Risks assessment for human health

Yves LEVI

UNIVERSITÉ PARIS-SUD 11

UMR 8079

cnrs AgroParisTech

Great challenge

Estimate risks for human health for all the population

Water
(drinking, bathing, pools
food preparation)

- 2 liters drinks
per day
- Inhalation ??

During 70
years

young

pregnant

Immuno
supressed

Combined with
other risk factors

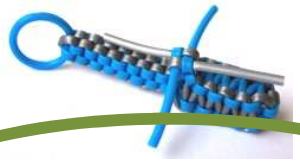
tobacco

alcohol

Indoor, outdoor
occupation
air pollution

Development of reuse, plastic materials, at-home treatments

A large diversity of chemicals



Plasticizers

Pesticides

Pharmaceuticals

Detergents
Biocides

Chemical structures and common molecules

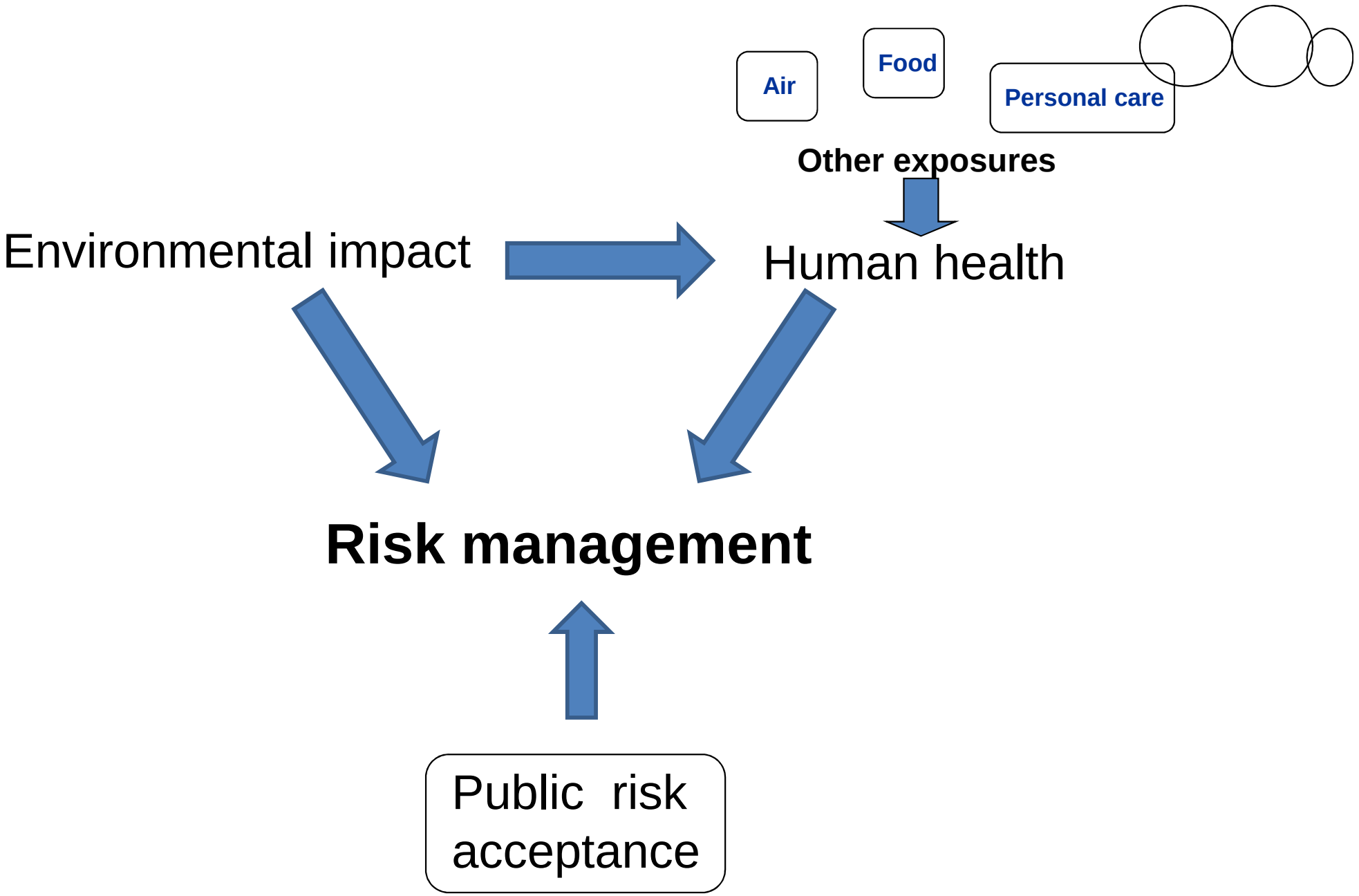
Personal care

Metals

Solvents

Hydrocarbons

Influencing factors

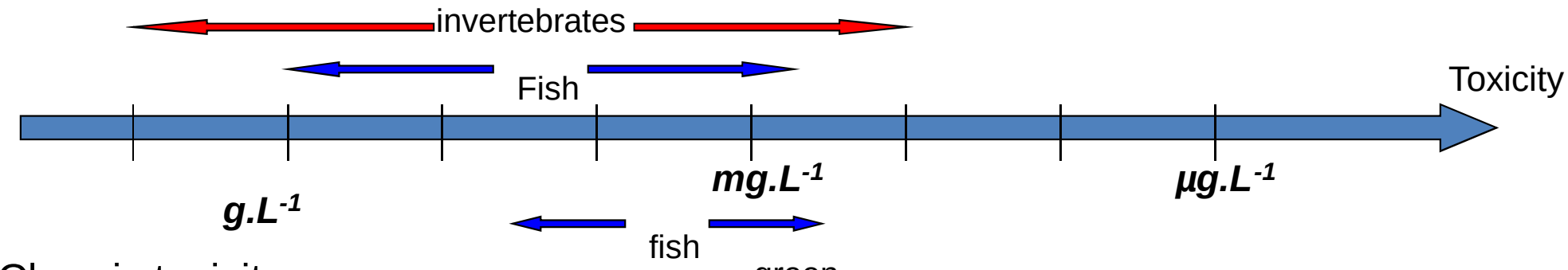


Some evidences

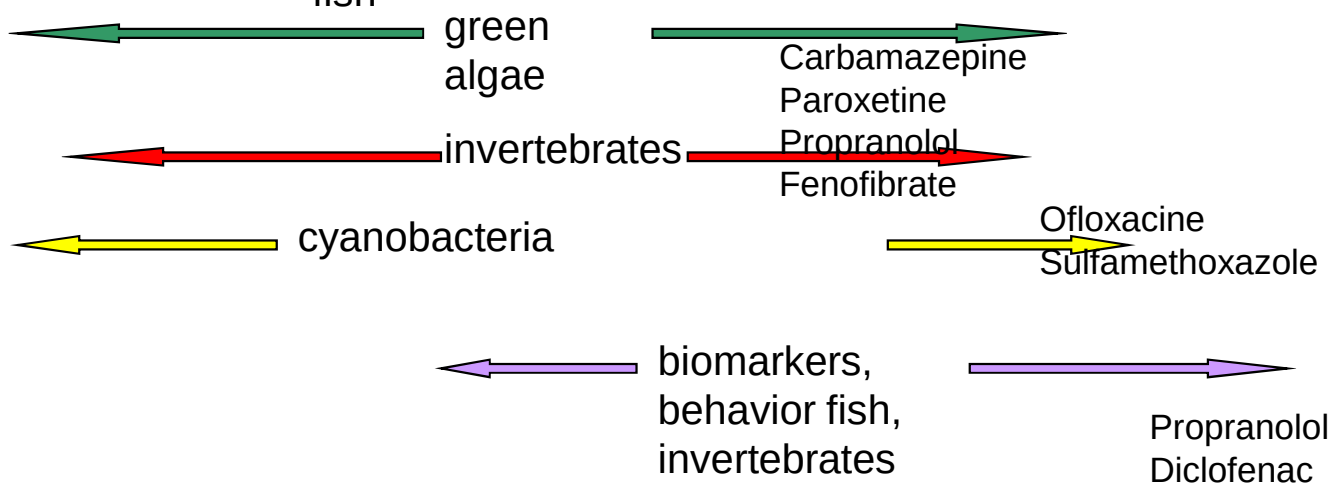
- Presence of EDs (mainly estrogen-like) and pharmaceuticals in tap water
- Mix of organic and mineral pollutants
- Different potential effects for one molecule, from others pollutants and from interactions
- Very low concentrations (sub ng/L to some µg/L)
- Long term exposure/effects
- Other exposition sources (food, air, personal care …)
- Maintain water quality from plant to the tap (+ container / at-home treatments)

Ecotoxicity scale

Acute toxicity: EC_{50} (survival 24H-96H)



Chronic toxicity :
NOEC.
reproduction,
growth



From Garric J., Cemagref, France

Risk evaluation is the major issue

Endocrine disruptors

Antidepressants Antipsychotics

Antibiotics antibioresistance

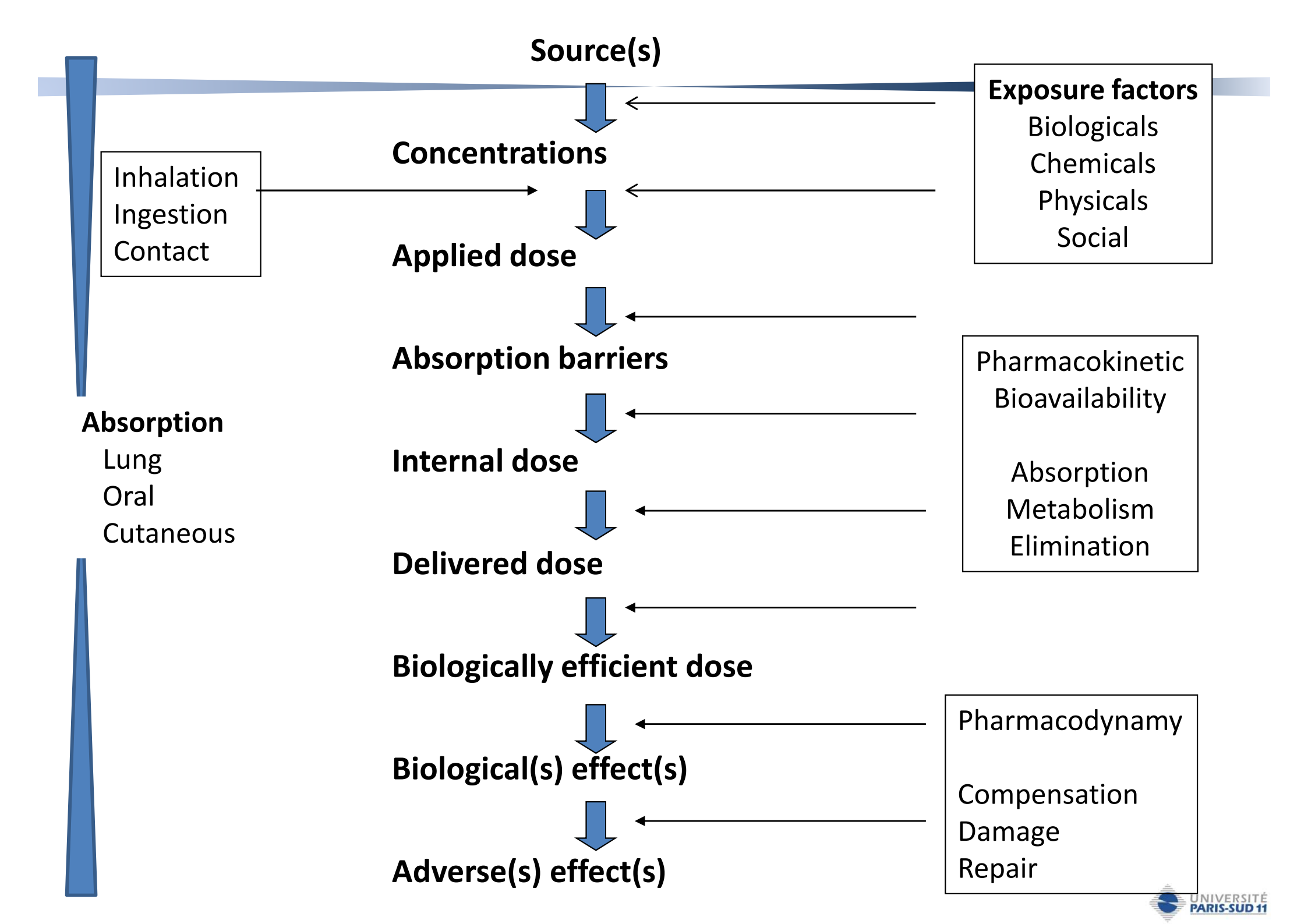
Anti-inflammatory

Genotoxics

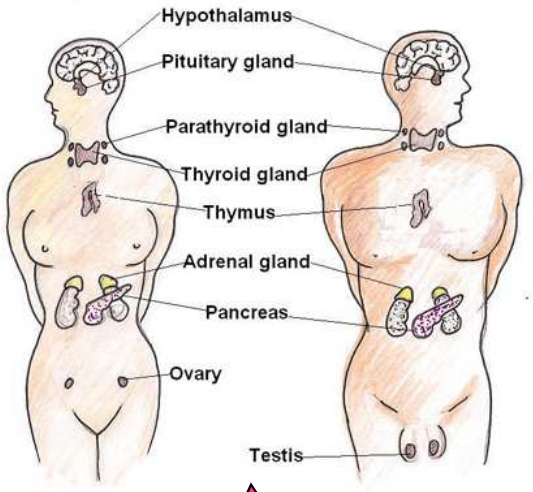
Immunosupressors

Dangers : Pesticides, plasticizers, detergents, flame retardants, HAP, PCB, heavy metals, solvents, disinfection by-products …….

A complex mixture, permanent and with heterogeneous distribution in resources



Complexity of EDCs targets



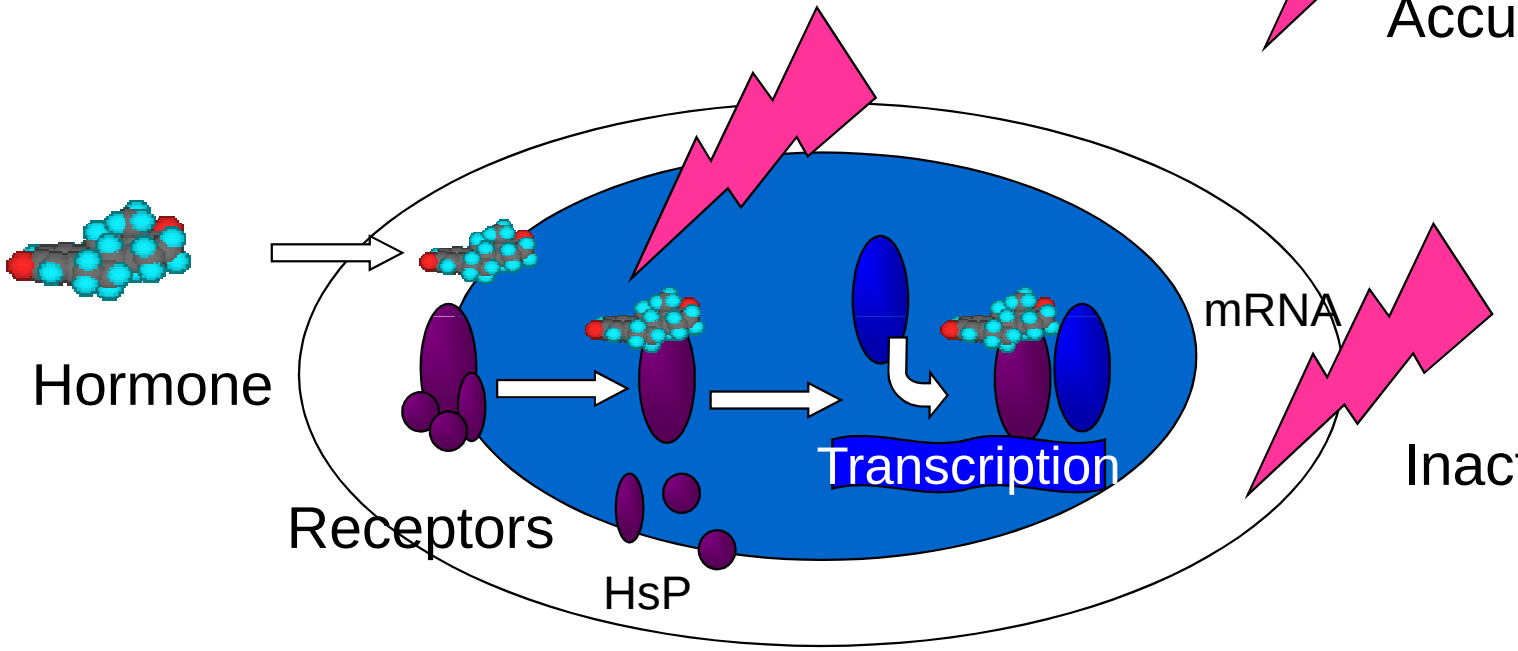
Endocrine glands

Inhibition of production

Transport

Hormones
Metabolism

Accumulation



Inactivation

Diversity of pharmaceuticals and targets

About 3 000 different molecules on the market

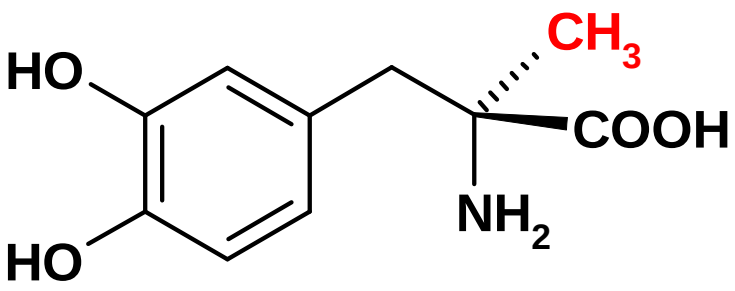
- Binding to a cellular receptor
- Modulation of an ion channel
- Modulation of enzyme activity
- Modulation of a carrier
- Modulation of genome transcription
- Interactions with microorganisms

Anatomical Therapeutic Chemical WHO Drug Classification

A: Alimentary Tract and Metabolism
B: Blood and blood forming organs
C: Cardiovascular System
D: Dermatologicals
G: Genito-Urinary Systems and Sex Hormones
H: Systemic Hormonal Preparations, Excl. Sex Hormones and Insulins
J: Anti-Infectives For Systemic Use
L: Antineoplastic and Immunomodulating Agents
M: Musculo-Skeletal System
N: Nervous System
P: Antiparasitic Products
R: Respiratory System
S: Sensory Organs
V: Various (Allergens , Diagnostic Agents , Contrast Media ..)

Structural analogy, diversity of the effects

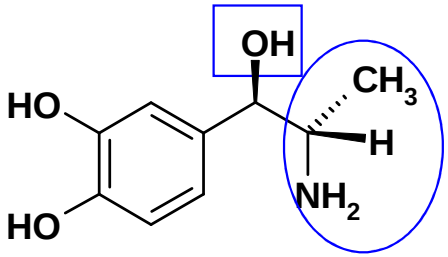
Antihypertensive



Methyldopa, Aldomet®

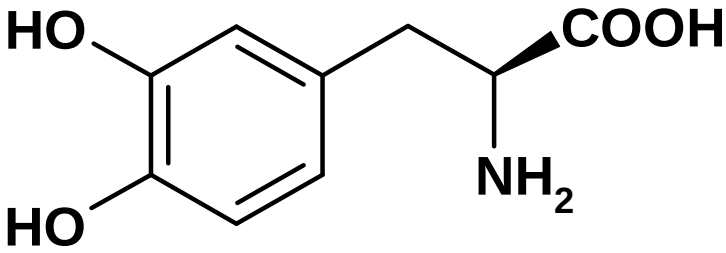
dopadécarboxylase

then dopamine hydroxylase



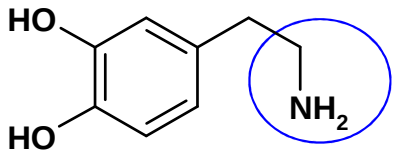
α methyl-noradrenaline
(activation of α_2 adrenergics receptors)

Antiparkinsonian



Levodopa, Modopar ®

L-dopadecarboxylase
In the brain



Dopamine
(déficient in the Parkinson disease)

From S. Ongery, Biocis

Providing data for risk assessment

Risk characterization

Lab/field data

Extrapolation methods

Identification of dangers

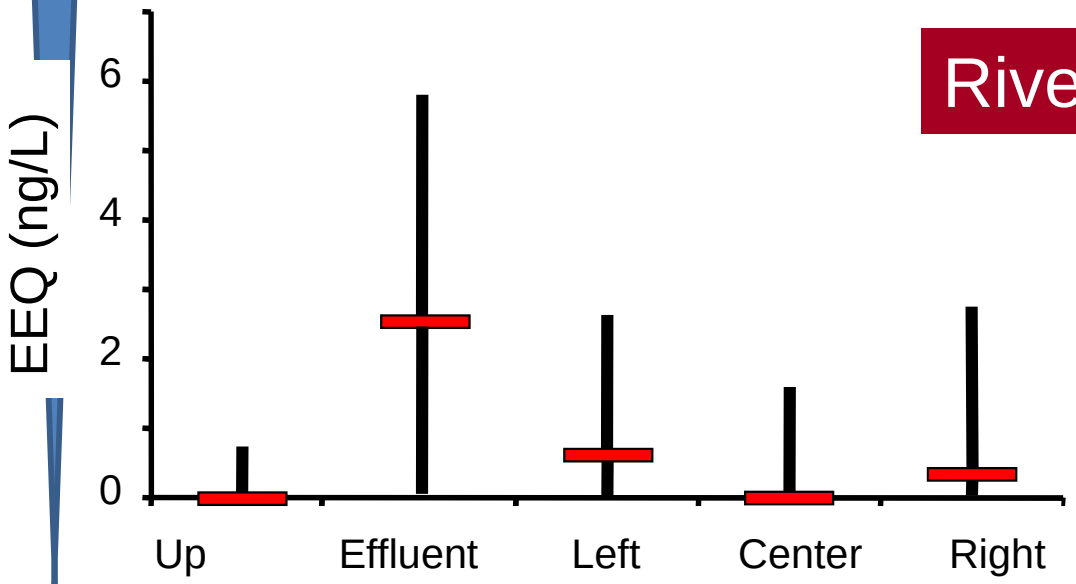
Dose-effect relationship

Evaluation of exposure

Risk quantification

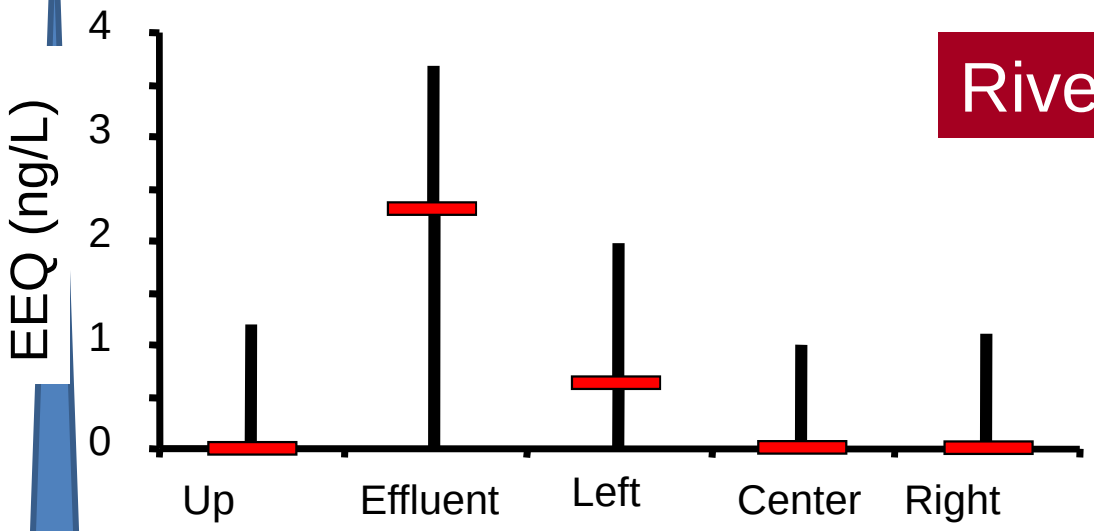
Risk management
Communication
Evaluation of actions

Estrogenic effects in river Seine (model MELN -ERα)



River Seine up and down WWTP1

- Max upstream : 0,8 ng/L EEQ
  (4 campaigns < LOQ)
- Max downstream : **2,6 ng/L EEQ**



River Seine up and down WWTP2

- Max upstream : 1,2 ng/L EEQ
  (4 campaigns < LOQ)
- Max downstream : **2 ng/L EEQ**

Medians n=7

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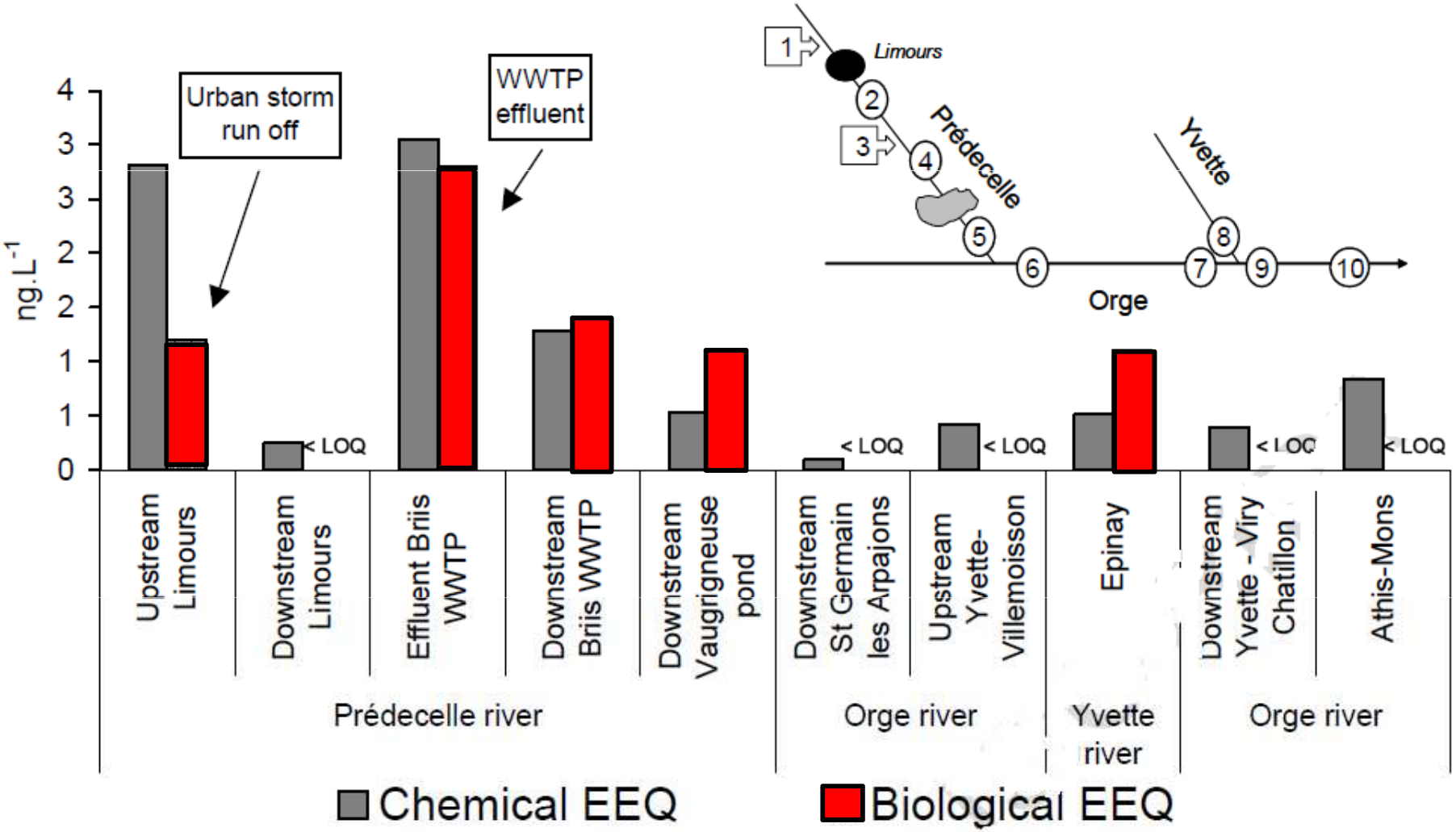
Estrogenics effects : comparison biological tests *vs* chromatography

(model MELN -ERα)



Miege *et al.*, TrAC, 2008

PIREN Seine

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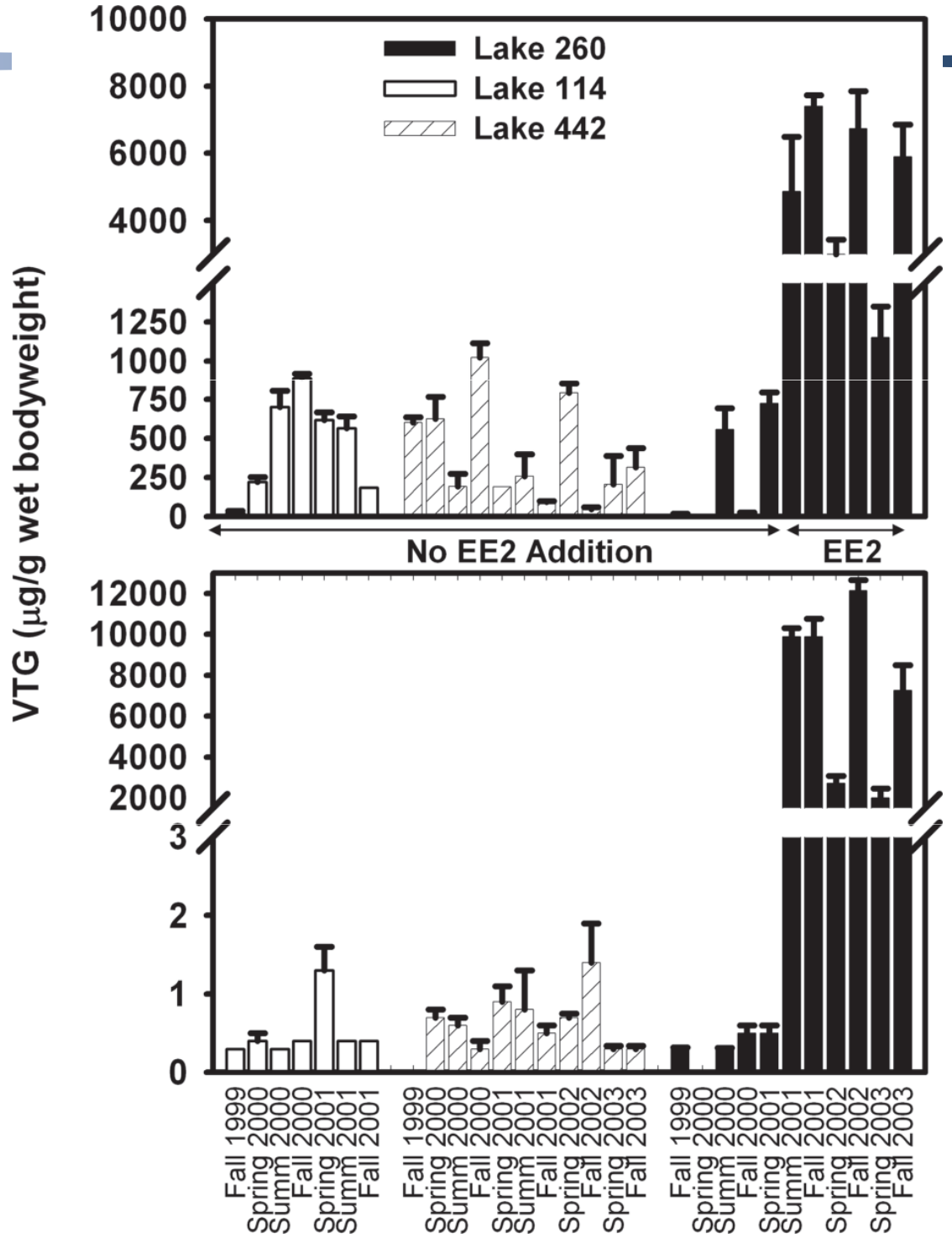


Kidd *et al.*,
PNAS, May 2007

Risks for pharmaceuticals ?

Before market authorization :

- development,
- pre-clinical trials : *in vitro* and *in vivo* toxicology, pharmacology …
- clinical trials phases I, II, III,
- collective evaluation by public agencies.

Human risks are normally fully minimized !!

Is there any direct effects ?? → risks
Is there any indirect effects ?? ….antibioresistance

A pharmacological approach

Cell signals
Imaging
Toxicity

Bioindicators
Biomarkers

in silico ⟷ *In vitro* ⟷ *In vivo* animals

In vivo Human

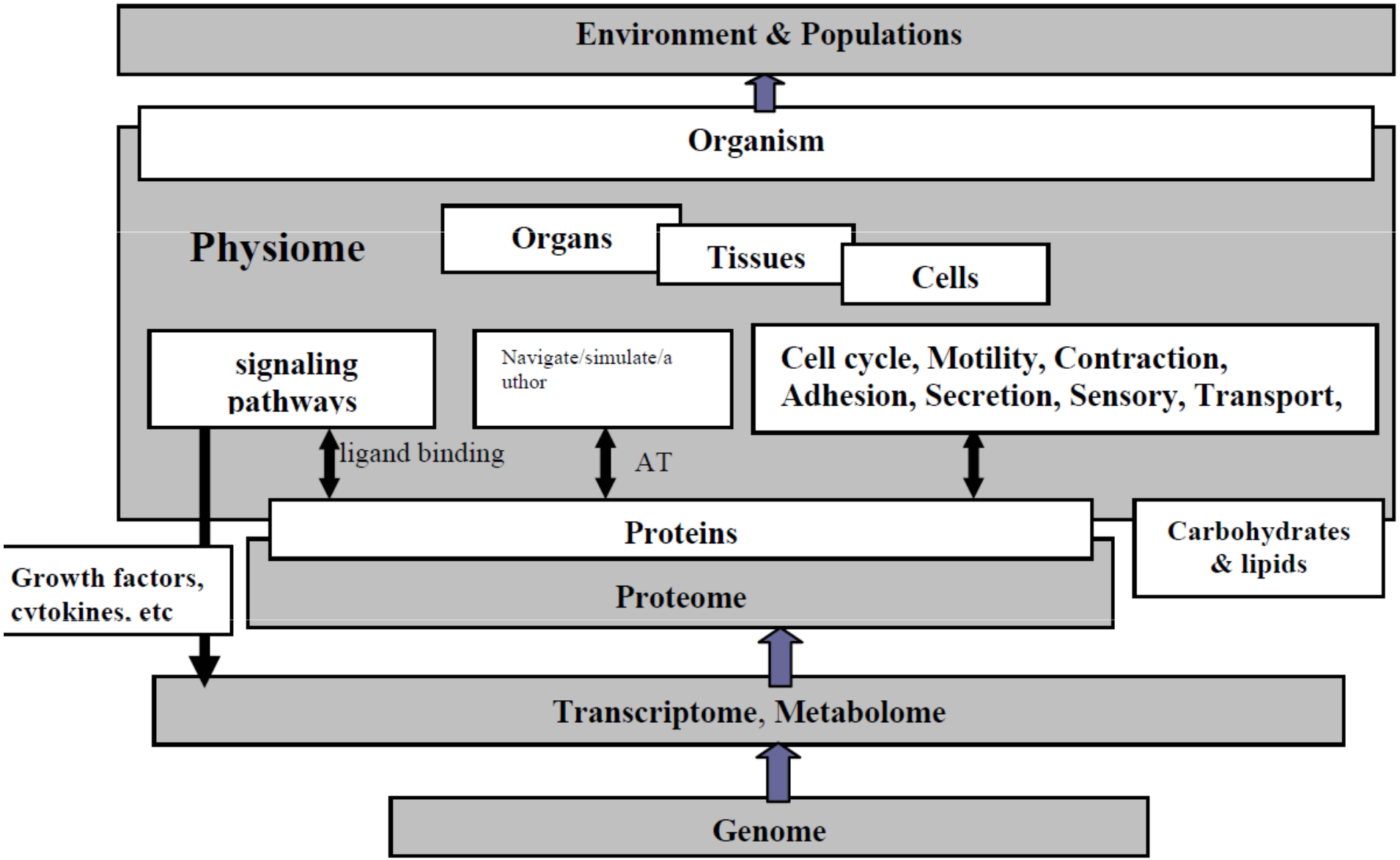
Epidemiology
Epidemiovigilance

Sampling strategy ➡ extraction ➡ models ➡ mechanisms ➡ extrapolation ➡ risk ➡ acceptability

500µL

?

A pharmacological approach



The International Union of Physiological Sciences Physiome Project.
Nature Reviews Molecular and Cell Biology. Vol 4, pp 237-243, 2003

EDCs and health (European commission)

- Sufficient **evidence exists**: increasing testicular cancer rates, apparent decline in sperm counts in some areas;

- Existing exposure information **generally insufficient** to definitely associate the human changes seen with chemical exposure.

- For wildlife, few cases within the EU were known where **effects could be clearly ascribed** to endocrine disrupters.

- **Some animal models** were available that could allow detection of many endocrine disrupting substances.

- Priority should initially be given to **detecting effects** rather than understanding the underlying mechanism of toxicity.

- Exposure monitoring studies would need to be integrated with **studies on human or wildlife effects**.

- There is a need to agree on experimental methods

- Measures to reduce exposure to endocrine disrupters should be in line with the Precautionary Principle, as described in Principle 15 of the 1992 Rio declaration.

EDCs and health (European commission)

- Priority to human epidemiology studies on compounds shown to be active in intact animal studies

- Exposures before and after birth, cohorts with different levels of exposure, effects of "lifestyle" factors, establish 'baseline' ……

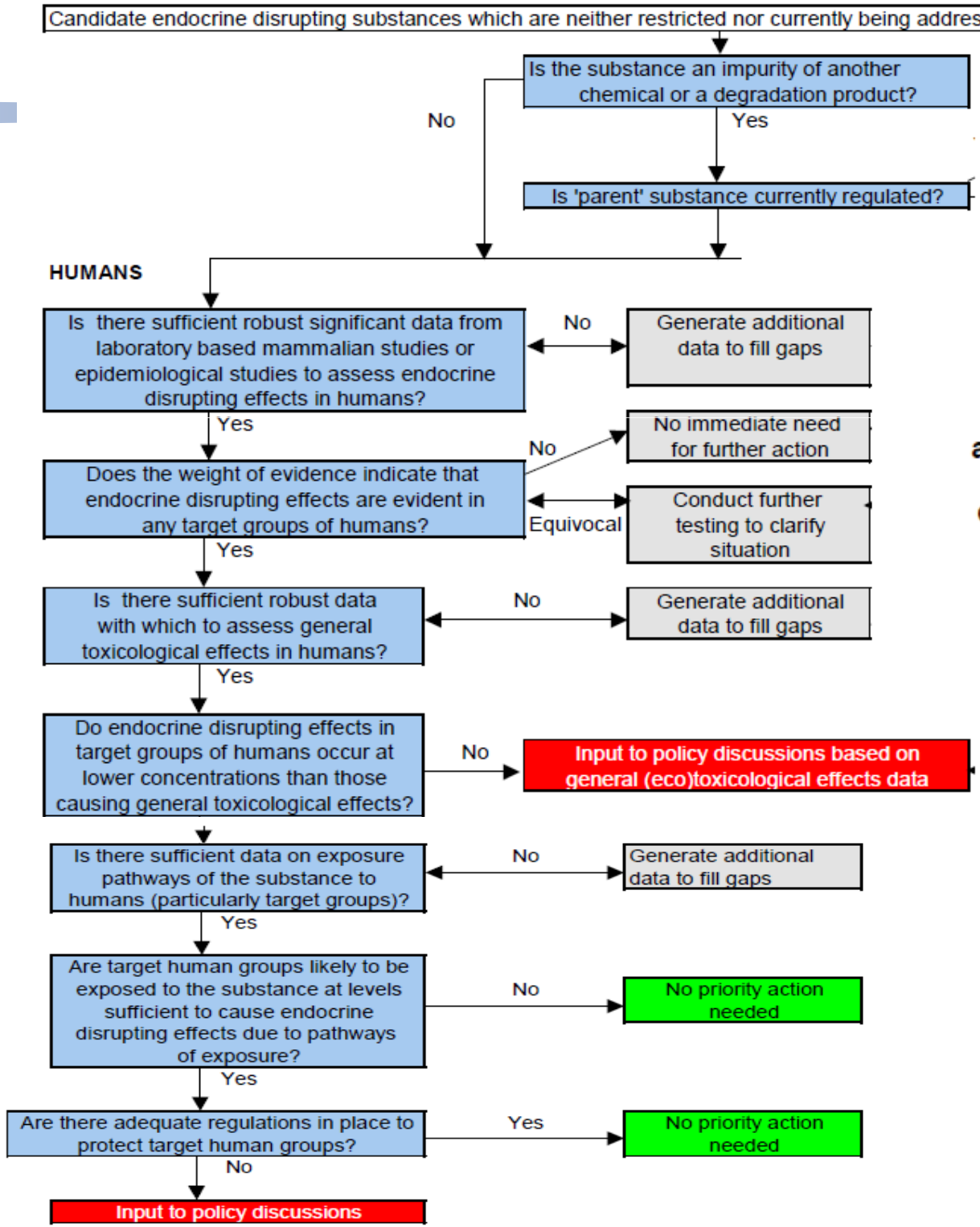
- Understanding the mechanisms by which effects occur, and developing models to use in research

- Validate animal models, study mechanisms of testicular descent, hypospadias and polycystic ovaries in humans , non- or minimally-invasive biomarkers, study neurodevelopmental and neurobehavioural effects …

- Exposure: Normal baseline ?, interactive effects of multiple exposures, studies of the cost and effectiveness of reductions in exposure

- Methods for testing and screening chemicals

- Develop computer based structure-activity relationship (SAR) models, new whole animal assays in fish and birds as possible replacements for rodent studies, predict effects of EDCs in neonates (new born) or weanlings



Framework for the proiritisation and review of potential endocrine disrupting substances

European commission
WRc-NSF, Nov 2002

Concept of ‘‘thresholds of toxicological concern” (TTC)

For chemicals without structural alerts for genotoxicity or evidence of genotoxicity and carcinogenicity

A daily dose of 1.5 µg per person per day was derived as ‘‘virtually safe” from a toxicity database.

Class I –Substances with structures and related data which suggest a low order of oral toxicity. **1800 µg/person/day**
Class II –Substances which are intermediate. Less innocuous than class I. Lack positive identification of toxicity. **540 µg/person/day**
Class III –Substances that permit no initial presumptions on safety or may suggest significant toxicity. **90µg/person/day**

(Cramer *et al.* 1978).
Except : Metals and metal containing compounds (long half-life), Proteins (potential type I allergens), Polyhalogenateddibenzodioxon, -dibenzofuransand biphenyls (bioaccumulation concerns), Aflatoxin-like, N-nitroso and azoxy-compounds (high potency carcinogens).

Cramer Class	Munro et al. (1996) database	Chemicals Used in Household and Personal Care Products
Cramer Class I	137 (22 %)	92 (63 %)
Cramer Class II	28 (5 %)	4 (3 %)
Cramer Class III	448 (73 %)	49 (34 %)
Total chemicals	613	145

Blackburn 2006

France : 5 years national plan to reduce pharmaceuticals in waters

➢ Two major objectives :

➢Assessing environmental and health risks through the acquisition of scientific and technical knowledge concerning the presence, fate and effects of pharmaceuticals on the environment and human health;

➢ Establish measures of environmental risk management and health through the control and reduction of emissions in the environment.

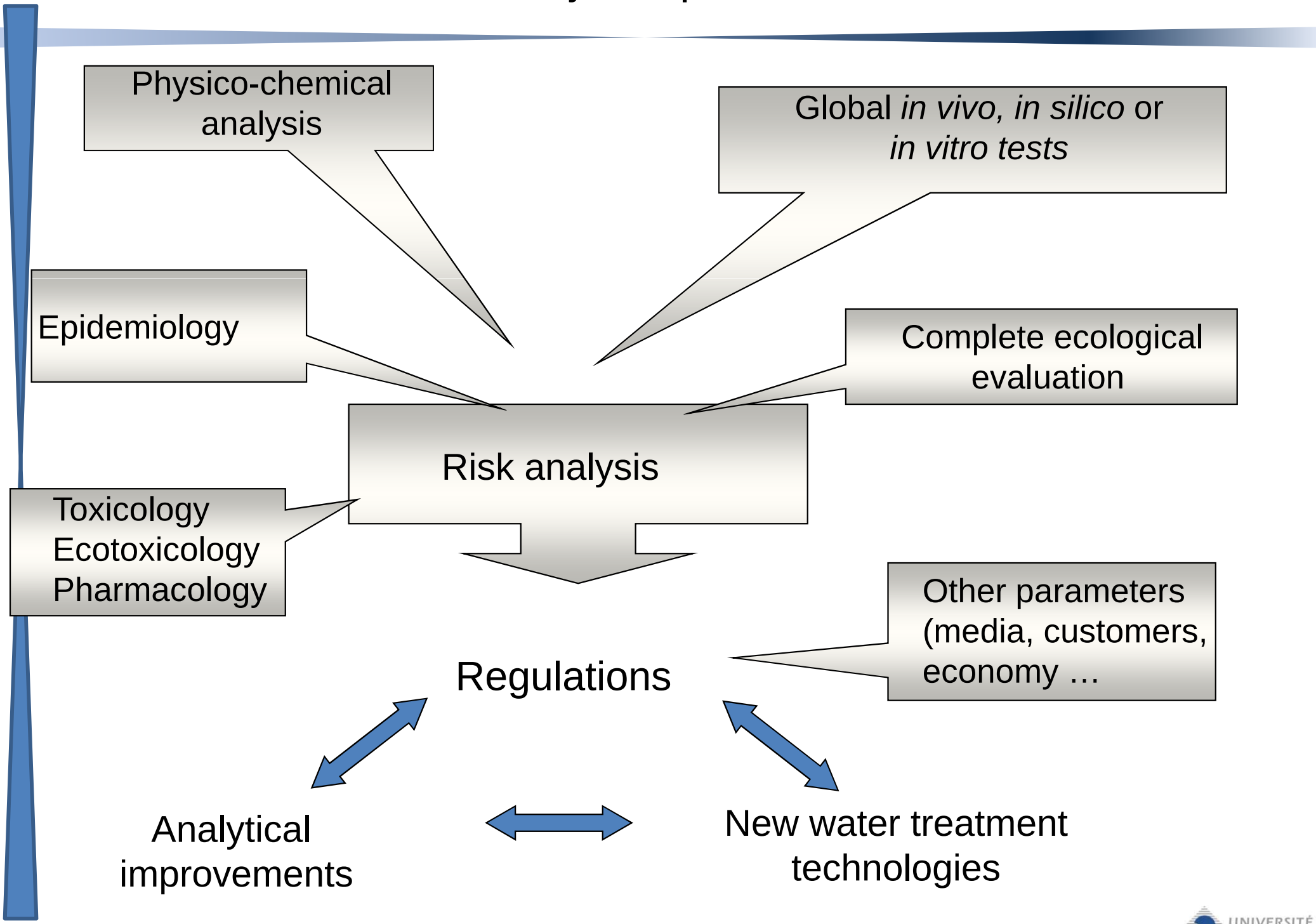
Based on the following three steps:

- Acquisition of knowledge : contamination levels of environment, levels of population exposure and effects on the environment and health;

- Research programs to develop analytical tools, ecotoxicity evaluation methods, health effects and impacts, predictive modeling of exposure;

- Training of professionals and develop information for the public.

Risk evaluation is of major importance for all



Merci - Thank you
Danke sehr

Analysis ***In vitro***

In vivo

Ecology

Qsar / ***in silico***

Epidemiology

20 Years of Research in the Field of Endocrine Disruptors & Pharmaceutical Compounds

Challenges and Solutions for the Water Sector

10 February 2010, Berlin

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