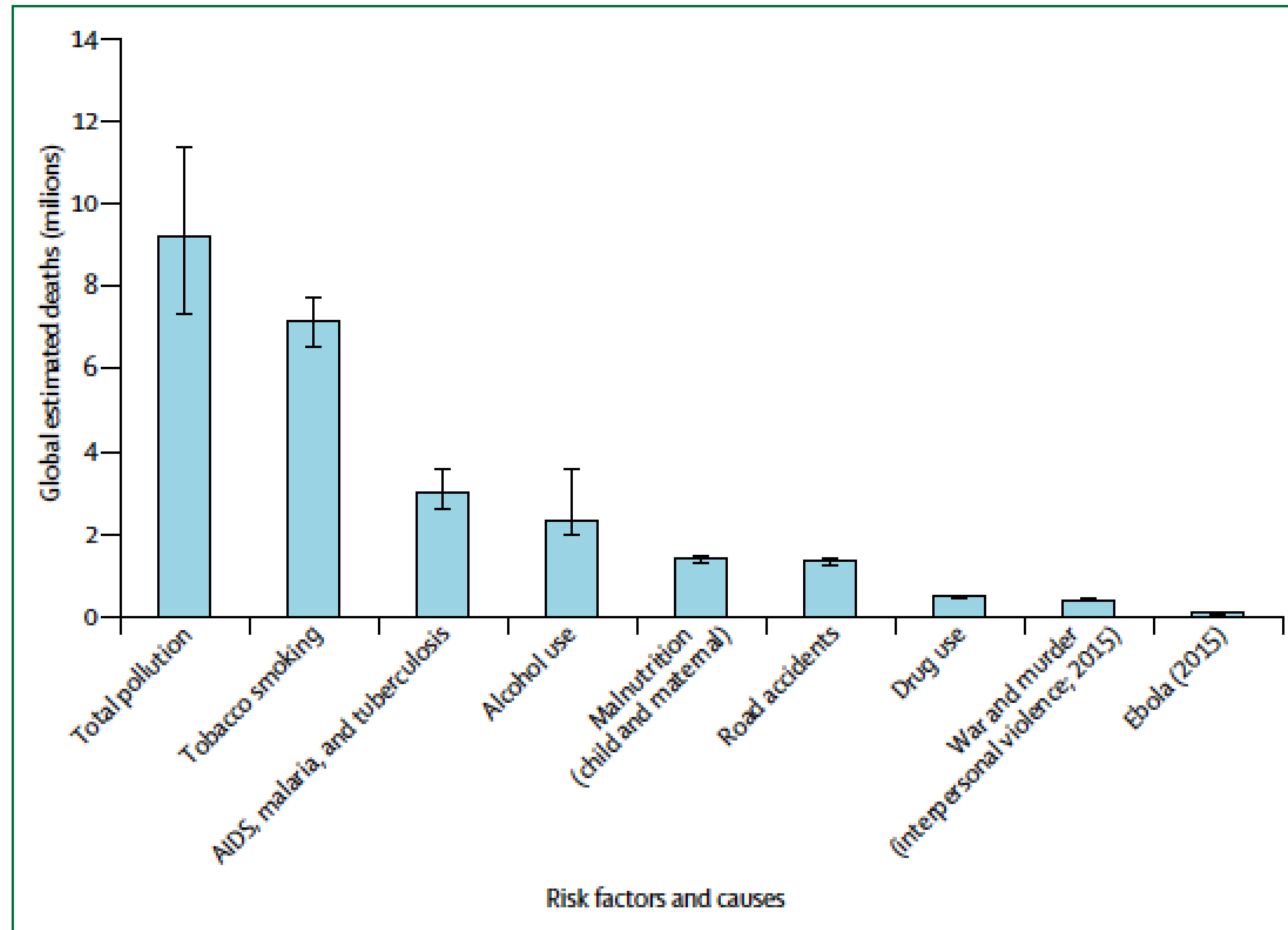


Figure 5: Global estimated deaths by major risk factor and cause, 2015
Using data from the GBD Study, 2016.⁴¹

L'univers chimique

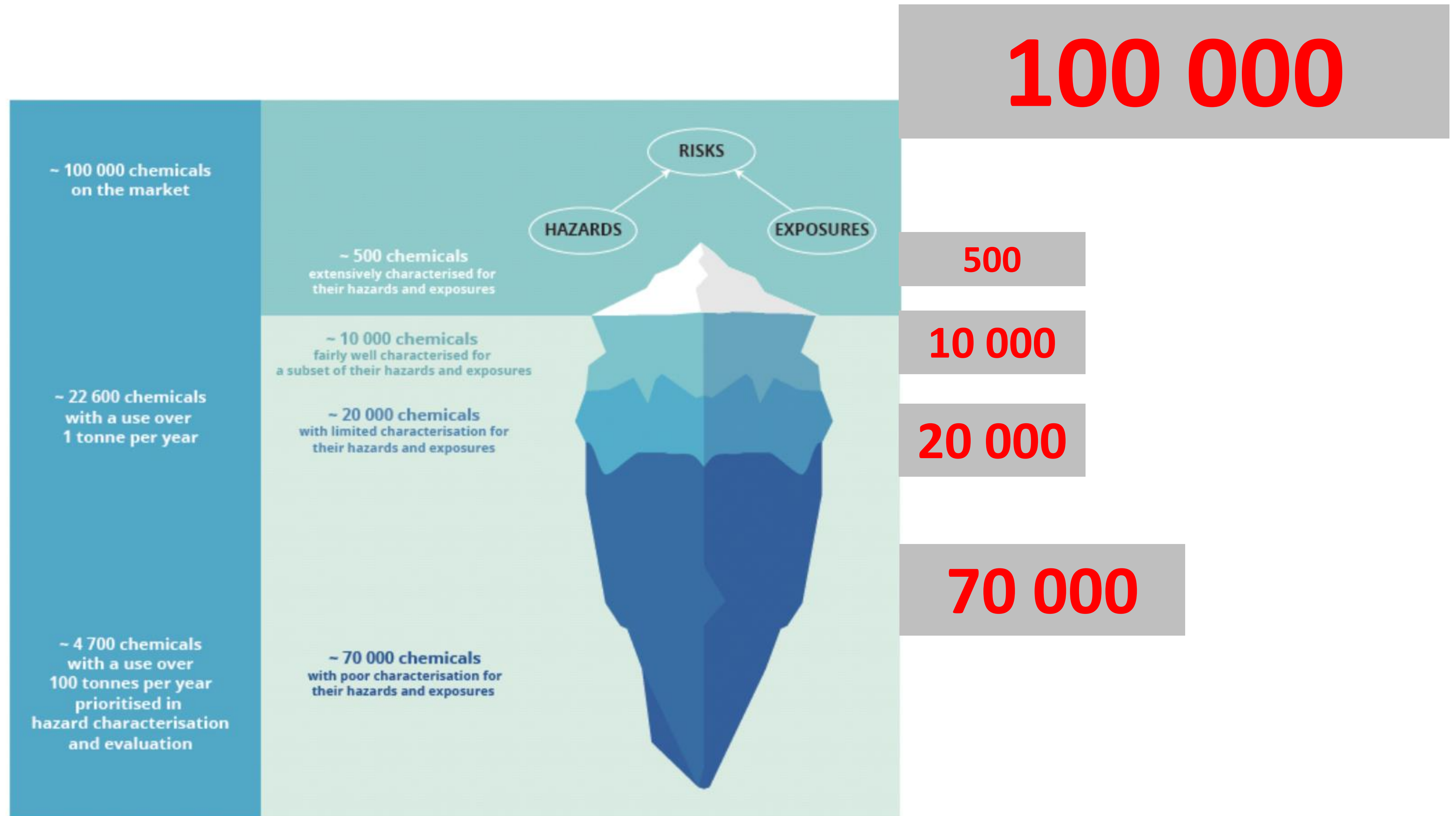
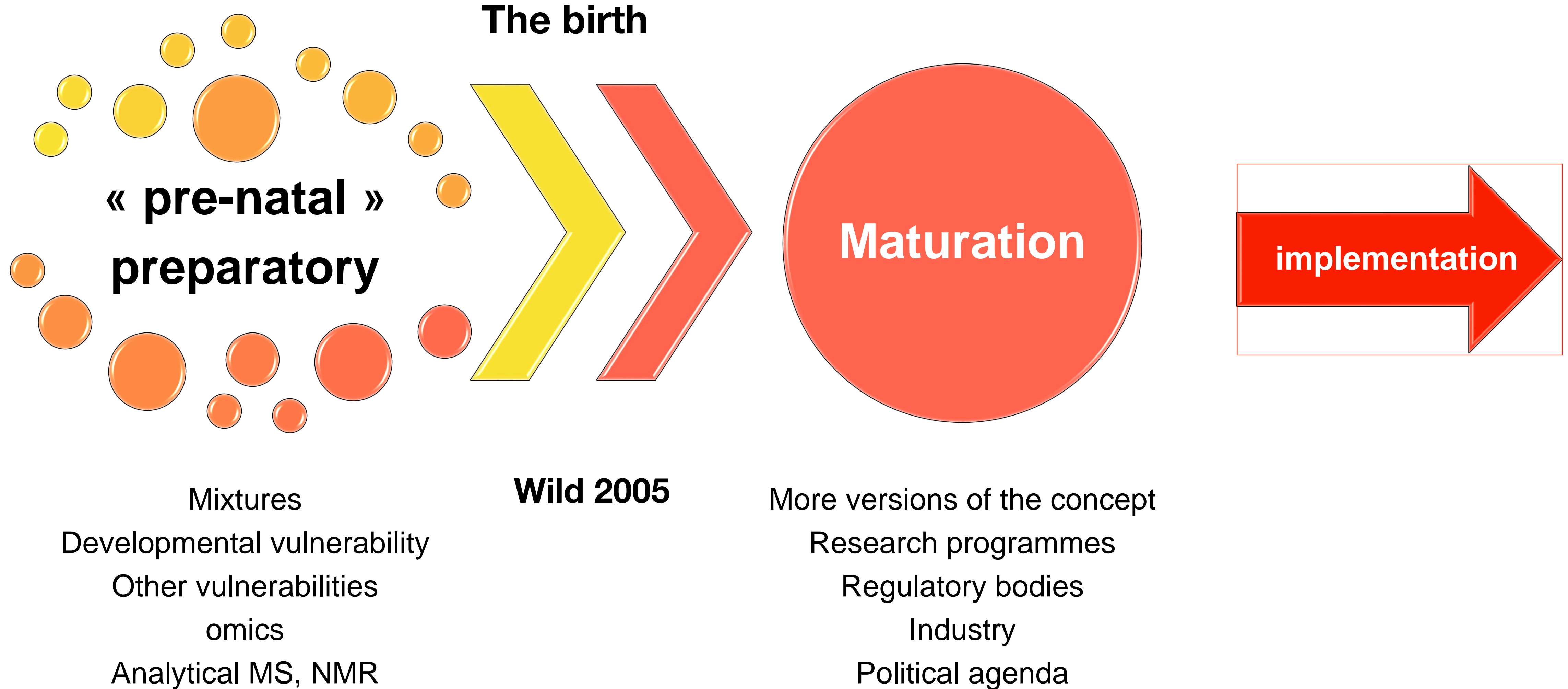


Figure: The unknown territory of chemical risks, EEA⁹⁶

Chemical Strategy for sustainability

La naissance d'un concept



Contributions au concept d'exposome

The Wild vision

Wild

- **All life-course environmental exposures** from prenatal period onwards; includes internal body processes, external exposures, and lifestyle factors.



Contributions au concept d'exposome

Analytical vision

Rappaport
and Smith

- Total exposures throughout life, where the “environment” is the body’s **internal chemical environment**

Toxicological vision

Miller

- The **cumulative measure** of environmental influences and **associated biological responses** throughout the lifespan

Ecotoxicological vision

NRC

- **Eco-exposome** extends the concept from point of contact between stressor and receptor, **inward into organism and outward to general environment**

Contributions au concept d'exposome

Price et al

- Integrate exposomics with other omics. Exposomics are strictly about exposures but **functional exposomics relate to the effects of the exposome** (similarly to functional genomics)

Vermeulen
et al

- **Network science**, offers a platform to help explore the mechanistic role of the chemicals in our exposome. Functional exposome is the biologically active fraction of the exposome

Vineis et
al

- **life-long trajectory of exposures**, that act via multistage mechanisms and express the biography of a person, where **socio-economic position is an overarching determinant of the trajectory**

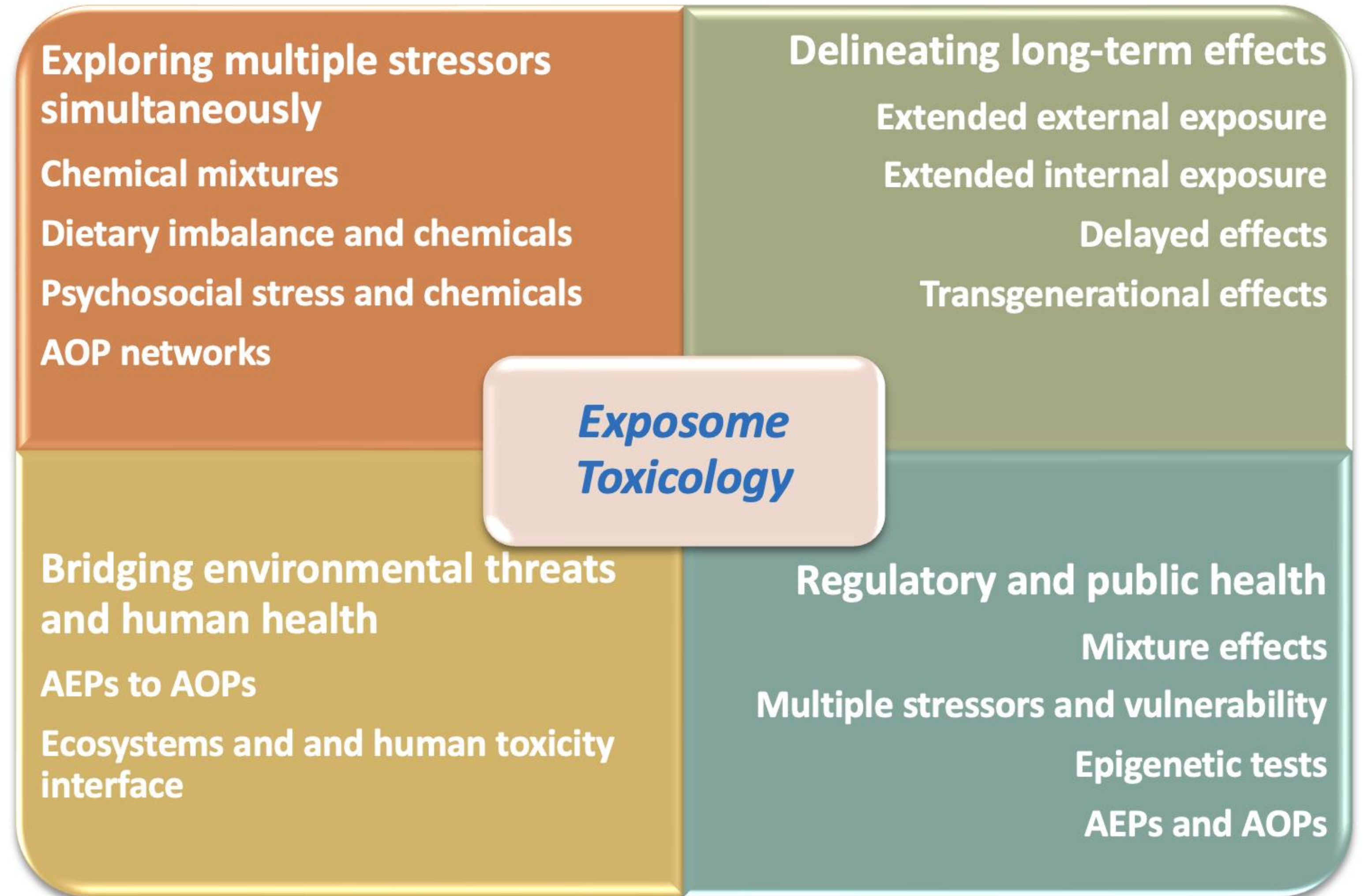
Exposome et toxicologie

The Exposome and Toxicology: A Win–Win Collaboration FREE

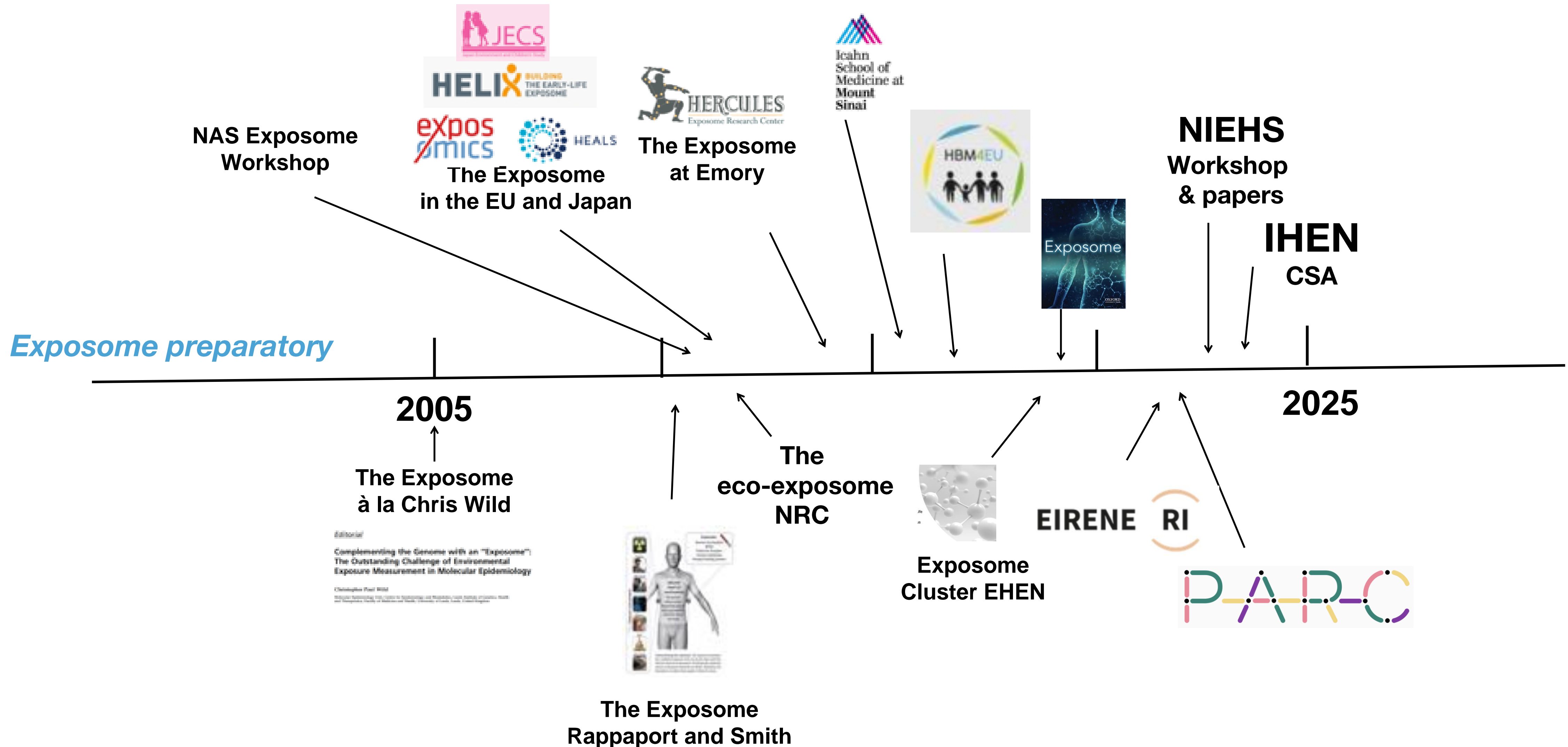
Robert Barouki ✉, Karine Audouze, Christel Becker, Ludek Blaha, Xavier Coumoul, Spyros Karakitsios, Jana Klanova, Gary W Miller, Elliott J Price, Denis Sarigiannis

Toxicological Sciences, Volume 186, Issue 1, March 2022, Pages 1–11,
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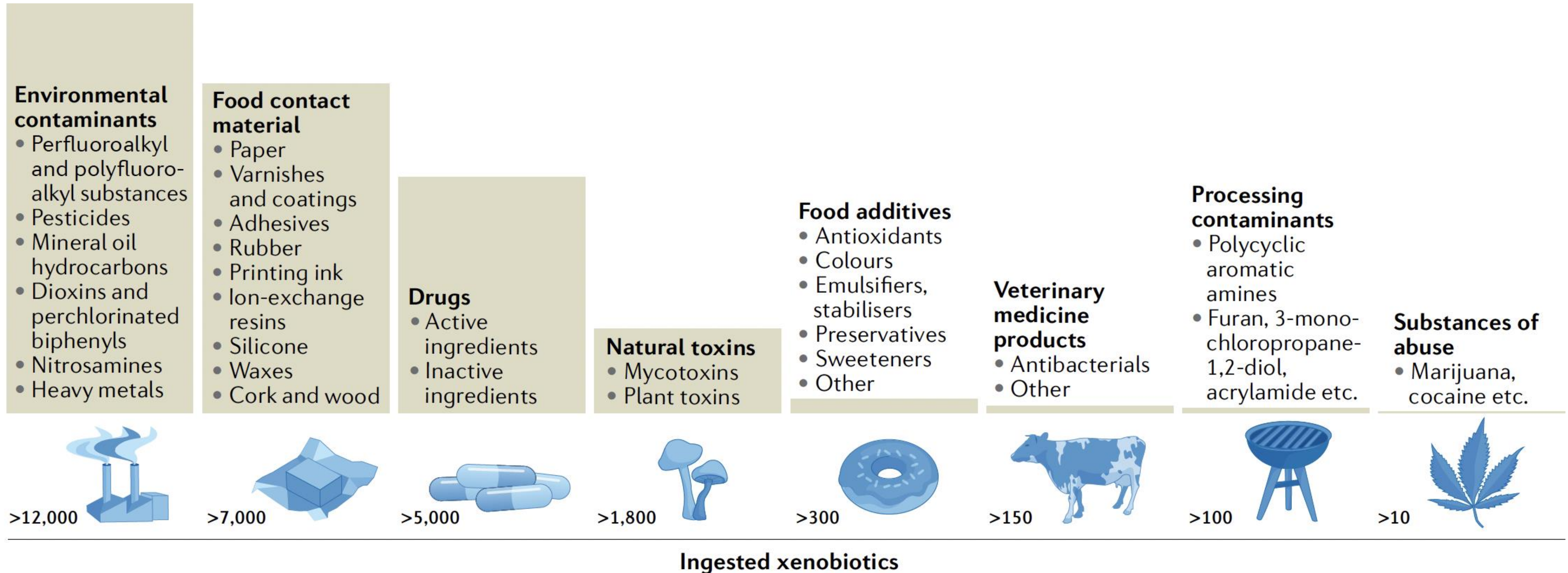


Les étapes de développement de l'exposome

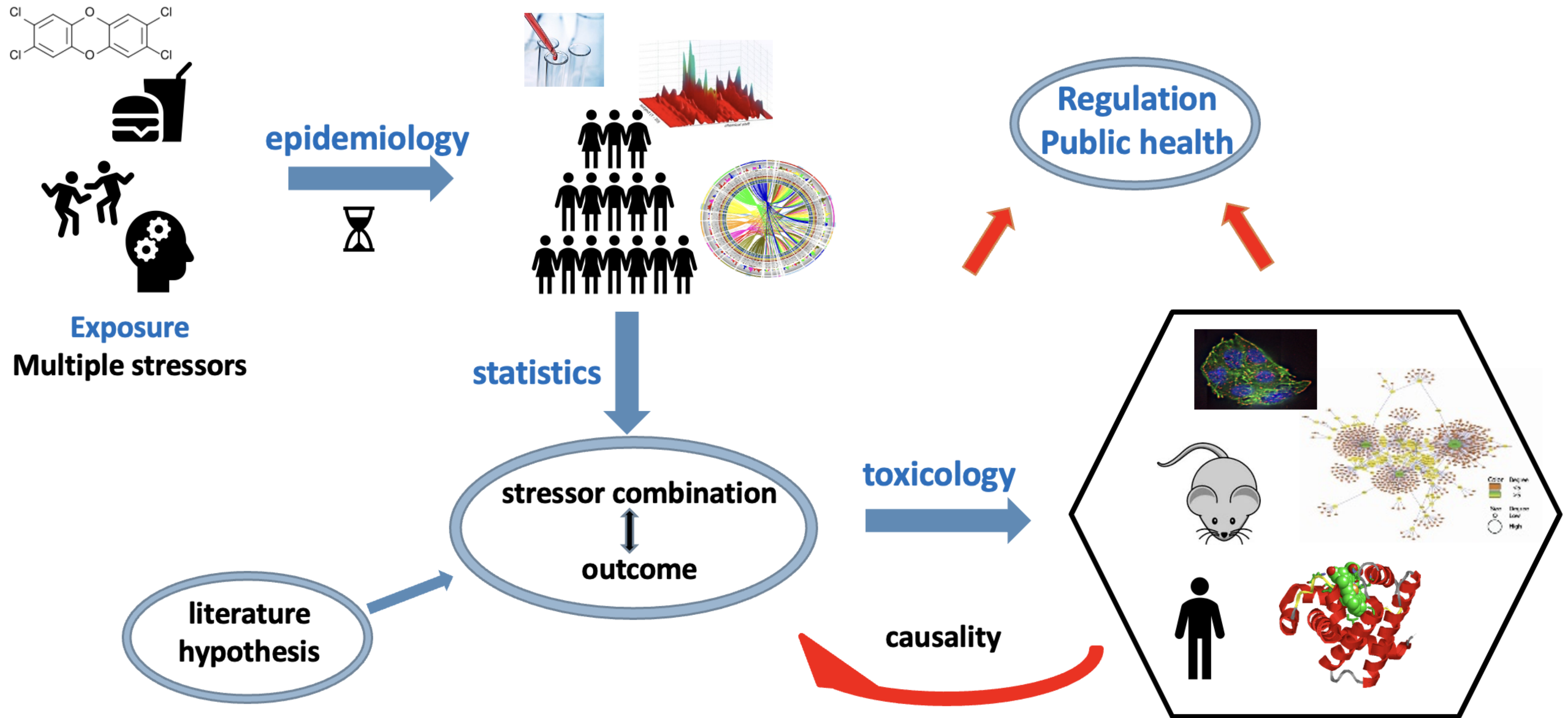


from G Miler with updates

Les origins diverses des contaminants

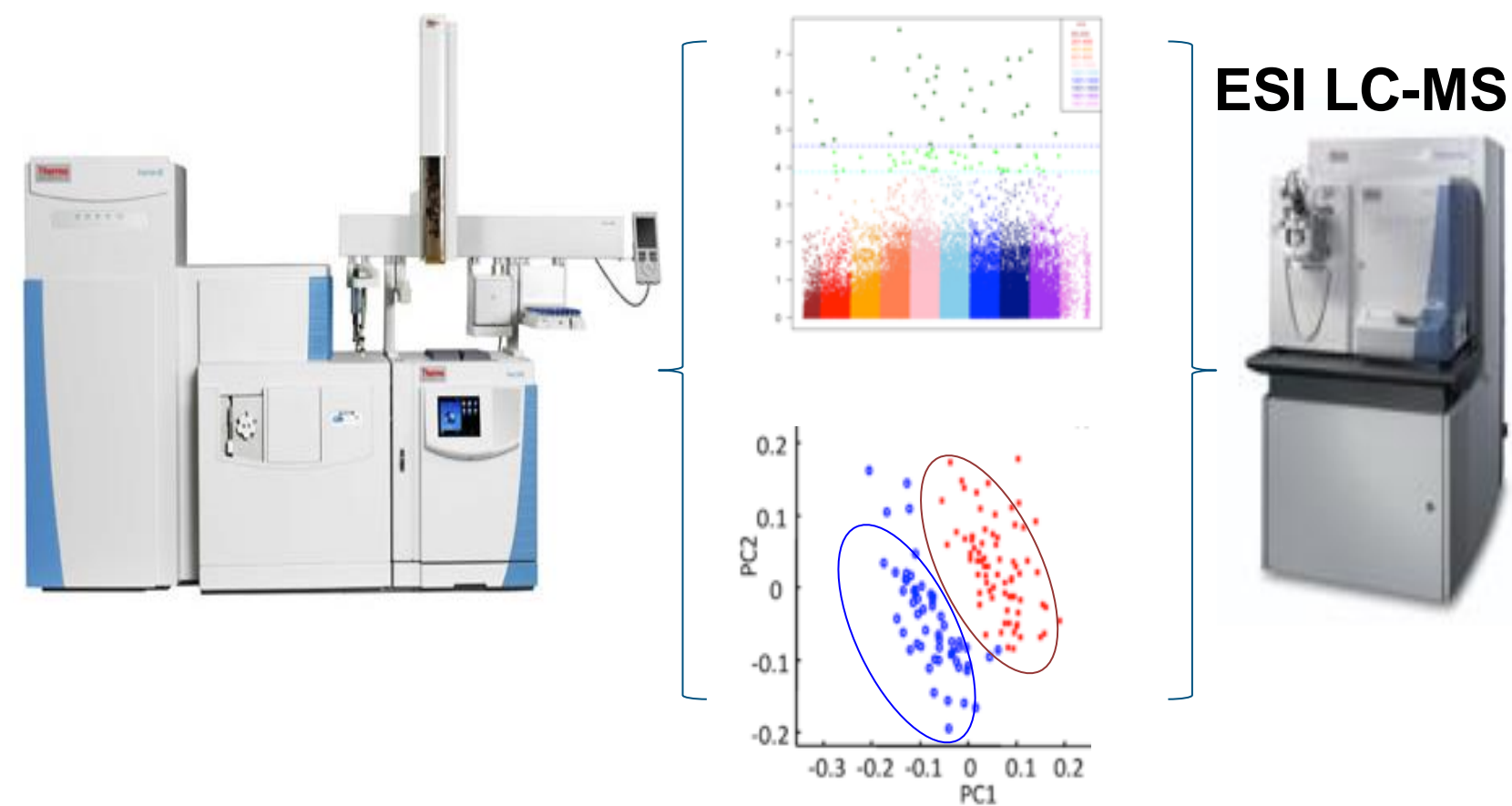


Une multitude de disciplines



Méthodes and technologies

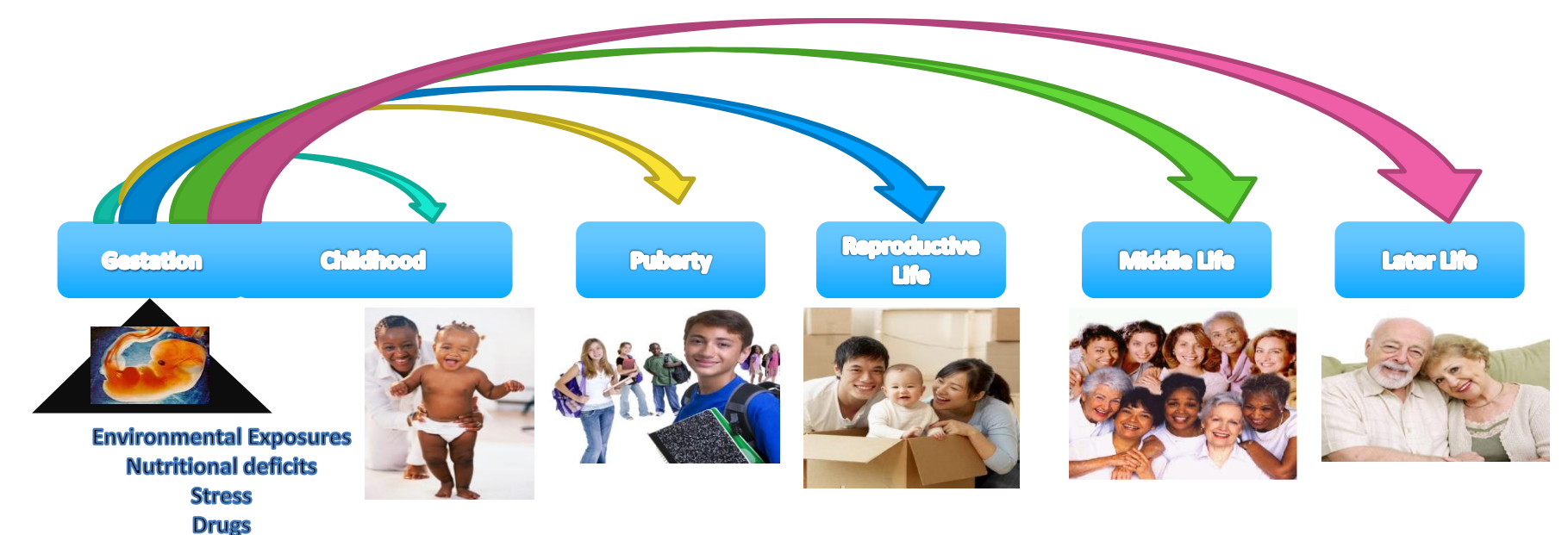
HRMS



detectors devices

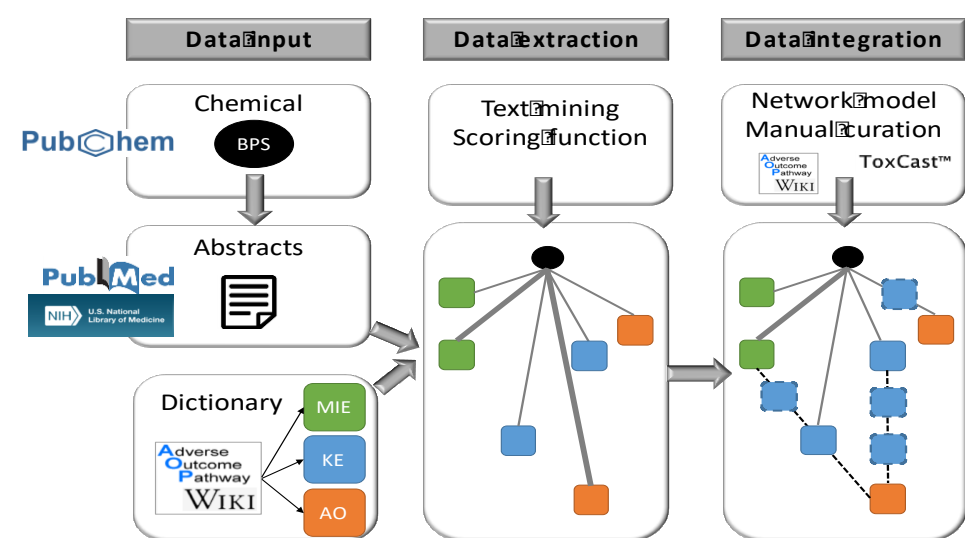


DOHaD



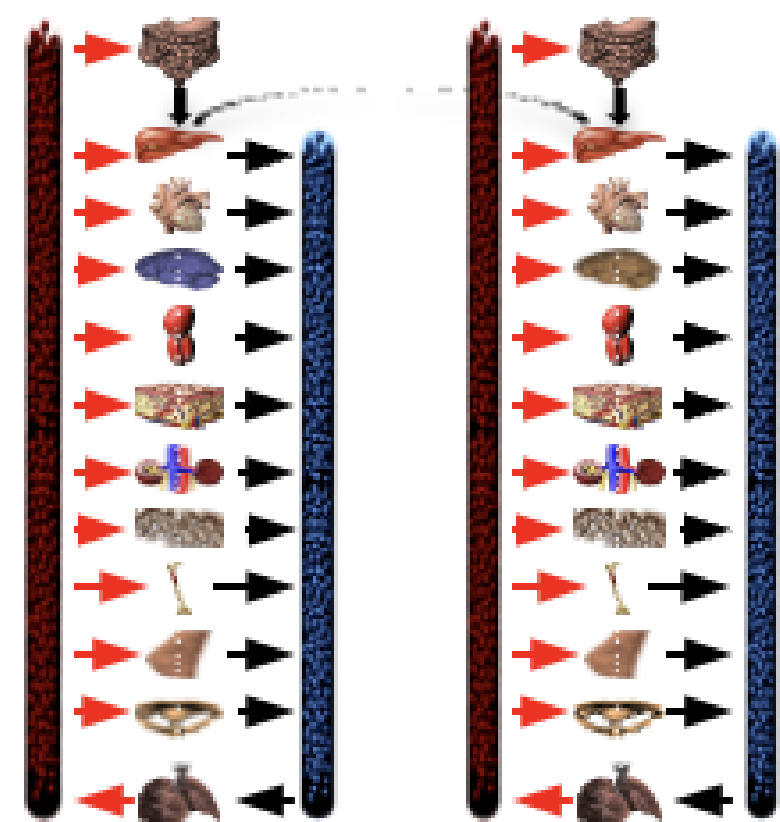
J Heindel

AI



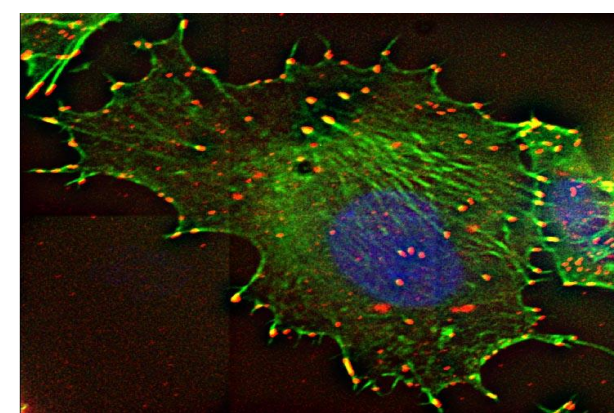
Carvaillo et al, EHP, 2019

PBTK

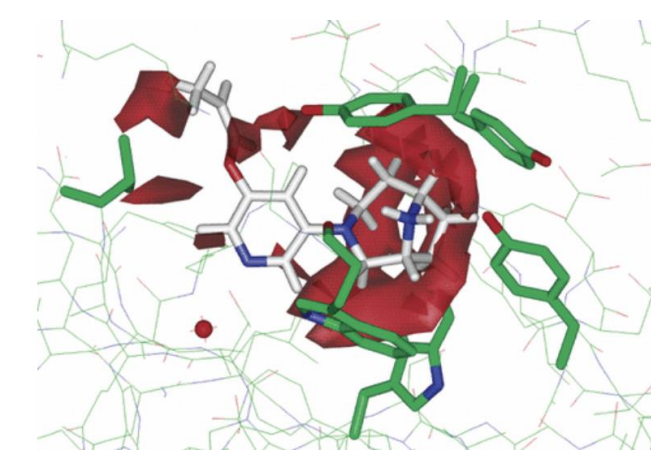


D Sarigiannis

NAMs

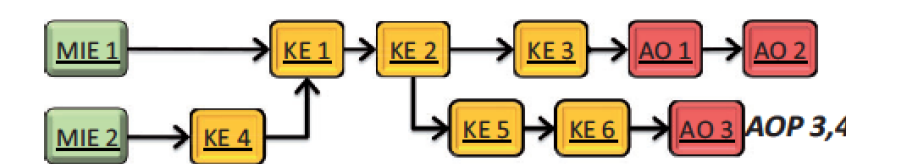


QSAR



Audouze et al, 2006

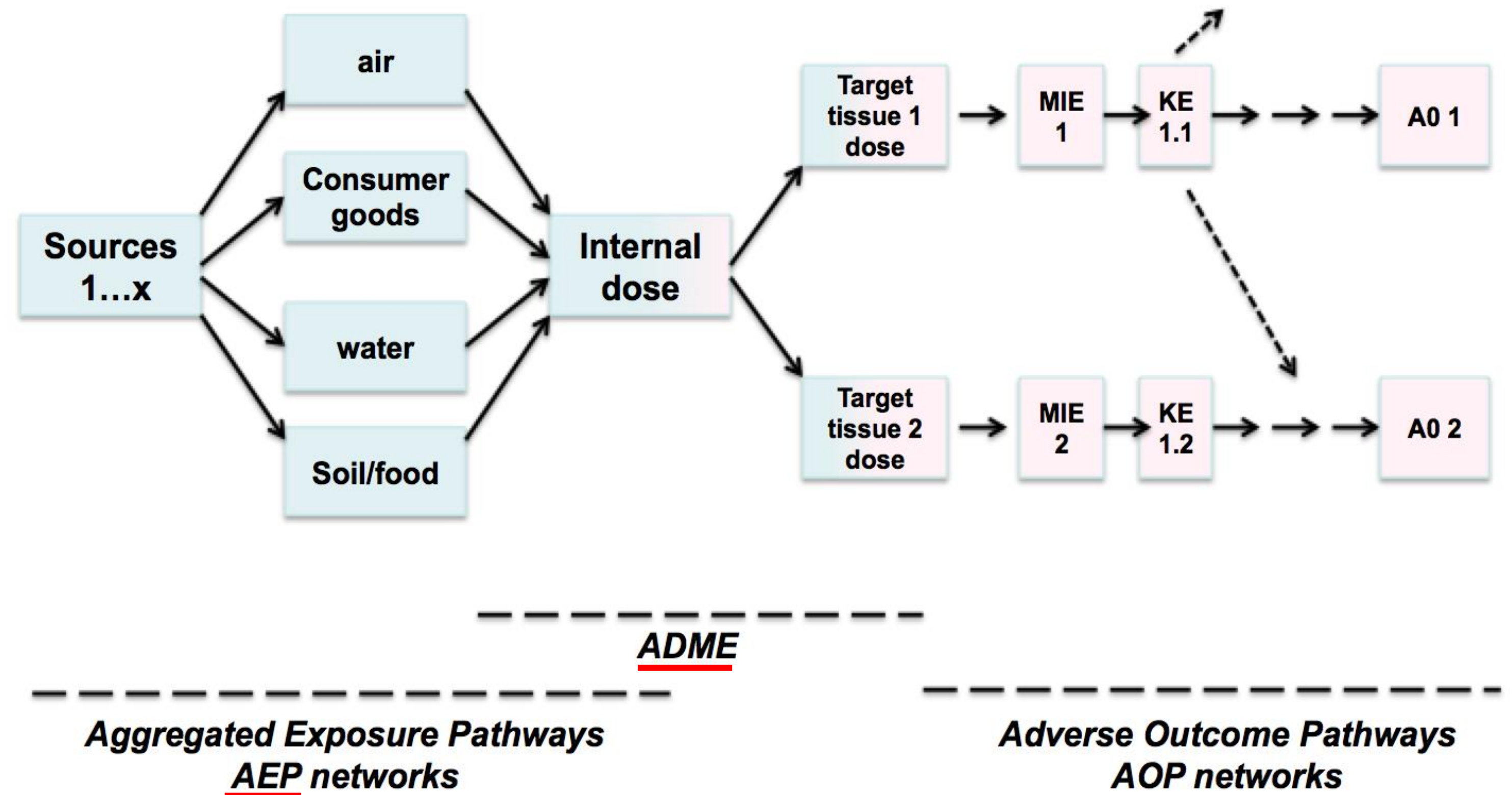
AOP



Villeneuve et al, Tox Sci, 2014

Expositions, cinétique et effets délétères

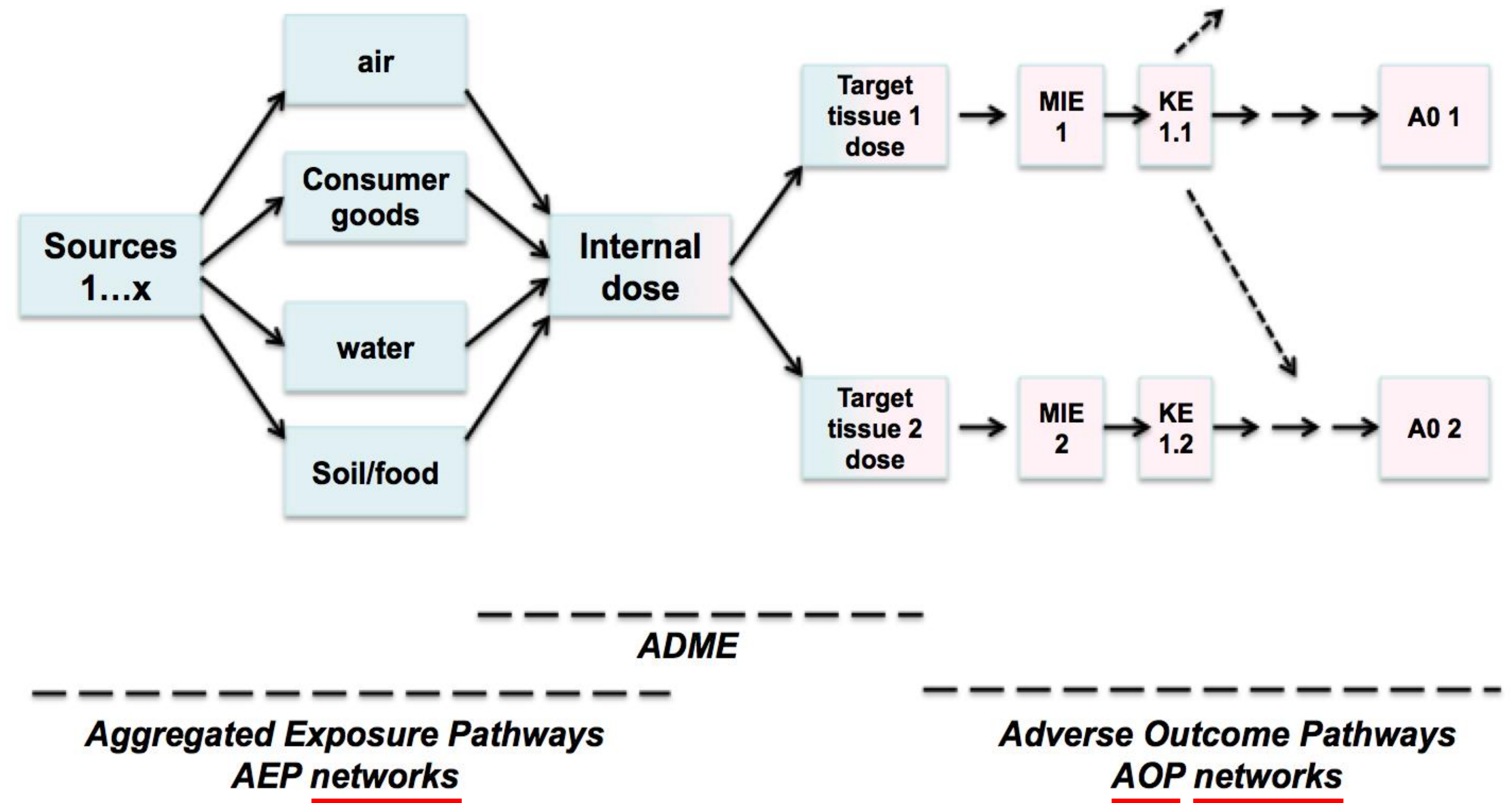
- ✓ Aggregated Exposure Pathways: from sources to different media to human
- ✓ ADME: Absorption, distribution, metabolism, excretion. Kinetic modeling describing fate of chemicals in human (or other species)



Expositions, cinétique et effets délétères

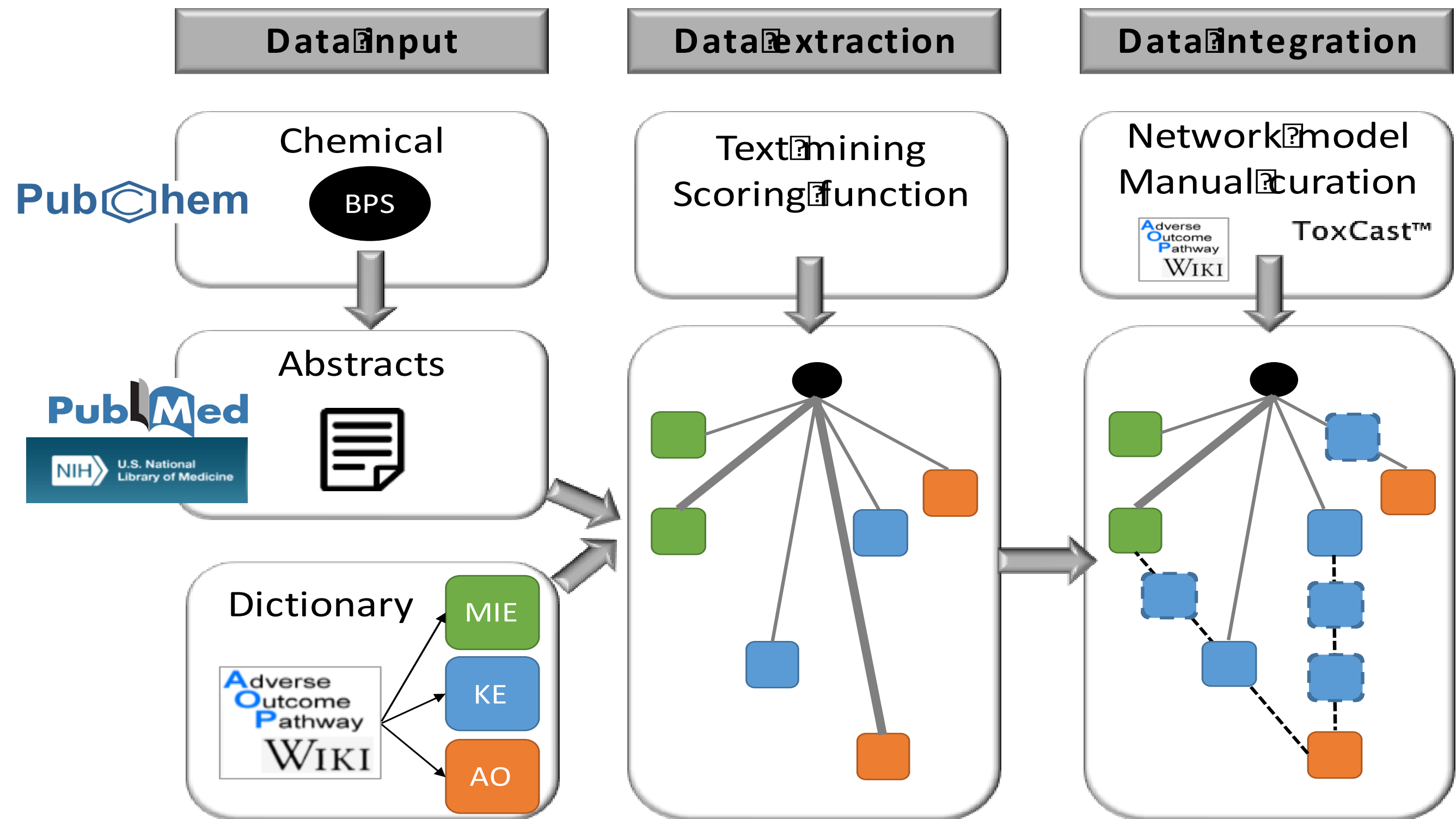
✓ **Adverse Outcome Pathways: a framework describing evidence-based relationships between molecular initiating events (MIE),; other key events (KE) and adverse outcomes.**

✓ **Networks: occur when different pathways intersect or interact. Can relate to single stressors or combination of stressors**



Comment associer une substance chimique à un événement d'une AOP

- ✓ Multiple toxicological and computational methods to link chemicals to outcomes or proteins (Quantitative Structure Activity relationship)
- ✓ Example: mining the literature and using network biology helps in accelerating the identification of such links
- ✓ Yet, careful human analysis of the retrieved studies is still necessary

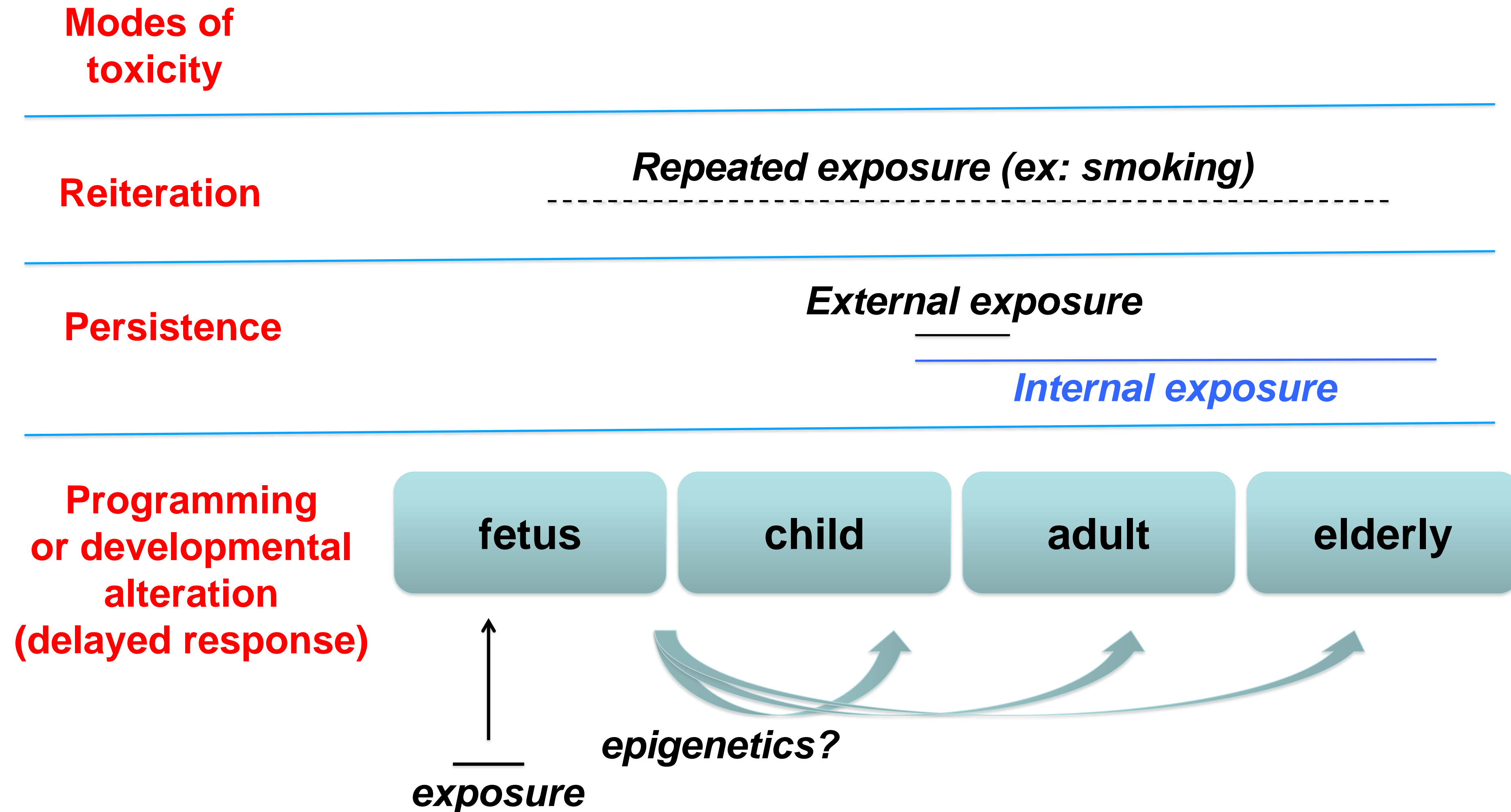


AOPhelpfinder

Les caractéristiques des impacts de l'environnement sur la santé

- ✓ **Genomic alterations and mutations (e.g. smoking, aflatoxin)**
- ✓ **Epigenetic alterations (e.g. endocrine disruptors, TBT, BPA)**
- ✓ **Mitochondrial dysfunctions (e.g. pesticides inhibitors of respiratory chain)**
- ✓ **Endocrine dysfunction (e.g. Bisphenols, DES, phthalates)**
- ✓ **Altered intercellular communications (e.g. dioxins)**
- ✓ **Altered microbiome communities (e.g. antibiotics)**
- ✓ **Impaired nervous system functions (e.g. lead)**
- ✓ **Oxidative stress and inflammation (e.g. paraquat)**
- ✓ **Immunotoxicity (e.g. PFAS)**

Le temps: effets à long terme



Effets des mélanges

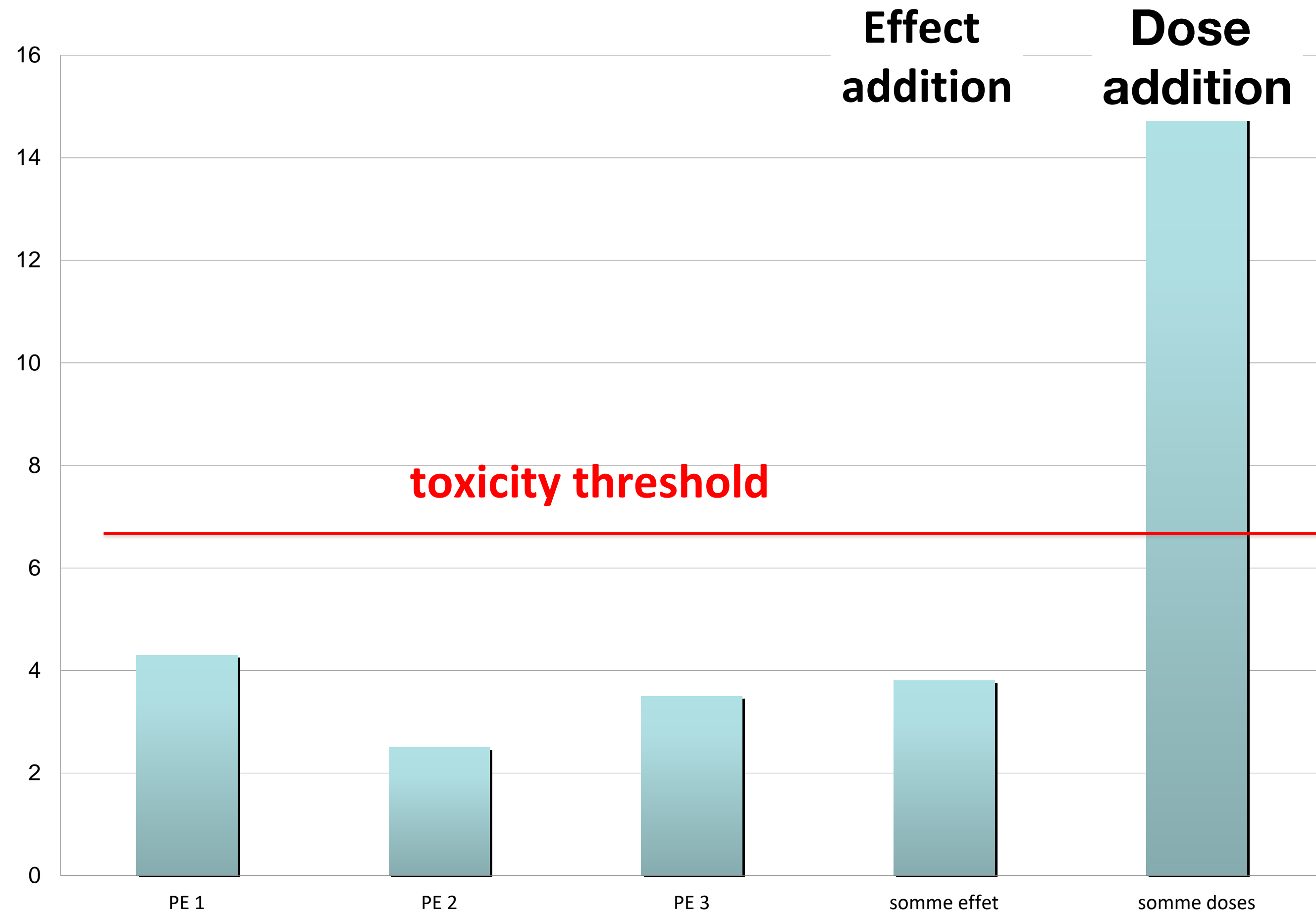
Identifying co-exposure to a group of pollutants

- Determine the profile of exposure in a certain setting (workplace, cities, ...). Network analysis

Identifying the health impact of a mixture of pollutants

- criteria for grouping substances (structure, mode of action, etc.)
- identify critical substances in a mixture
- identify additional outcomes related to the mixture as compared to individual substances

Implications réglementaires



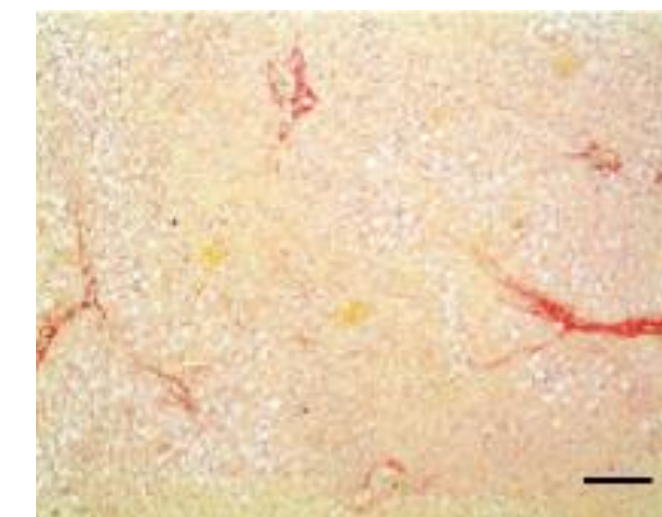
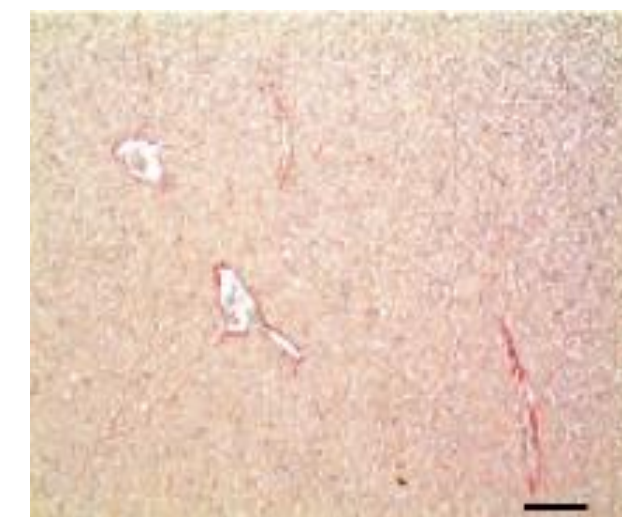
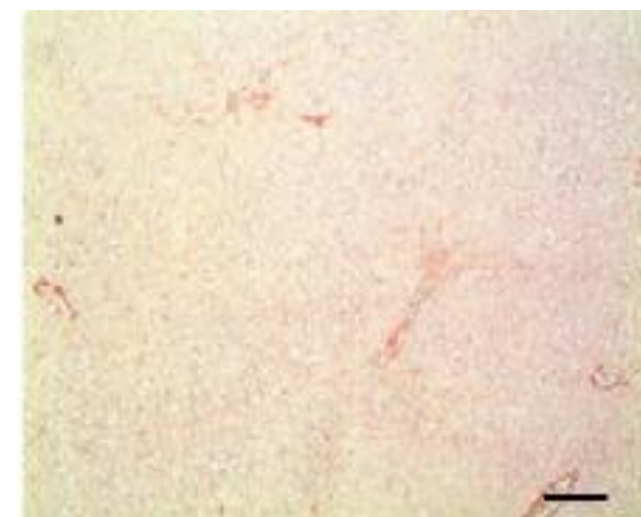
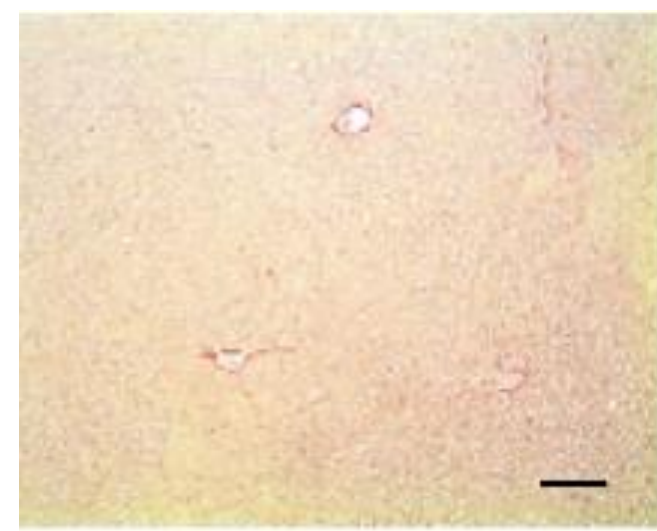
Theoretical graph

Kortenkamp, EHP, 2007

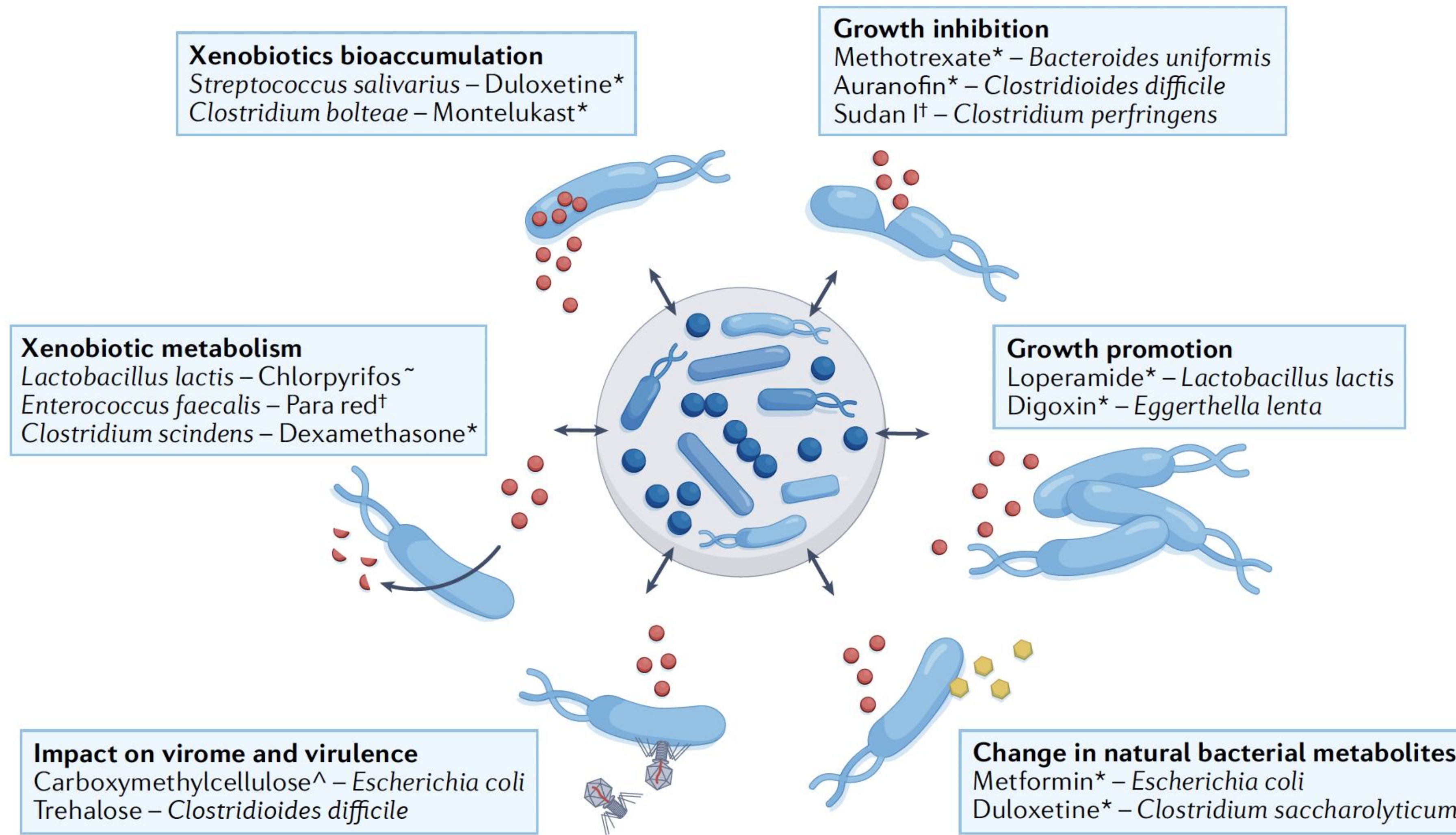
Interaction entre regime alimentaire et contaminants chimiques

	control	dioxin	High fat diet	dioxin + high fat diet
fibrosis	100	115	125	220
Fat accumulation	100	230	130	500

Sirius red (fibrosis)



Intéractions entre microbiote et xénobiotiques



● Xenobiotic ◐ Xenobiotic metabolite ● Natural bacterial metabolite
 * Human-targeted drugs † Dyes ~ Pesticides ^ Emulsifiers

Défense et adaptation à l'exposome chimique

L'exposome est d'une très grande diversité: **100 000** substances à un certain tonnage en circulation en Europe

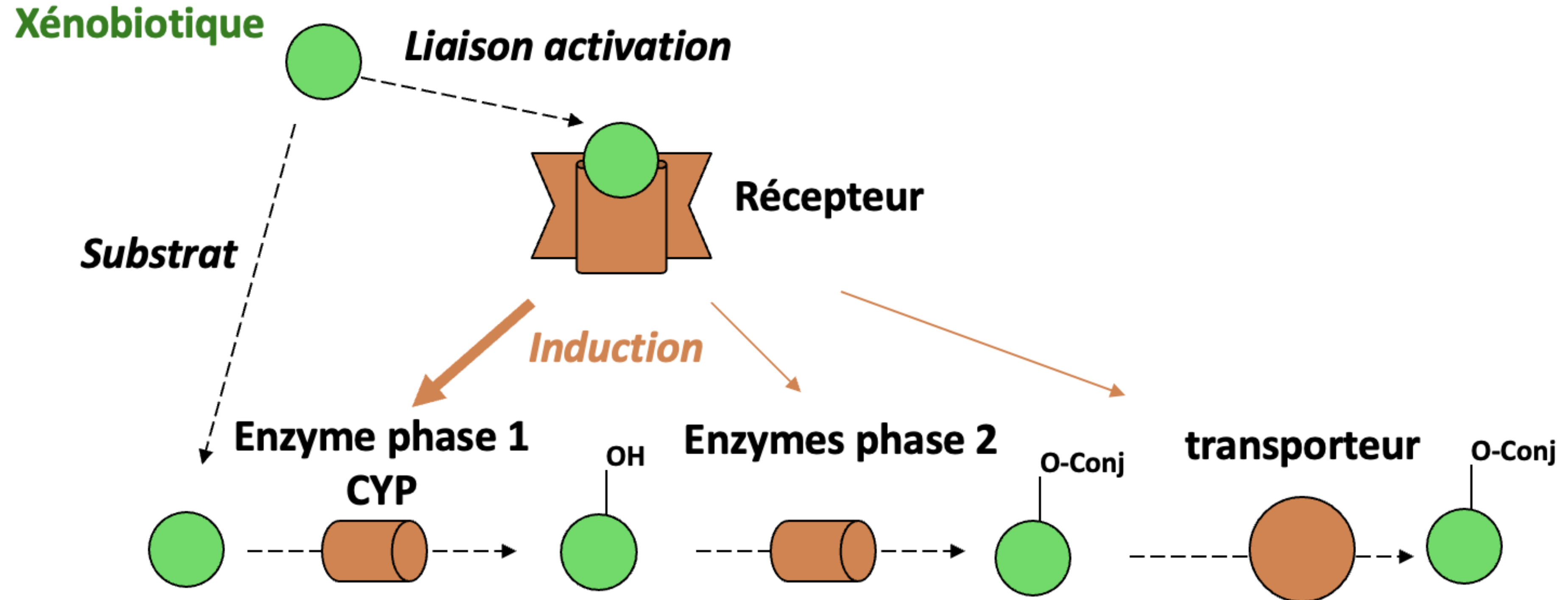
Une partie de ces substances est susceptible d'exercer une toxicité: réactivité chimique, hydrophobicité

L'adaptation se fait à court terme par l'induction des voies du métabolisme des xénobiotiques

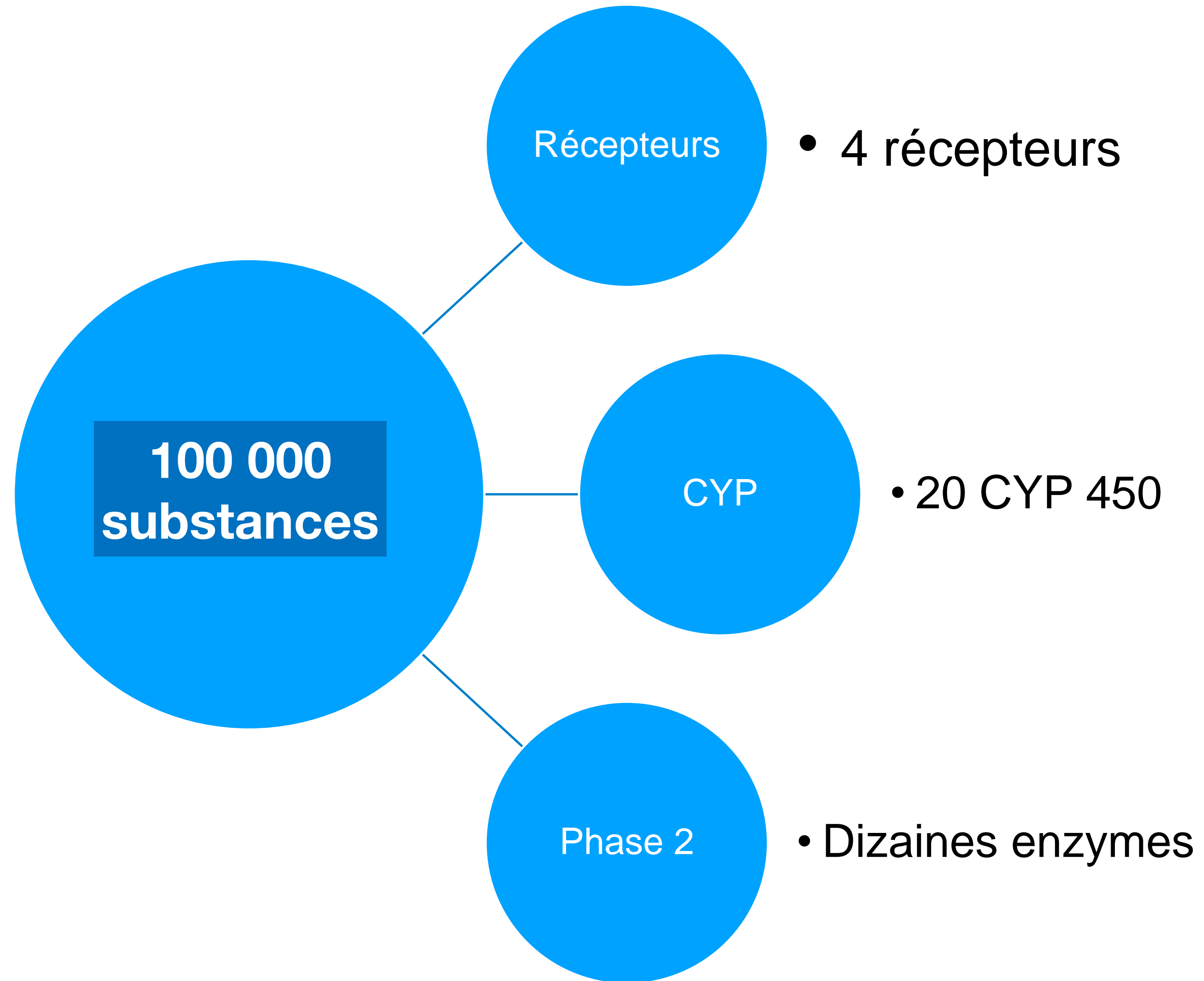
Il existe sans doute des adaptations à long terme, voire transgénérationnelles impliquant des mécanismes épigénétiques mais elles sont mal connues chez les mammifères

Nous ne discuterons ici que des voies du métabolisme des xénobiotiques et du coût de l'activation de ces voies tenant compte de l'extrême diversité de l'exposome chimique

La voie du métabolisme et d'élimination des xénobiotiques: système inductible d'adaptation à l'exposition chimique

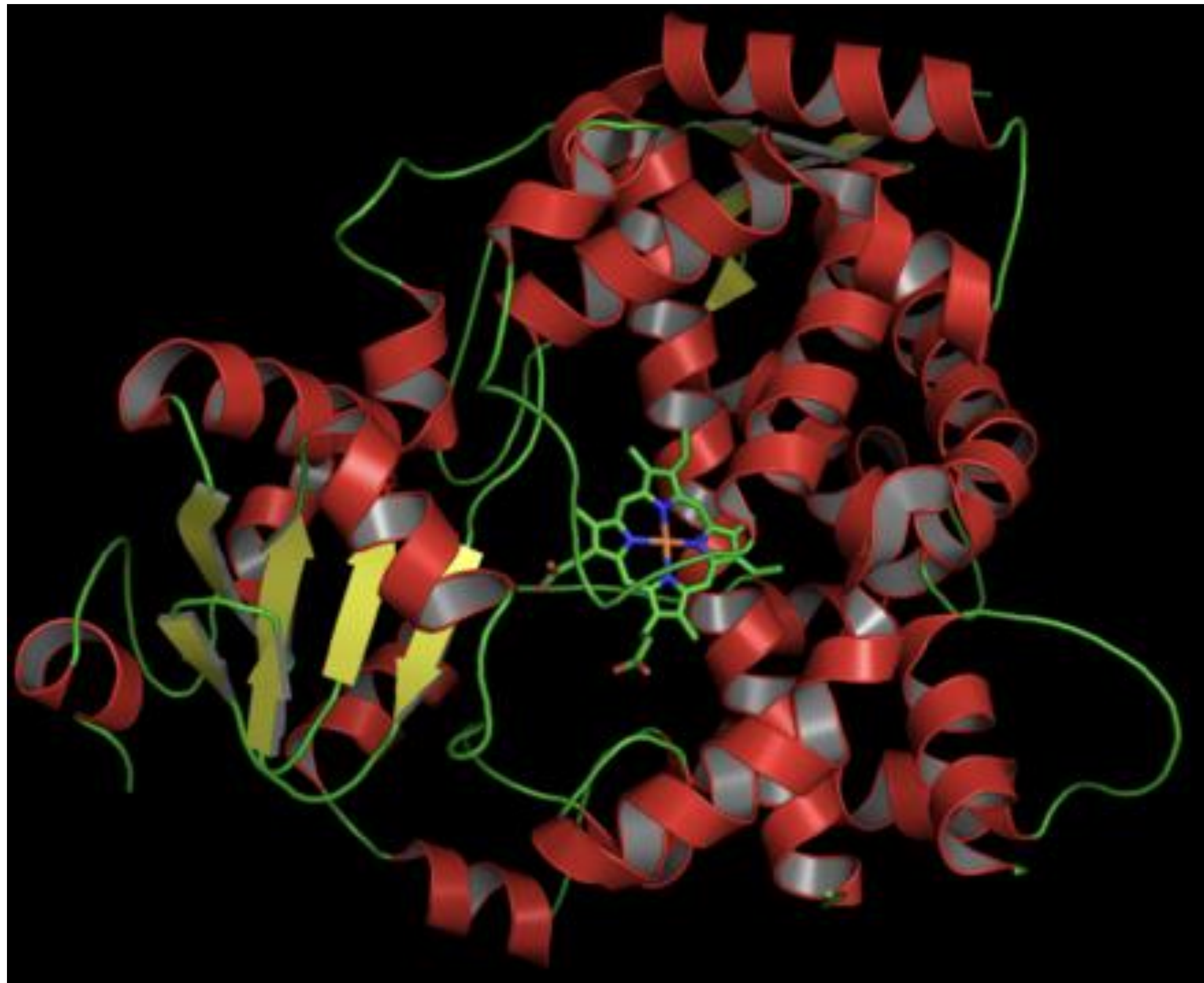


Dissociation entre le nombre de substances et de protéines dédiées

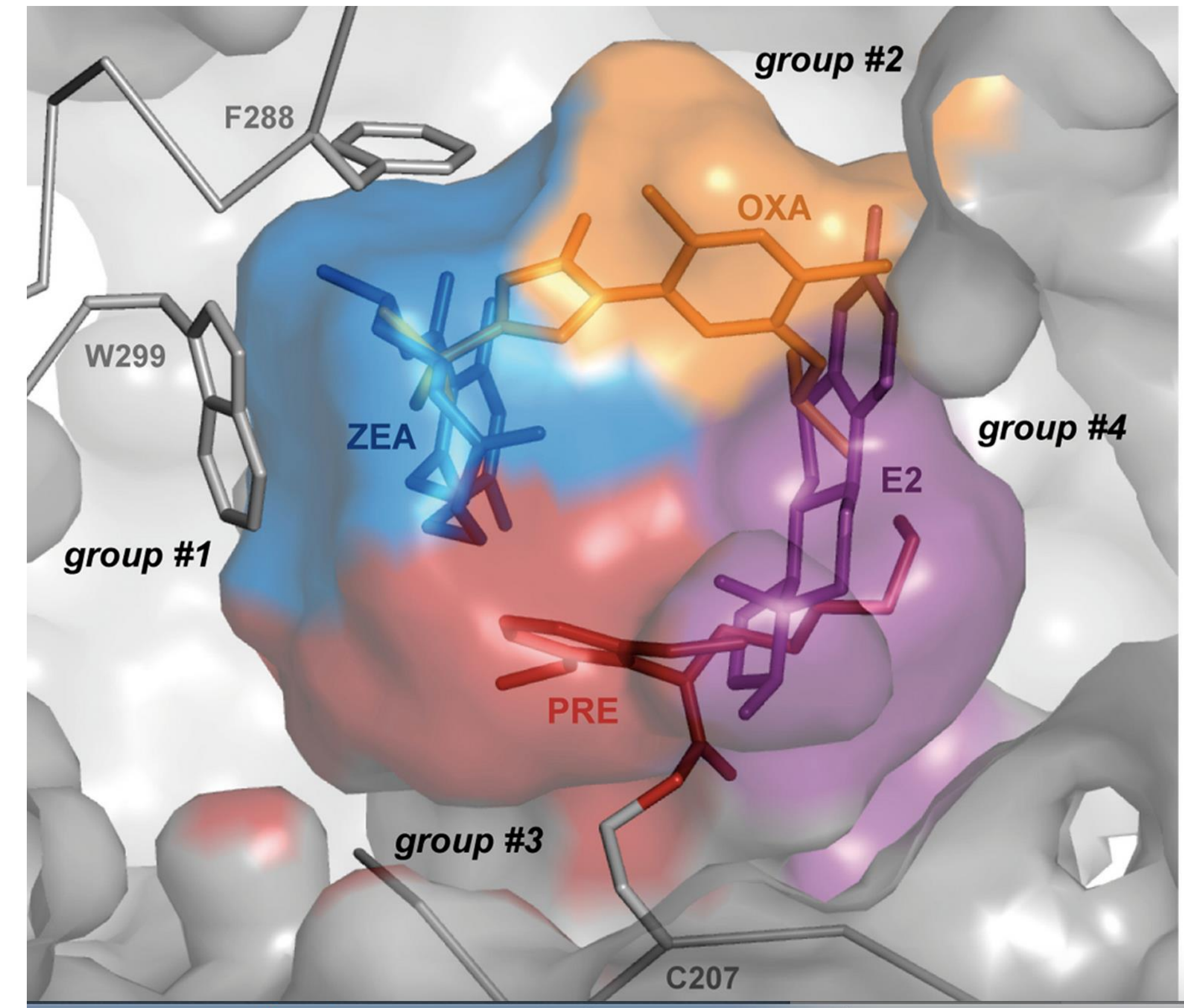


Propriétés structurales: flexibilité, poches de site actif larges capables de lier différentes structures chimiques

Certains récepteurs et certaines enzymes ont des centaines de substrats

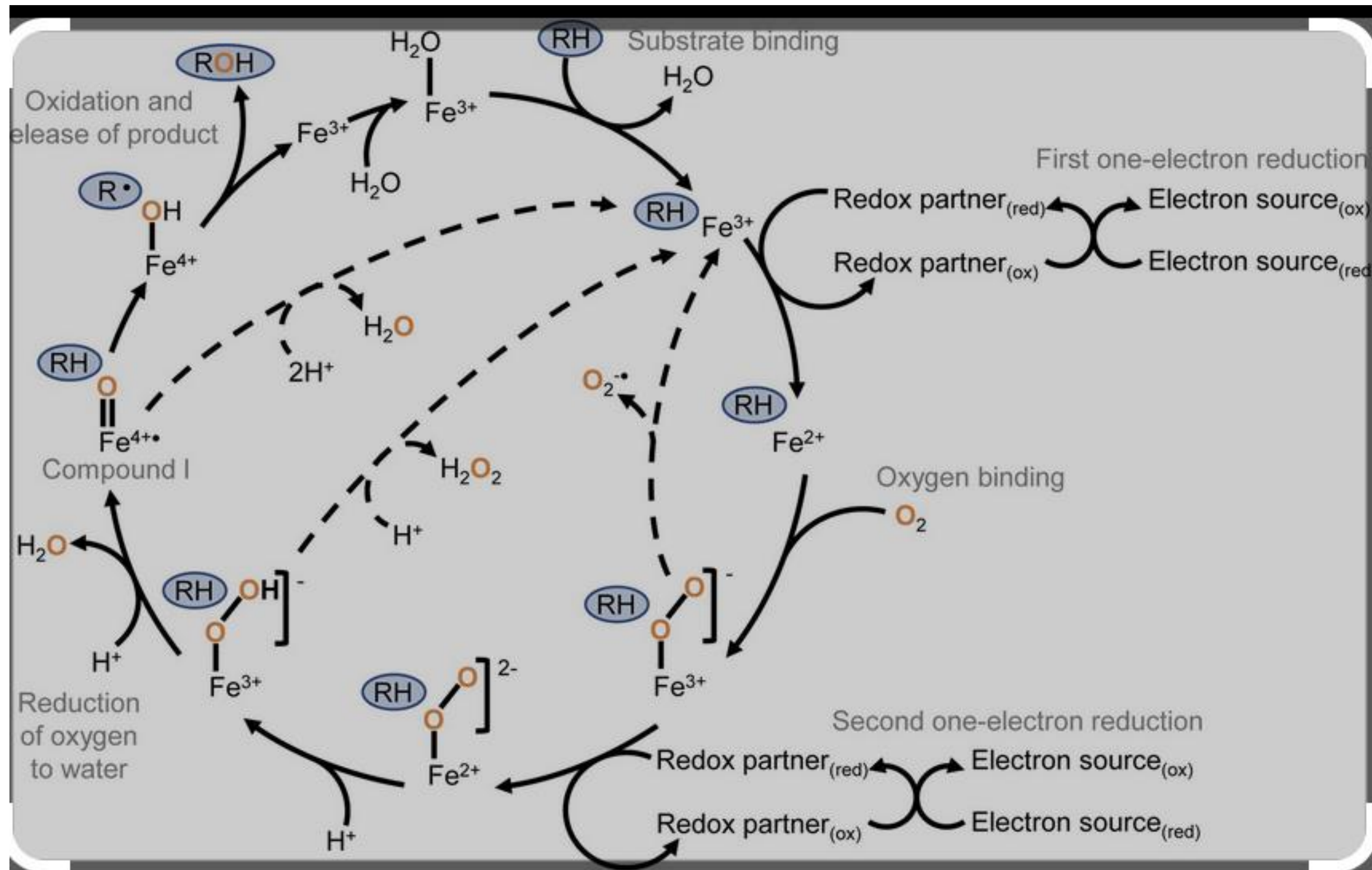


CYP3A4 (Wikipedia, banque de données)

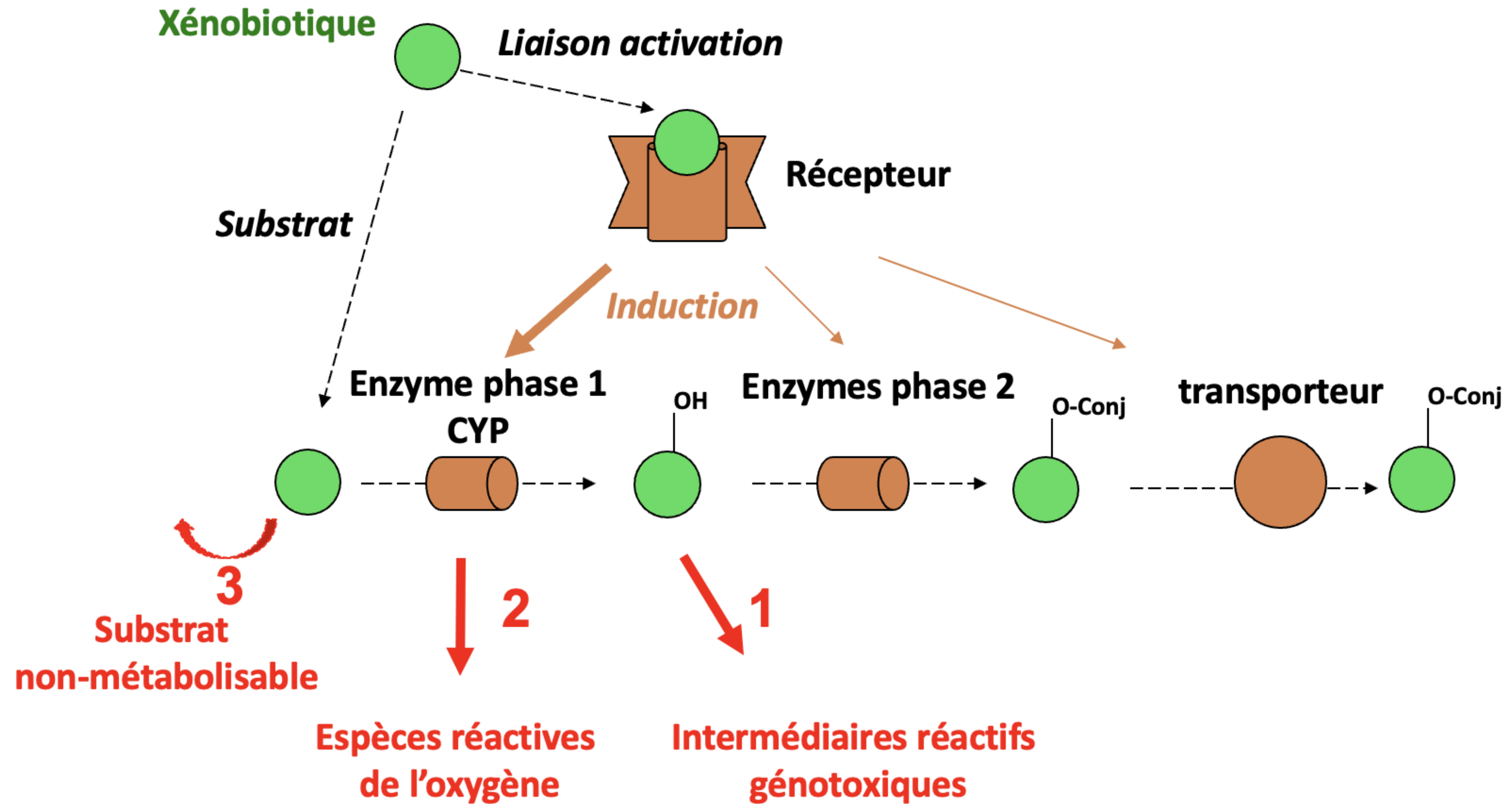


Différentes poches avec 4 différents ligands du PXR, Delfosse et al, PNAS USA, 2020

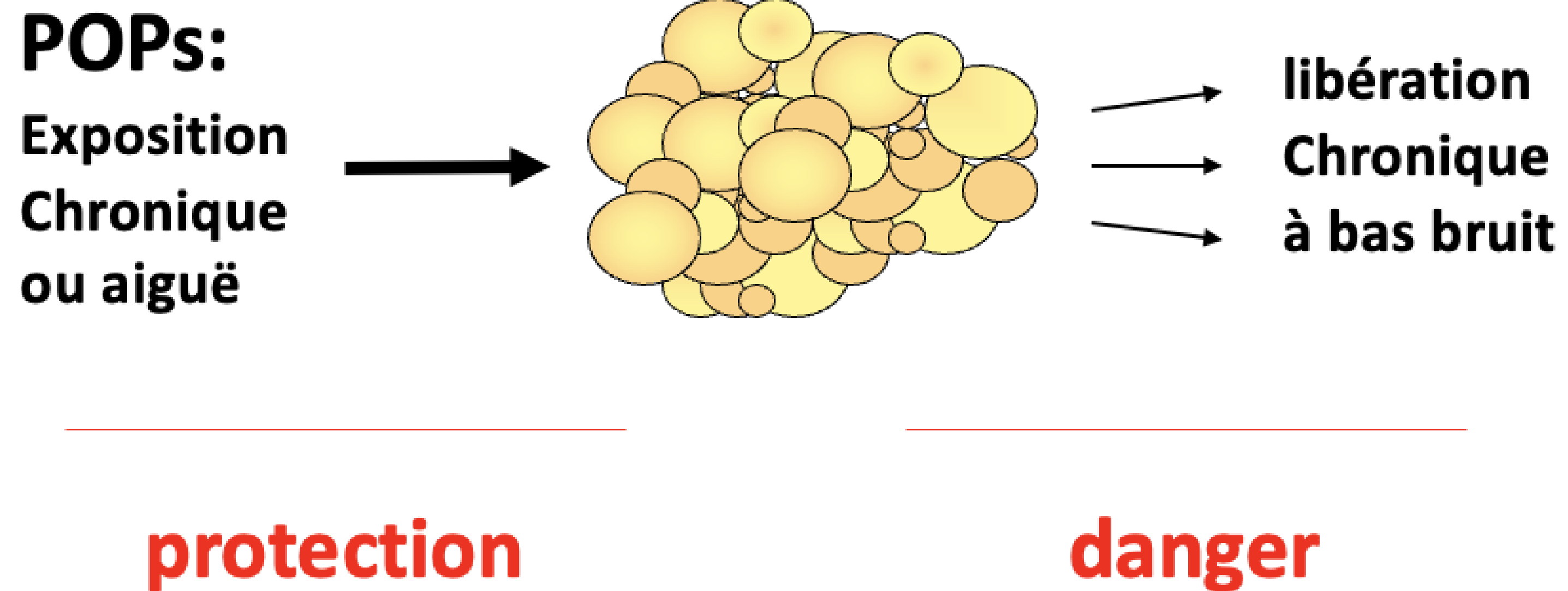
Le cycle enzymatique du cytochrome P450 peut produire des espèces réactives de l'oxygène: substrats découplés



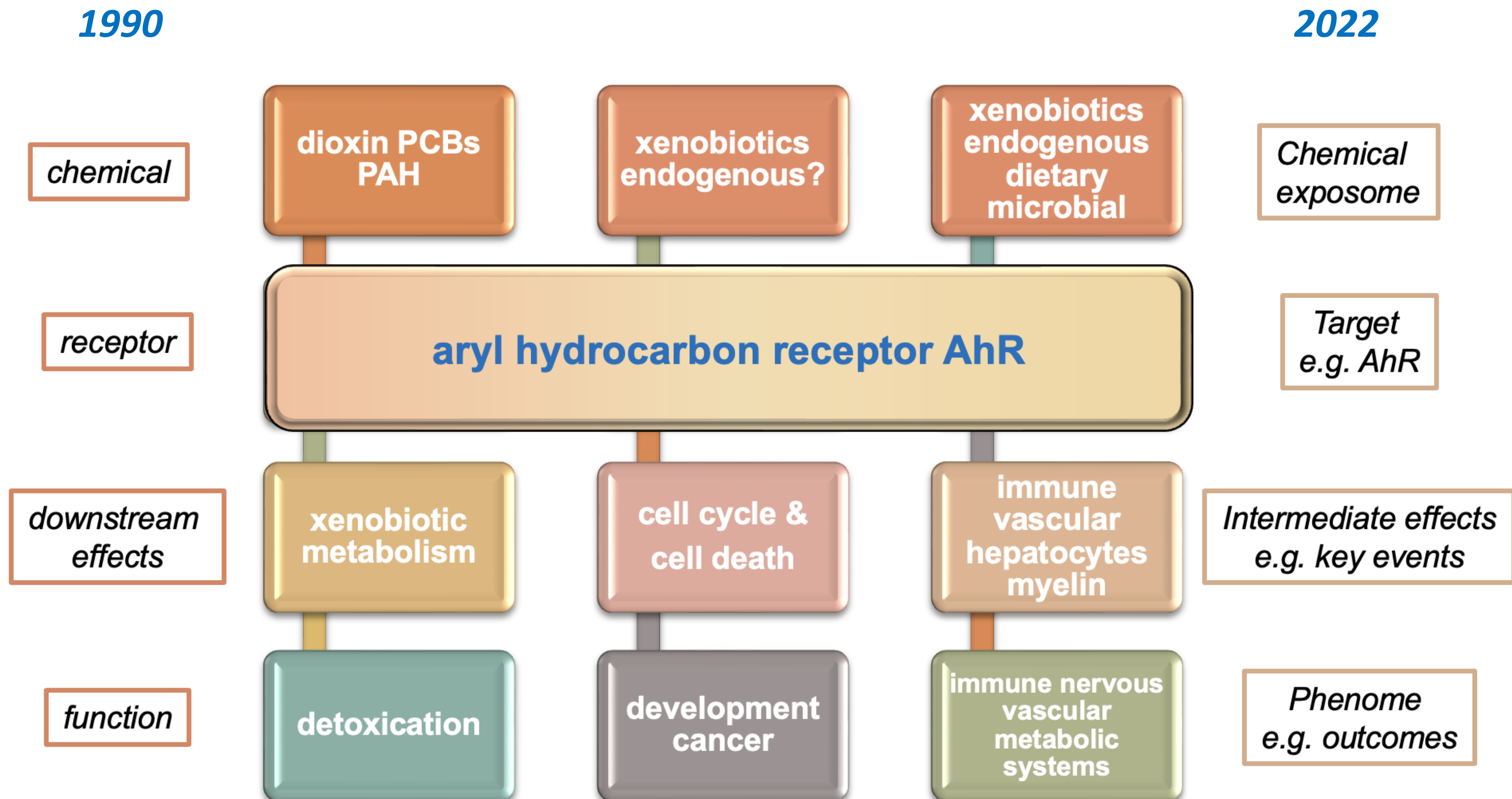
Mécanismes de toxicité liés à la voie adaptative de métabolisme des xénobiotiques



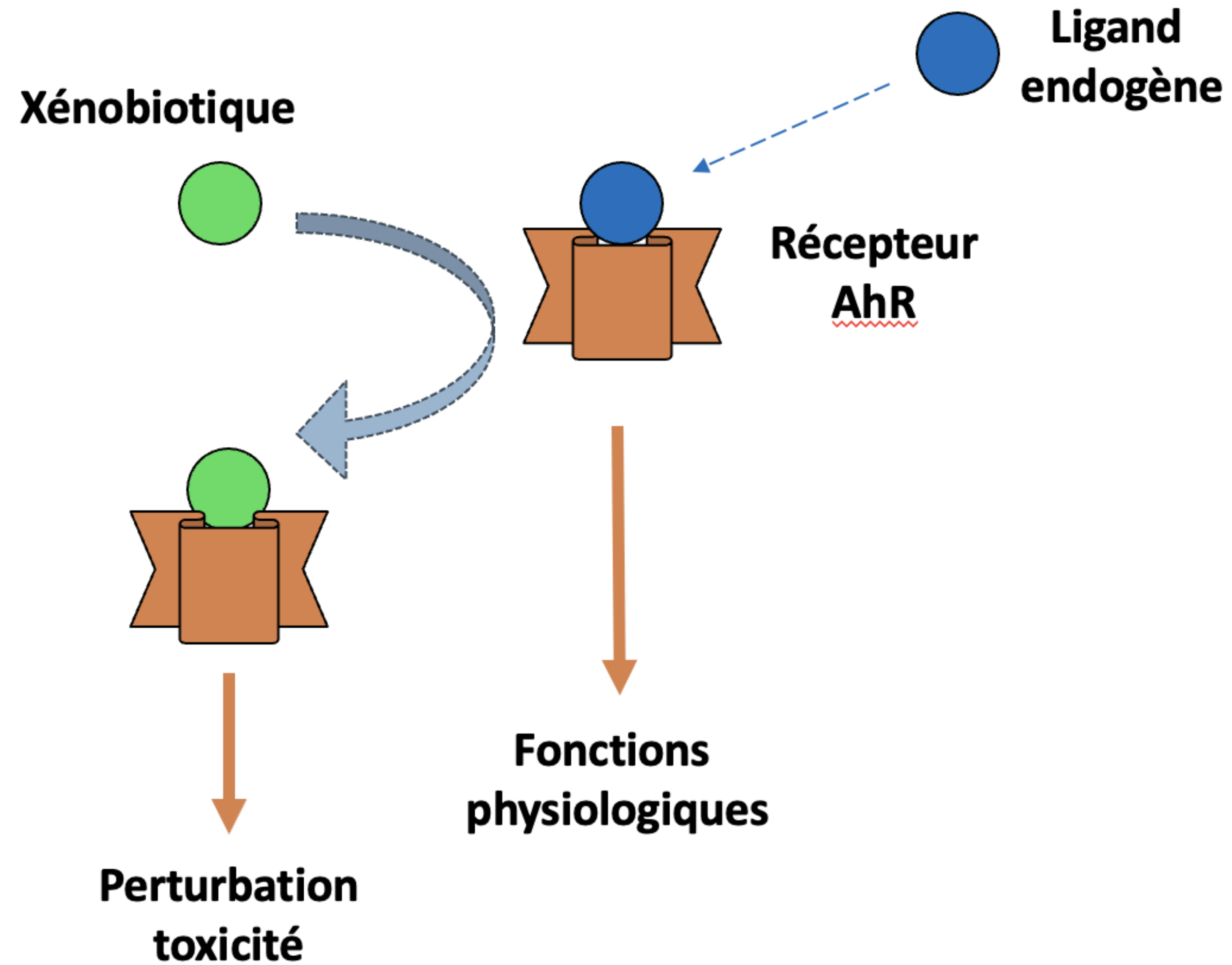
Le double rôle du tissu adipeux vis à vis des Polluants Organiques Persistants



Le cas du récepteur de la dioxine AhR: multiplicité des fonctions et de la nature des ligands

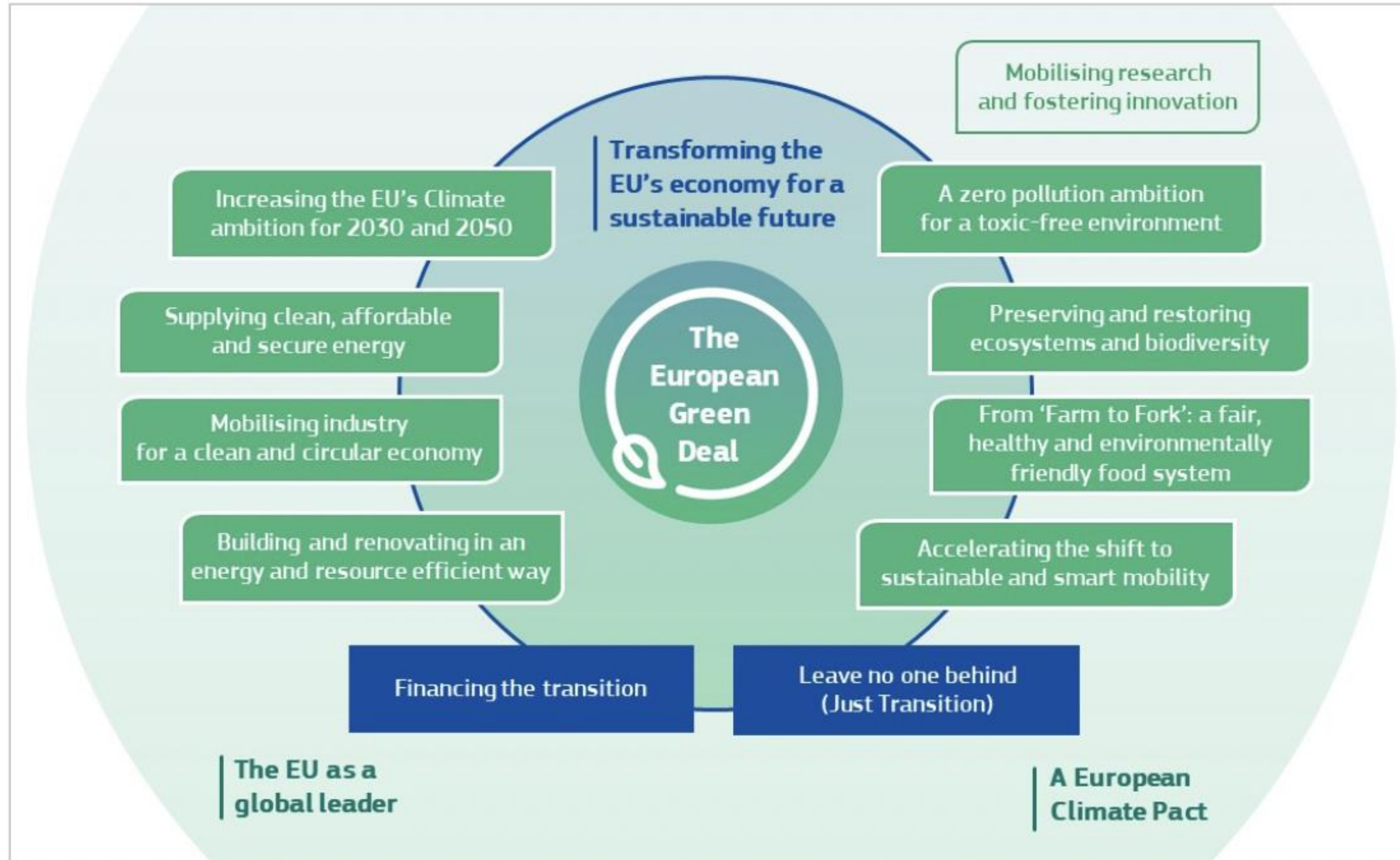


Compétition entre différents ligands du AhR



Des solutions?

La volonté politique



Climate neutral

Clean energy

Zero pollution

Preserving biodiversity

Food to Fork

Sustainable mobility

Financing the transition

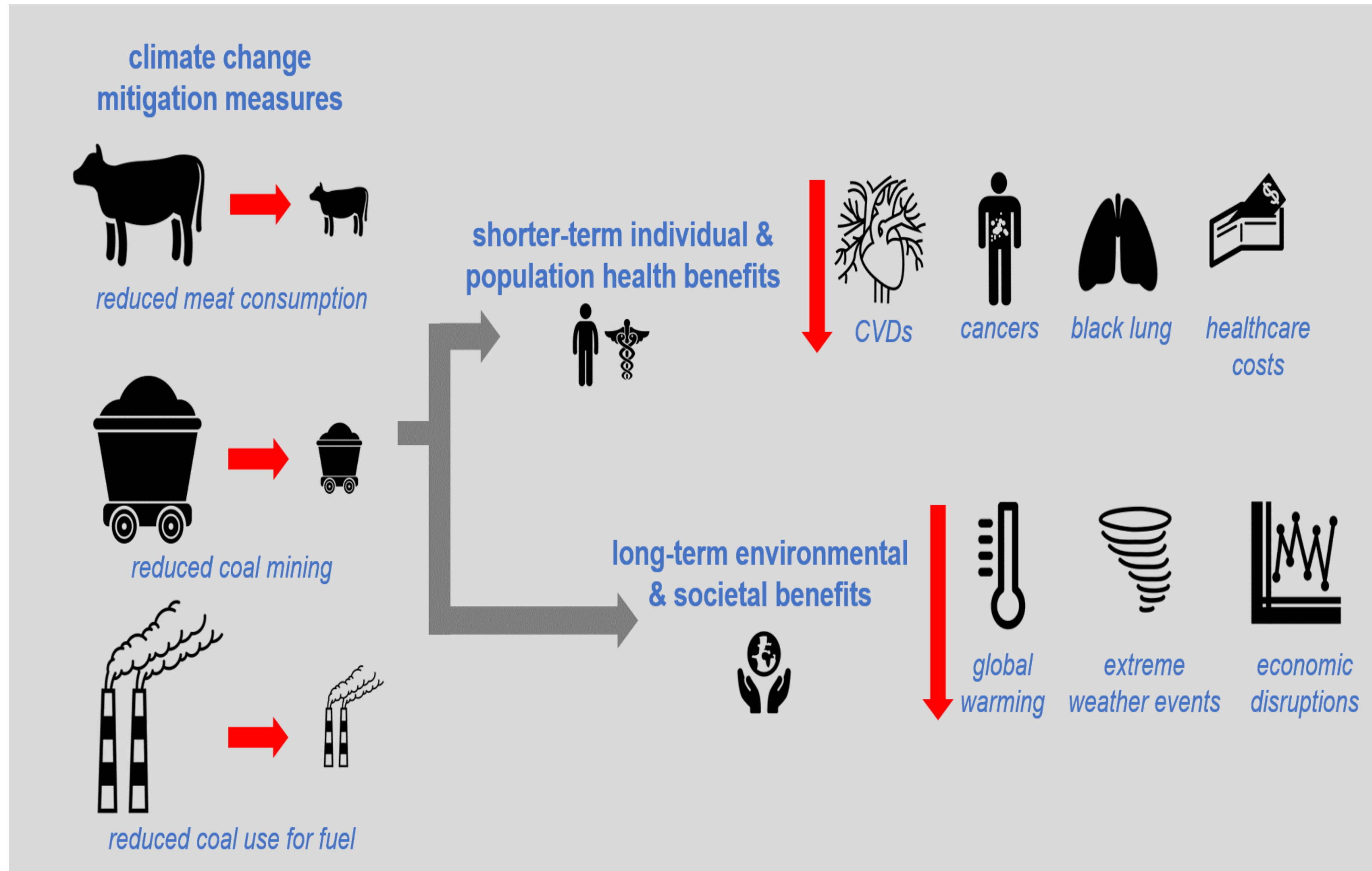
Leave no one behind

Le poids économique de l'inaction

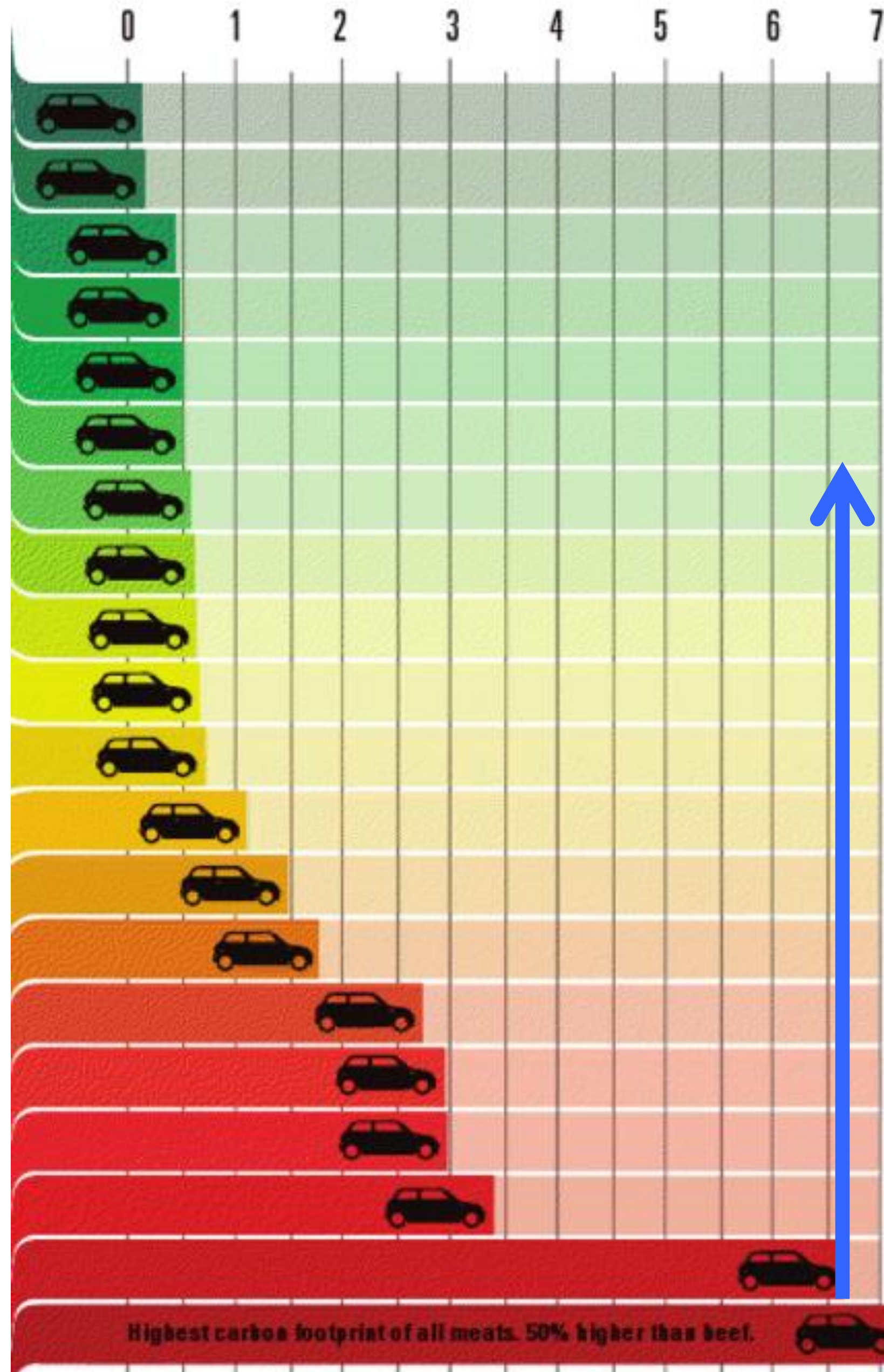
Median costs of EDCs health burden in the EU is **163 billion € per year!**

Exposure	Outcome	Strength of human evidence	Strength of toxicologic evidence	Probability of causation	Base estimate	Low estimate	High estimate
Polybrominateddiphenyl ethers (PBDE)	IQ Loss and Intellectual Disability	Moderate-to-high	Strong	70–100%	€ 9.59 billion	€ 1.58 billion	€ 22.4 billion
Organophosphate pesticides	IQ Loss and Intellectual Disability	Moderate-to-high	Strong	70–100%	€ 146 billion	€ 46.8 billion	€ 195 billion
Dichlorodiphenyltrichloroethane (DDE)	Childhood obesity	Moderate	Moderate	40–69%	€ 24.6 million	€ 24.6 million	€ 86.4 million

Les co-bénéfices



CARBON FOOTPRINT
Car Miles Driven per 4oz. Consumed



GHG emissions for food

CO₂ eq / g protein
ruminant meats up to 250 x legumes

- Lentils
- Tomatoes
- Milk
- Beans
- Tofu
- Broccoli
- Yoghurt
- Nuts
- Peanut butter
- Rice
- Potatoes
- Eggs
- Tuna
- Chicken
- Turkey
- Salmon
- Pork
- Cheese
- Beef
- Lamb

Highest carbon footprint of all meats. 50% higher than beef.

Des villes vertes



Green spaces in cities mean decreased urban heat islands, more exercise, "nicer" neighborhoods

Green space is associated with a large number of health benefits, including lower premature mortality, longer life expectancy, fewer mental health problems, less cardiovascular disease, better cognitive functioning in children and the elderly, and healthier babies



Top 10 EU cities with highest mortality due to lack of Green Spaces

L'exposome: un concept utile

- ✓ **Better integration with other disciplines: strengthens evidence and causality**
- ✓ **Link to exposure, therefore risk assessment**
- ✓ **Mechanistic assessment of various types of stresses, not only chemical**
- ✓ **Mixtures and beyond**
- ✓ **Integrate vulnerability**
- ✓ **Long term effects**

L'exposome: un concept utile

- ✓ **Regulatory implications**
- ✓ **Vulnerable populations (developmental, genetic, associated disease, diet, social, economic, etc)**
- ✓ **Public health messages supporting general prevention**
- ✓ **Precision prevention**
- ✓ **Toxiscore?**